NCT03523728

AMENDED CLINICAL TRIAL PROTOCOL 07

COMPOUND: venglustat/GZ402671

Multicenter, randomized, double-blind, placebo-controlled two stage study to characterize the efficacy, safety, tolerability and pharmacokinetics of GZ/SAR402671 in patients at risk of rapidly progressive Autosomal Dominant Polycystic Kidney Disease (ADPKD)

STUDY NUMBER: EFC15392

STUDY NAME: STAGED-PKD

VERSION DATE/STATUS: 19-Apr-2021/Approved

Version Number:	1	EudraCT	2017-004084-12
		NCT number	NCT03523728
		IND Number(s)	130913
		WHO universal trial number	U1111-1202-0775
Date:	19-Apr-2021	Total number of pages:	190

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/Countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 07	All	19 April 2021, version 1 (electronic 7.0)
Amended Clinical Trial Protocol 06	NL, USA, CAN	16 December 2020, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 05	All	17 August 2020, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 04	All	14 August 2019, version 1 (electronic 4.0)
Amended Clinical Trial Protocol 03	All	01 October 2018, version 1 (electronic 3.0)
Amended Clinical Trial Protocol 02	All	25 May 2018, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	19 April 2018, version 1 (electronic 1.0)
Original Protocol	All	08 February 2018, version 1 (electronic 1.0)

AMENDED PROTOCOL 07 (19 April 2021)

This amended protocol 07 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

This amendment is made to optimize the scope and frequency of ophthalmological examination in the EFC15392 study based on the recommendations of the Ophthalmological Advisory Board (March 2021). The other main change is the conduct of the Measured Glomerular Filtration Rate (mGFR) substudy that has been extended to all countries participating in the EFC15392 study. Additional clarifications to the text of the protocol are described in the summary of changes table.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary, Study objective(s), Stage 1, Stage 2 Section 5.1.3 (Exploratory objectives) Section 5.2.3 (Exploratory objectives) Section 9.3.2 (Stages 1 and 2) Section 9.4.4 (Adverse events)	Exploratory objectives and corresponding endpoints were updated to consider all-cause hospitalization.	Clarification
Clinical trial summary, Assessment schedule, Stage 1, Stage 2, Section 1.3 (Study flow chart for Stage 1) - footnote p, Section 1.4 (Study flow chart for Stage 2) - footnote p, Section 9.4.10 (Ophthalmological examination) Section 10.1.2.2 (Visit 4, 6, 8, 10, 12/Months 1, 6, 12, 18, 24 (Day 30, 180, 360, 540, 720), Section 10.1.2.3 (Visit 5, 7, 9, 11/Month 3, 9, 15, 21 (Day 90, 270, 450, 630)	Pupil dilation was added to the non-dilated pupil slit-lamp examination at Visit 6 (Month 6) (Stage 1 and Stage 2) and Visit 10 (Month 18) (Stage 2). The visual acuity examination was removed from Visits 5, 7, 9, 11/Months 3, 9, 15, 21. Rules about when to perform ophthalmological examinations with pupil dilation after the decline in ≥2 lines of BCVA or after a change of WHO Grade ≥1.0 were optimized: If at any time during study participation patient experiences a decline of ≥2 lines in BCVA compared with that at baseline or previous assessment, a slit-lamp examination with pupil dilation must be performed. A slit-lamp examination with pupil dilation must be performed again in 3 months. If no new cataract is seen during this examination, a normal schedule of ophthalmological examinations with pupil dilation can be resumed. If patient had a change of WHO Grade ≥1 in any of the 3 features (nuclear, cortical, and posterior subcapsular opacification) of the lens, the next scheduled ophthalmic assessment (in 3 months) in this patient must include pupil dilation and evaluation of observed cataract(s) and observations graded with the WHO simplified cataract grading system. If no new change of WHO Grade ≥1 is seen during this examination, a normal schedule of ophthalmological examinations with pupil dilation can be resumed.	The Ophthalmological Advisory Board (March 2021) did not identify safety signals related to development of new, or worsening of the existing, cataract in adult patients treated with venglustat in the completed and ongoing studies. The board recommended continuing every 6-month ophthalmological assessments with slit-lamp examination with pupil dilation and measurement of BCVA. Considering as low utility of the non-dilated pupil slit lamp examination for the examination of the lens and the fundus of the eye, slit lamp examinations at Month 6 (Visit 6) (Stage 1 and Stage 2) and Month 18 (Visit 10)(Stage 2) were supplemented with pupil dilation. In line with recommendations of the Ophthalmological Advisory Board, the schedule of ophthalmological examinations and rules about when to perform unscheduled ophthalmological examinations with pupil dilation were optimized.
Sections 1.3 (Study flow chart for Stage 1) - footnote b, Section 1.4 (Study flow chart for Stage 2) - footnote b.	Added clarification that for patients to be screened for the long-term extension study after Month 24 (Visit 12) and prior to Month 13 (Visit 13), the last in Study EFC15392 should coincide with the first visit in the long-term extension study.	Clarification.

Section # and Name	Description of Change	Brief Rationale
Sections 1.3 (Study flow chart for Stage 1) - footnote t, Section 1.4 (Study flow chart for Stage 2) - footnote t.	The following information was added in footnote t. For patients enrolled or screened for the long-term extension study prior to 30 days after the last dose of IMP, all SAEs, AEs, and AEs of special interest (AESIs) will be collected up to the last visit in Study EFC15392, which will coincide with the first visit in the long-term extension study. Details of ongoing AEs and ongoing medications at the time of the last visit in Study EFC15392 will be duplicated as such into the long-term extension study.	Clarification.
Section 1.4 (Study flow chart for Stage 2) - footnote i and l. Clinical trial summary, assessment schedule, Stage 2. Section 10.1.2.2 (Visit 4, 6, 8, 10, 12/Month 1, 6, 12, 18, 24 (Day 30, 180, 360, 540, 720).	Added information that samples for exploratory biomarkers analysis collected in Stage 2 of the study will be analyzed only if results of this analysis during Stage 1 are considered as useful for further investigation. Removed collection of serum/plasma and urine biomarker samples at Visit 4 (Month 1) in Stage 2.	Optimization, clarification.
Section 7.2.3 (Exclusion criteria related to the current knowledge of venglustat investigational medicinal product)	Relevant medical history and surgical history (if available) and previous and concomitant medications (if available) were deleted from the list of data to be entered into the database for screen failure patients.	Clarification
Section 8.8 (Concomitant medication)	Section was supplemented with new subsection 8.8.2 COVID-19 vaccine.	Section was updated with assessments and recommendations related to the use of an approved COVID-19 vaccine for study patients.
Section 9.4.13 (Pharmacodynamic and exploratory biomarkers)	Numbers of patients and samples for pharmacodynamics and exploratory biomarkers were updated.	Correction
Section 9.4.14.1 (Sampling time)	Numbers of patients and samples for pharmacokinetics were updated	Correction
Section 10.1.1.2 (Visit 2: run-in Day -15). Section 10.1.2.2 (Visit 4, 6, 8, 10, 12/Month 1, 6, 12, 18, 24 (Day 30, 180, 360, 540, 720))	Clarified at what study visits ophthalmological examination includes measurement of the corneal thickness (or endothelial cell density) and measurement of intraocular pressure.	Clarification
Section 10.3.3 (List of criteria for permanent treatment discontinuation)	Text changed from “stop the treatment” or “discontinuation from the study” to “study treatment will be discontinued”. “Two visits apart” as 2 points of time, when if a patient experiences a reduction in eGFR below 30 mL/min/1.73 m^2, the treatment will be discontinued, was replaced with “2 occasions separated by a period of 3 months during the course of this study”.	Correction, clarification. Clarification and harmonization with the provisions of the long-term extension study.
Section 11.4.3 (Analyses of safety data)	The definition of residual treatment period was updated.	Clarification

Section # and Name	Description of Change	Brief Rationale
Appendix C (General guidance for the follow-up of laboratory abnormalities by Sanofi), Acute Kidney Injury	Defined 'abrupt' reduction in kidney function.	Correction and clarification.
Appendix L	Changes in previous amendment 06 (Appendix N) that were specific to the USA, the Netherlands, and Canada will be now applicable for all the countries for this amendment 07, with the exception of the additional inclusion criteria asking for an eGFR between 45 and 89.9 mL/min/1.73 m^2 that is no longer applicable for participants enrolling to the sub-study.	To extend the conduct of the Measured Glomerular Filtration Rate (mGFR) substudy to all countries participating in the EFC15392 study. Correction (all patients, patients with any screening eGFR value, in Stage 2 can be potentially eligible for mGFR study).
Appendix N (Protocol amendment history)	Added protocol amendment 06	Administrative update
Throughout	Typos have been corrected where necessary. Minor editorial and document formatting revisions were made.	To provide clarifications.

CLINICAL TRIAL SUMMARY

COMPOUND:
venglustat/GZ402671

STUDY No.: EFC15392
STUDY NAME: STAGED-PKD

TITLE	Multicenter, randomized, double-blind, placebo-controlled two stage study to characterize the efficacy, safety, tolerability and pharmacokinetics of GZ/SAR402671 in patients at risk of rapidly progressive Autosomal Dominant Polycystic Kidney Disease (ADPKD)
INVESTIGATOR/TRIAL LOCATION	International, multi-center trial
PHASE OF DEVELOPMENT	Phase 2/3
STUDY OBJECTIVE(S)	**Stage 1** **Primary objective:** • To determine the effect of venglustat on the rate of total kidney volume (TKV) growth in patients at risk of rapidly progressive ADPKD. **Secondary objectives:** • To determine the effect of venglustat on the rate of renal function (estimated glomerular filtration rate [eGFR]) decline. • To determine the effect of venglustat on pain and fatigue, based on patient reported diary • To evaluate the pharmacokinetics (PK) of venglustat in ADPKD patients. • Safety/tolerability objectives: - To characterize the safety profile of venglustat. - To evaluate the effect of venglustat on mood using Beck Depression Inventory-II (BDI-II). - To evaluate the effect of venglustat on the lens by ophthalmological examination. **Exploratory objectives:** • To explore the impact of venglustat on total liver volume (TLV) (in patients with height adjusted TLV [htTLV] >2 L/m). • To explore the effect of venglustat on kidney concentrating ability by assessing urine osmolality (in patients not on diuretic). • To explore the effect of venglustat on nocturia, based on patient reported diary • To explore the effect of venglustat on systolic blood pressure (SBP) and diastolic BP (DBP). • To explore the effect of venglustat on biomarkers associated with ADPKD (eg, Fibroblast Growth Factor 23 [FGF23], Asymmetric Dimethylarginine [ADMA]). • To explore the effect of venglustat on pain and fatigue based on Brief Pain Inventory [BPI] and Brief Fatigue Inventory [BFI] questionnaires, and general health status (based on EuroQoL 5-dimension 5-level [EQ-5D-5L] questionnaire). • To explore the effect of venglustat on type, frequency and dosage of analgesic/over the counter (OTC) pain medication administration. • To explore the effect of venglustat on all-cause hospitalization. • To explore the pharmacodynamic (PD) effects of venglustat by measuring downstream metabolites of glucosylceramide synthase (GCS) in plasma and urine.

	Stage 2 **Primary objective:** • To determine the effect of venglustat on rate of renal function (eGFR) decline as compared to placebo in patients at risk of rapidly progressive ADPKD. **Secondary objectives:** • To determine the effect of venglustat on the rate of TKV growth. • To determine the effect of venglustat on pain and fatigue, based on patient reported diary • To evaluate the PK of venglustat in ADPKD patients. • Safety/tolerability objectives: - To characterize the safety profile of venglustat. - To evaluate the effect of venglustat on mood using BDI-II. - To evaluate the effect of venglustat on the lens by ophthalmological examination. **Exploratory objectives:** • To explore the impact of venglustat on TLV (in patients with htTLV >2 L/m). • To explore the effect of venglustat on kidney concentrating ability by assessing urine osmolality (in patients not on diuretic). • To explore the effect of venglustat on nocturia, based on patient reported diary. • To explore the effect of venglustat on SBP and DBP. • To explore the effect of venglustat on measured GFR (mGFR) (substudy). • To explore the effect of venglustat on biomarkers associated with ADPKD (eg, FGF23, ADMA). • To explore the effect of venglustat on pain and fatigue based on Brief Pain Inventory [BPI] and Brief Fatigue Inventory [BFI] questionnaires, and general health status (based on EuroQoL 5-dimension 5-level [EQ-5D-5L] questionnaire). • To explore the effect of venglustat on type, frequency and dosage of analgesic/over-the-counter (OTC) pain medication administration. • To explore the effect of venglustat on all-cause hospitalization. • To explore the PD effects of venglustat by measuring downstream metabolites of GCS in plasma and urine. • To explore the effect of venglustat on eGFR (CKD-EPI equation) from baseline to 24 months in patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2.
STUDY DESIGN	This is an international, multicenter, randomized, double-blind, placebo-controlled two-stage study in adult patients at risk of rapidly progressive ADPKD aged 18 to 50 years in Stages 1 and 2 (and aged 18 to 55 years for patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2 in Stage 2). The study is divided into 2 stages: **Stage 1:** An up to 30-day screening period including a 2-week single-blind placebo run-in (to identify patients who are unlikely to follow the assigned treatment regimen), followed by a randomized double-blind comparative placebo-controlled core treatment period of 24 months duration.

	After run-in, eligible patients will be randomized with a 1:1:1 ratio to placebo, 8 mg venglustat, or 15 mg venglustat. Patients will be stratified based on their predicted ADPKD progression rate (1C versus 1D versus 1E) according to Mayo Imaging Classification and by geographic region (North America, Europe, China, Japan, Republic of Korea, Rest of the World). If after reviewing the unblinded aggregate safety data from Stage 1 (after at least 1 month of treatment of the first 150 randomized patients from Stage 1), the Data Monitoring Committee (DMC) recommends the 8 mg dose for Stage 2, then the DMC may recommend switching patients on 15 mg treatment arm, in Stage 1, to the 8 mg arm. **Stage 2:** After the first 150 randomized patients from Stage 1 have completed at least 1 month of treatment (or have prematurely discontinued), the DMC will review in an unblinded fashion the aggregate safety data from Stage 1 and will select the venglustat dose 8 mg or 15 mg for Stage 2 patients. The selected dose will be the highest dose determined to be safe and well tolerated in Stage 1. Stage 2 will start with an up to 30-day screening period including a 2-week single-blind placebo run-in (to identify participants who are unlikely to follow the assigned treatment regimen), followed by a randomized double-blind comparative core treatment period of 24 months duration. After run-in, patients will be randomized with a 1:1 ratio to placebo and venglustat (dose to be determined in Stage 1). Patients will be stratified based on their predicted progression rate (1C versus 1D versus 1E) and by geographic region (North America, Europe, China, Japan, Republic of Korea, Rest of the World).
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Male or female adult with ADPKD with an age at the time the consent is signed: - between 18 and 50 years (inclusive) for patients in Stage 1 - between 18 and 50 years (inclusive) for patients in Stage 2 with an eGFR between 45 and 89.9 mL/min/1.73 m^2 during the screening period* - between 18 and 55 years (inclusive) for patients in Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 during the screening period* Diagnosis of ADPKD in patients with a family history, will be based on unified Pei criteria. In the absence of a family history, the diagnosis will be based on the presence of renal cysts bilaterally, totaling at least 20, in the absence of findings suggestive of other cystic renal diseases. • Mayo Imaging Classification of ADPKD Class 1C, 1D, or 1E**. **TKV volume must be confirmed by a central reader prior to Visit 3. • Estimated glomerular filtration rate between 45 and 89.9 mL/min/1.73 m^2 during the screening period* (Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] equation) for Stage 1. Estimated glomerular filtration rate between 30 and 89.9 mL/min/1.73 m^2 during the screening period* (CKD-EPI equation) for Stage 2. *Eligibility will be confirmed by the eGFR value from one of the two first pre-randomization eGFR measurements (Visit 1 or Visit 2 measurements or Visit 1 and an additional measurement performed at the Investigator's discretion between Visit 1 and Visit 2). • Stable treatment regimen of antihypertensive therapy for at least 30 days prior to the screening visit for hypertensive patients.

	• Able to read, comprehend and respond to the study questionnaires. • Patient has given voluntary written informed consent before performance of any study related procedures not part of standard medical care. • Patient does not have access to tolvaptan at the time of study start or tolvaptan is not indicated for treatment of patient according to treating physician (patient does not meet recommended criteria for treatment, refuses to initiate or does not tolerate treatment with tolvaptan). **Exclusion criteria:** • Systolic BP >160 mmHg* at run-in and baseline visits. *mean value of three or five systolic BP measurements (See Section 9.4.5). • Administration within 3 months prior to the screening visit of tolvaptan or other Polycystic Kidney Disease-modifying agents (somatostatin analogues). • The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study or unable to undergo study assessments (eg, has contraindications to pupillary dilation or unable to undergo magnetic resonance imaging [MRI]) [For example: patient's weight exceeds weight capacity of the MRI, ferromagnetic metal prostheses, aneurysm clips, severe claustrophobia, large abdominal/back tattoos]). • The patient has, according to World Health Organization (WHO) Grading, a cortical cataract ≥1-quarter of the lens circumference (Grade cortical cataract-2 [COR-2]) or a posterior subcapsular cataract ≥2 mm (Grade posterior subcapsular cataract-2 [PSC-2]). Patients with nuclear cataracts will not be excluded. • 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. • The patient has received strong or moderate inducers or inhibitors of CYP3A4 within 14 days or 5 half-lives, whichever is longer, prior to randomization. This also includes the consumption of grapefruit, grapefruit juice, or grapefruit containing products within 72 hours of starting venglustat administration.
Total expected number of patients	Stage 1: Approximately 240 patients (80 patients per arm). Stage 2: Approximately 400 patients (200 patients on venglustat and 200 patients on placebo).
STUDY TREATMENT(S) **Investigational medicinal product(s)** **Formulation:** **Route(s) of administration:**	 Venglustat, matched placebo. Venglustat is provided in capsule formulation containing 4 mg or 15 mg of venglustat (active moiety). Matched placebo is provided as a capsule indistinguishable from venglustat. Oral.
Dose regimen:	Run-in period: Placebo. Stage 1: Placebo, 8 mg, or 15 mg of venglustat once per day for 24 months. Stage 2: Placebo or venglustat once per day (dose to be determined in Stage 1) for 24 months.

ENDPOINT(S)	**Stage 1** **Primary endpoint:** • Annualized rate of change in TKV based on MRI from baseline to 18 months. **Secondary endpoints:** • Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 18 months. • Change in pain (BPI - Item 3) from baseline to 18 months, from the daily symptom diary. • Change in fatigue (BFI - Item 3) from baseline to 18 months, from the daily symptom diary. • Plasma venglustat concentrations. • Safety/tolerability endpoints: - 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). Adverse event data will be collected throughout the study. Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator opinion), or become serious during the treatment period. The treatment period is defined as the time from first dose of study treatment up to 30 days after last dose of study treatment. Full details of safety reporting and AE monitoring procedures are provided in Section 10.1. - Change in score of BDI-II during the treatment-emergent period. - Change in the lens clarity by ophthalmological examination during the treatment-emergent period. **Exploratory endpoints:** • Annualized rate of change in total liver volume based on MRI (in patients with htTL >2 L/m) from baseline to 18 months: Change in: - Urine osmolality from baseline to 18 months (in patients not on diuretic). - Systolic BP during the treatment-emergent period. - Diastolic BP during the treatment-emergent period. - Pain (BPI), fatigue (BFI), and health status (EQ-5D-5L) from baseline to 18 months. - Nocturia from baseline to 18 months based on patient reported diary. - Type, frequency, and dosage of analgesic/over the counter (OTC) pain medication administration from baseline to 18 months. - Biomarkers associated with ADPKD (eg, FGF23 and ADMA) from baseline to 18 months. - Glucosylceramide (GL-1) and monosialodihexosylganglioside (GM3) from baseline to 18 months. • Rate of all-cause hospitalization. • Time to confirmed 30% reduction in eGFR. • Time to confirmed 40% reduction in eGFR.

	Stage 2 **Primary endpoint:** • Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months. **Secondary endpoints:** • Annualized rate of change in TKV based on MRI from baseline to 18 months. • Change in Pain (BPI - Item 3) from baseline to 24 months, from the daily symptom diary. • Change in fatigue (BFI - Item 3) from baseline to 24 months, from the daily symptom diary. • Plasma venglustat concentrations. • Safety/tolerability endpoints: - Safety in terms of TEAEs/AEs/SAEs, laboratory parameters, vital signs, electrocardiogram and findings from physical examination will be assessed through the study and will be reported in the eCRF. Adverse event data will be collected throughout the study. Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator opinion), or become serious during the treatment period. The treatment period is defined as the time from first dose of study treatment up to 30 days after last dose of study treatment. Full details of safety reporting and AE monitoring procedures are provided in Section 10.1. - Change in score of BDI-II during treatment-emergent period. - Change in the lens clarity by ophthalmological examination during treatment-emergent periods. **Exploratory endpoint(s):** • Annualized rate of change in total liver volume based on MRI (in patients with htTL >2 L/m) from baseline to 18 months. Change in: • Systolic BP during treatment-emergent period. - Diastolic BP during treatment-emergent period. - Pain (BPI), fatigue (BFI), and health status (EQ-5D-5L) from baseline to 24 months. - Nocturia from baseline to 24 months based on patient reported diary. - Urine osmolality from baseline to 24 months (in patients not on diuretic). - Type, frequency, and dosage of analgesic/OTC pain medication administration from baseline to 24 months. - Biomarkers associated with ADPKD (eg, FGF23 and ADMA) from baseline to 24 months. - Glucosylceramide (GL-1) and GM3 from baseline to 24 months. • Rate of all-cause hospitalization. • Time to confirmed 30% reduction in eGFR. • Time to confirmed 40% reduction in eGFR. • Annualized rate of change in mGFR from baseline to 24 months (substudy). • Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months in patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2.

ASSESSMENT SCHEDULE	**Stage 1** Efficacy assessments: MRI during screening period (at Visit 1 or Visit 2), Months 1, 9, and 18. eGFR (CKD-EPI) at screening, run-in, baseline, Month 1, Month 3, and then every 3 months. Safety/tolerability assessments: Vital signs, physical examination, clinical laboratory evaluation will be performed at all visits. Ophthalmological assessments will be performed at Months -0.5, 6, 12, 18, and 24. Beck Depression Inventory-II will be assessed at Months -0.5, 3, and then every 3 months. Biomarker assessments: Screening, Months 1, 6, 12, 18, 24, and at 30 days follow-up (Month 25). PK assessments: Blood samples for plasma venglustat concentrations assessment will be collected in all patients at following visits: • Day 1: 3 (±1) hour post dose. • Month 1: pre-dose and 3 (±1) hours post dose. • 6 months and 18 months: pre-dose sample. Patient Reported Outcome (PRO) Assessments: Pain (BPI) and fatigue (BFI) data will be collected at the baseline visit and at each study visit prior to administration of procedures and the disease and treatment discussion with the patients. Patient global impression of severity will be collected at run-in, baseline and Months 3, 12, 18, and 24. Patient global impression of change will be collected at Months 3, 12, 18, and 24. Health status (EQ-5D-5L) will be collected at baseline and Months 3, 6, 12, 18, and 24. Daily diary data on symptoms of ADPKD (pain: BPI Item 3, fatigue: BFI Item 3,and nocturia) will be entered by the patients for specified consecutive days during the administration period prior to Baseline visit, from Baseline visit to Month 3, and prior to the site visit at Months 12, 18, and 24. Patients who prematurely and permanently discontinue study medication should complete rapidly (within 7 days) an end of treatment assessment visit. End-of-treatment visit should include all procedures of Visit 12 and additionally a PK sample should be collected. In 30 days, a Follow-up visit should be performed. Investigator should ask patient to continue study visits for safety and efficacy assessments up to and including the last scheduled visit, if possible. If the patient refuses to attend all scheduled visits and to continue answering all PRO questionnaires, Investigator should ask the patient to continue answering questions of "Daily symptoms of ADPKD" diary, and also return to the site at Month 18 to have at least MRI performed, and at Month 24 to have at least blood sample (for eGFR) collected. Other assessments planned at Month 18 and/or Month 24 should also be done if possible. **Stage 2** Efficacy assessments: MRI during screening period (at Visit 1 or Visit 2) and Month 18. eGFR (CKD-EPI) at screening, run-in, baseline, Month 1, Month 3, and then every 3 months. Iohexol will be administered in a substudy in approximately 15% of patients at the baseline visit, Months 12 and 24 to evaluate mGFR. Safety/tolerability assessments: Vital signs, physical examination, clinical laboratory evaluation will be performed at all visits. Ophthalmological assessments will be performed at Months -0.5, 6, 12, 18, and 24. BDI-II will be assessed at Months -0.5, 3, and then every 3 months. Biomarkers: Screening, Months 6, 12, 18, 24, and at 30 days follow-up (Month 25).

	PK assessments: Blood samples for plasma venglustat concentrations assessment will be collected from all patients at following visits: • Month 1: Pre-dose and 3 (±1) hours post dose. • Month 24: Pre-dose sample. Patient Reported Outcome (PRO) Assessments: Pain (BPI) and fatigue (BFI) data will be collected at the baseline visit and at each study visit prior to administration of procedures and the disease and treatment discussion with the patients. Patient global impression of severity will be collected at run-in, baseline and Months 3, 12, 18, and 24. Patient global impression of change will be collected at Months 3, 12, 18 and 24. Health status (EQ-5D-5L) will be collected at baseline and Months 3, 6, 12, 18, and 24. Daily diary data on symptoms of ADPKD (pain: BPI Item 3, fatigue: BFI Item 3, and nocturia) will be entered by the patients for specified consecutive days during the administration period at screening, baseline to Month 3 and prior to the site visit at Months 12, 18, and 24. Patients who permanently discontinue study medication should complete rapidly (within 7 days) an end-of-treatment assessment visit. End-of-treatment visit should include all procedures of Visit 12. In 30 days, a Follow-up visit should be performed. Investigator should ask patient to continue study visits for safety and efficacy assessments up to and including the last scheduled visit, if possible. If the patient refuses to attend all scheduled visits and to continue answering all PRO questionnaires, Investigator should ask the patient to continue answering questions of "Daily symptoms of ADPKD" diary, and also return to the site at Month 18 to have at least MRI performed, and at Month 24 to have at least blood sample (for eGFR) collected and samples for mGFR measurement (for patients participating in the mGFR substudy) collected. Other assessments planned at Month 18 and/or Month 24 should also be done if possible.
STATISTICAL CONSIDERATIONS	**Sample size determination:** In Stage 1, approximately 240 patients will be randomized (with randomization ratio 1:1:1) to placebo (n=80) or venglustat 8 mg (n=80) or venglustat 15 mg (n=80). In Stage 2, approximately 320 patients with an eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening will be randomized (with randomization ratio 1:1) to placebo (n=160) or venglustat (n=160). In addition, 80 patients with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will be randomized (with randomization ratio 1:1) to placebo (n=40) or venglustat (n=40). The patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 will not be included in the primary efficacy and safety analyses populations but the data from these patients will be analyzed separately. This sample size will provide approximately 89% power to detect a 50% reduction in annualized rate of change in TKV at end of Stage 1 and approximately 87% power to detect a 30% reduction in annualized rate of change in eGFR between venglustat and placebo at end of Stage 2. Overall, the total sample size will provide approximately 87% power to detect an effect on both TKV and eGFR. Sample size and power calculations were based on simulations, assuming different scenarios regarding the dose-response relationship. The following model parameters were estimated based on available databases from the similar patient population (patients aged 18 to 50 years with Mayo Class 1C-1E and baseline eGFR from 45 to 90 mL/min/1.73 m^2) in 2 historical studies (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) and the Polycystic Kidney Disease Treatment Network [HALT-PKD]): • A slope of $\log_{10}$(TKV) of 0.02591, 0.02832 and 0.03141 in patients from Mayo Class 1C, 1D and 1E respectively (corresponding to 6.1%, 6.7%

	and 7.5% increase per year in TKV), and average slope of 0.02764 (6.6%/year) assuming 50% of 1C, 33% of 1D and 17% of 1E. • Standard deviation for the residual error of TKV (on the log_{10} scale) of 0.02566 and standard deviation for the random effect of slope of 0.01477. • A slope of eGFR of -3.16, -3.88 and -4.69 mL/min/1.73 m² per year in patients from Mayo Class 1C, 1D and 1E respectively and average slope of -3.66 mL/min/1.73 m² per year assuming 50% of 1C, 33% of 1D and 17% of 1E. • Standard deviation for the residual error of eGFR of 6.34 and standard deviation for the random effect of slope of 1.98. In addition, sample size and power calculations assumed an overall significance level of 0.05 (2-sided), 10% dropout rate and included adjustments for handling of multiplicity of tests and futility analysis (as described in later sections). A sample size of 80 patients (40 per arm) with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will provide approximately 80% probability to detect a treatment effect in this subgroup at the 0.20 significance level (two-sided), based on a model evaluating the dependence of the treatment effect on baseline eGFR. **Analysis population:** <u>Stage 1:</u> Stage 1 intent-to-treat (ITT) population will include all patients who are randomized in Stage 1. Primary analysis in Stage 1 will include all data from Stage 1 available at the cut-off date (ie, including data reported up to Month 24, if any). The cut-off date will be defined as the date all patients from Stage 1 have completed the Month 18 visit (or have discontinued the study). <u>Stage 2:</u> The combined Stage 1 and Stage 2 ITT population will include all patients with an eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening who are randomized in Stage 1 or Stage 2, analyzed according to the treatment group allocated by randomization (venglustat 15 mg, venglustat 8 mg, or placebo). Patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will not be included in the primary efficacy and safety analyses population but the data from these patients will be analyzed separately. Primary analysis in the combined Stage 1 and Stage 2 will include all data available from baseline to the end of the 24-month double-blind core treatment period. **Primary analysis:** A linear mixed effect model will be fitted to the log_{10}-transformed TKV, which will include fix effects of treatment (venglustat 15 mg, venglustat 8 mg or placebo), Mayo Imaging classification (as per randomization: Class 1C versus 1D versus 1E), time (as continuous variable), treatment * time interaction and Mayo Imaging classification * time interaction, and will include random intercept and slope. Time will be based on actual TKV assessment date relative to randomization date (in years). Overall effect of venglustat will be assessed using a Multiple Comparison Procedure (MCP). Multiple trend tests will be performed using optimal contrasts determined from a set of pre-specified candidate models for the dose-response relationship. Optimal contrasts will apply to the treatment * time interaction term in the linear mixed effect model. P-value will be adjusted for multiple trend tests. The same analysis will be performed for annualized rate of change in eGFR. No log-transformation will be used for eGFR. Analysis will be based on randomized treatment group, regardless of the treatment

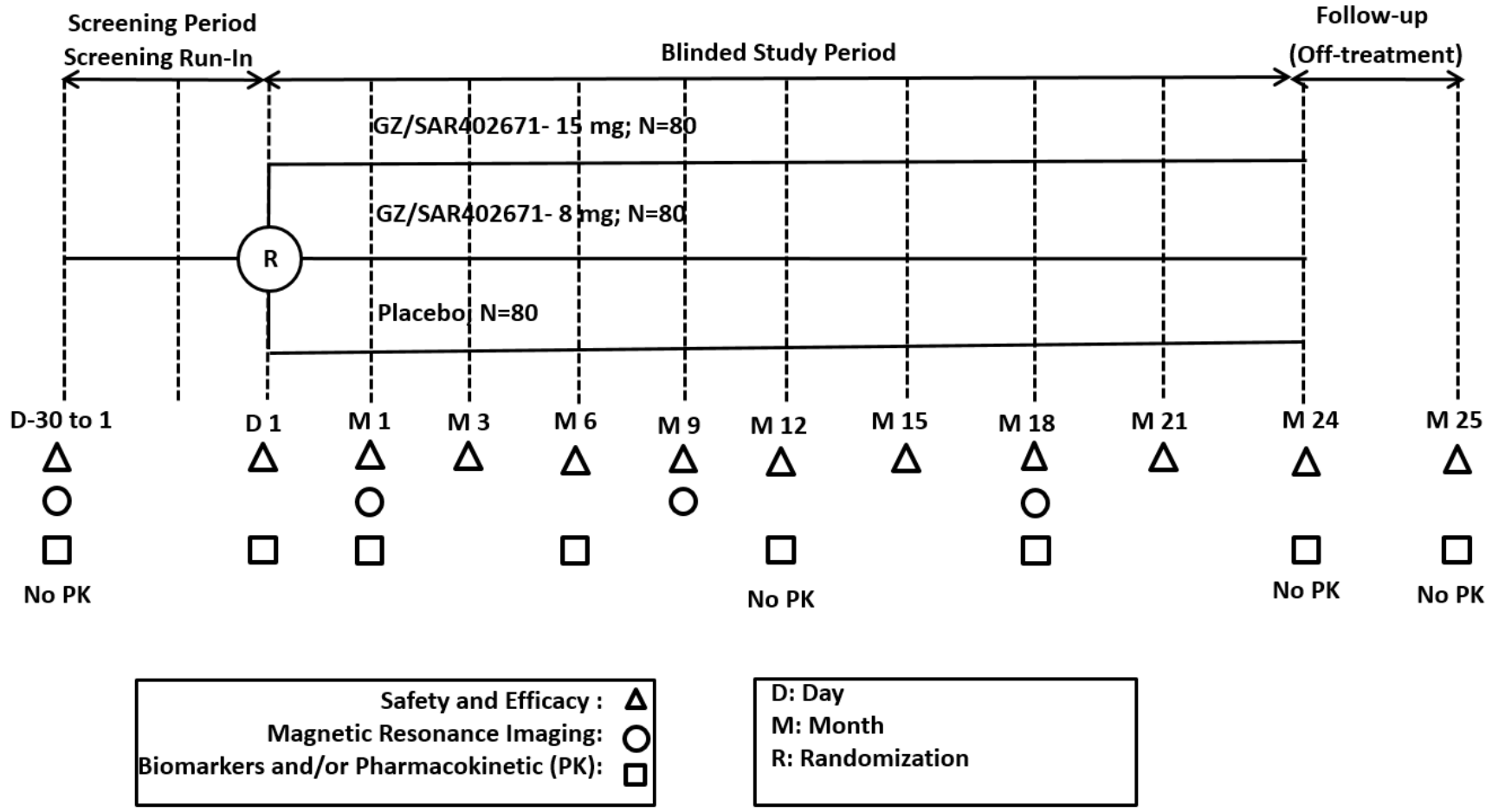
	actually received and regardless of whether or not patients completed the treatment period (treatment policy strategy). Patients who prematurely and permanently discontinue study medication will be requested to undergo MRI scan and obtain eGFR up to the planned end of study. All efforts will be made to minimize the amount of missing data for the primary and secondary efficacy endpoints. Missing data will be handled using a multiple imputation method, that will include separate slopes of $\log_{10}$(TKV) during the on-treatment period and after permanent treatment discontinuation. Patients with missing data after permanent treatment discontinuation will have their data imputed based on the mean slope estimated during the post-treatment period in patients from the same treatment arm, who discontinued the treatment but had TKV data available during the post-treatment period. After imputation, data will be analyzed using the proposed linear mixed effect model. **Analysis of secondary endpoints:** In Stage 1, the annualized rate of change in eGFR (CKD-EPI equation) is a secondary efficacy endpoint. The analysis eGFR in Stage 1 will be identical to those of Stage 2. In Stage 1, change from baseline to Month 18 in pain (BPI Item 3) and change from baseline to Month 18 in fatigue (BFI Item 3) are secondary endpoints and will be analyzed using a mixed effect model with repeated measures (MMRM). In Stage 2, the annualized rate of change in TKV is a secondary efficacy endpoint. The analysis of TKV in Stage 2 will be identical to those of Stage 1. In Stage 2, change from baseline to Month 24 in pain (BPI Item 3) and change from baseline to Month 24 in fatigue (BFI Item 3) are secondary endpoints and will be analyzed using MMRM. Multiplicity of endpoints and multiplicity of analyses (at end of Stage 1 and end of Stage 2) will be handled using a weighted Bonferroni-based closed test procedure, ensuring a strong control of the type I error rate for the entire study. **Safety analysis:** Treatment-emergent AEs (TEAEs) will be tabulated (counts and percentages). Adverse event of special interest (AESI), SAEs, and discontinuations due to AEs will be summarized. Additional safety data including clinical laboratory tests, vital signs, and ophthalmological tests will be summarized descriptively by treatment/dosing groups. All safety analyses will be performed on the safety population, defined as all patients who are randomized and received at least one dose or part of a dose of the double-blind investigational medicinal product (IMP), analyzed according to the treatment actually received. **Pharmacodynamic and pharmacokinetic analysis:** Pharmacodynamics (PD) parameters will be summarized and compared between venglustat 15 mg, venglustat 8 mg and placebo using descriptive statistics at each time point, including assessment of observed values and percent change from baseline. For PK analysis: Trough concentrations will be summarized separately using descriptive stats, along with other single time-point plasma concentration data by dose and visit. Plasma concentrations will be reported for individual patients and summarized using descriptive statistics by dose and visit separately for Stage 1 and Stage 2. Plasma venglustat concentration data might be used for population PK modeling if considered necessary and the results of population PK modeling will be reported

	separately from the study report. The population PK analyses will characterize the inter- and intra-subject variability in PK parameters and evaluate the effect of covariates such as, renal function status (creatinine clearance) on the venglustat PK. An evaluation of the correlation between exposure and efficacy (in particular TKV and eGFR) and safety may be performed to evaluate exposure-response relationships. **Patient reported outcome analysis:** Both total scores and subscale scores of PROs will be calculated. Each PRO will be scored according to their scoring guidelines, including handling the missing items. The daily diaries baseline average scores and thereafter the average score over the assessment prior to the visits will be calculated. The calculation of a diary score requires less than 50% of missing data. The Least Square Mean (LSM) changes from baseline to Month 18 (Stage 1) and Month 24 (Stage 2) for each score on PRO questionnaires and the daily diary will be calculated. **Interim analysis:** An interim analysis for futility will be performed under the supervision of the DMC when all patients from Stage 1 have completed the first 9 months of treatment and approximately 30% have completed 18 months of treatment with TKV available (or have prematurely discontinued). **Final analysis:** The analysis will be conducted in 2 steps: • First step: conducted when all patients from Stage 1 have been randomized and have completed the Month 18 visit (or have discontinued the study). This analysis will be conducted after a partial database lock. First step analysis in Stage 1 will include all collected and validated data from Stage 1 population, up to the cut-off date (including data reported up to Month 24 visit, if any). • Second step: conducted when all patients from Stage 2 have completed the study and will consist of the final analysis of the combined Stage 1 and Stage 2 study. This analysis will be conducted after the final database lock. The results of the first step analysis will not be used to change the conduct of the ongoing study in any aspect. This first analysis will be used for the submission of the registration dossier to health authorities accepting TKV growth rate change as a surrogate endpoint reasonably likely to predict changes in eGFR slope. First step analysis will be conducted before all patients from Stage 1 have completed the 24-month treatment period. However, treatment allocated to each individual patient will not be released to anyone who is directly involved in the conduct of Stage 1 of the study until Stage 1 is fully completed.
DURATION OF STUDY PERIOD (per patient)	**Stage 1** Total study duration: 26 months (maximal). • Screening period: - Initial screening: up to 15 (+3) days. - Placebo run-in period: 15 days ±3 days. • Core treatment period: 24 months. • Follow-up: 30 days after final dose of IMP. Not applicable for patients who may be eligible for a potential long-term extension study after completion of 24 months of treatment.

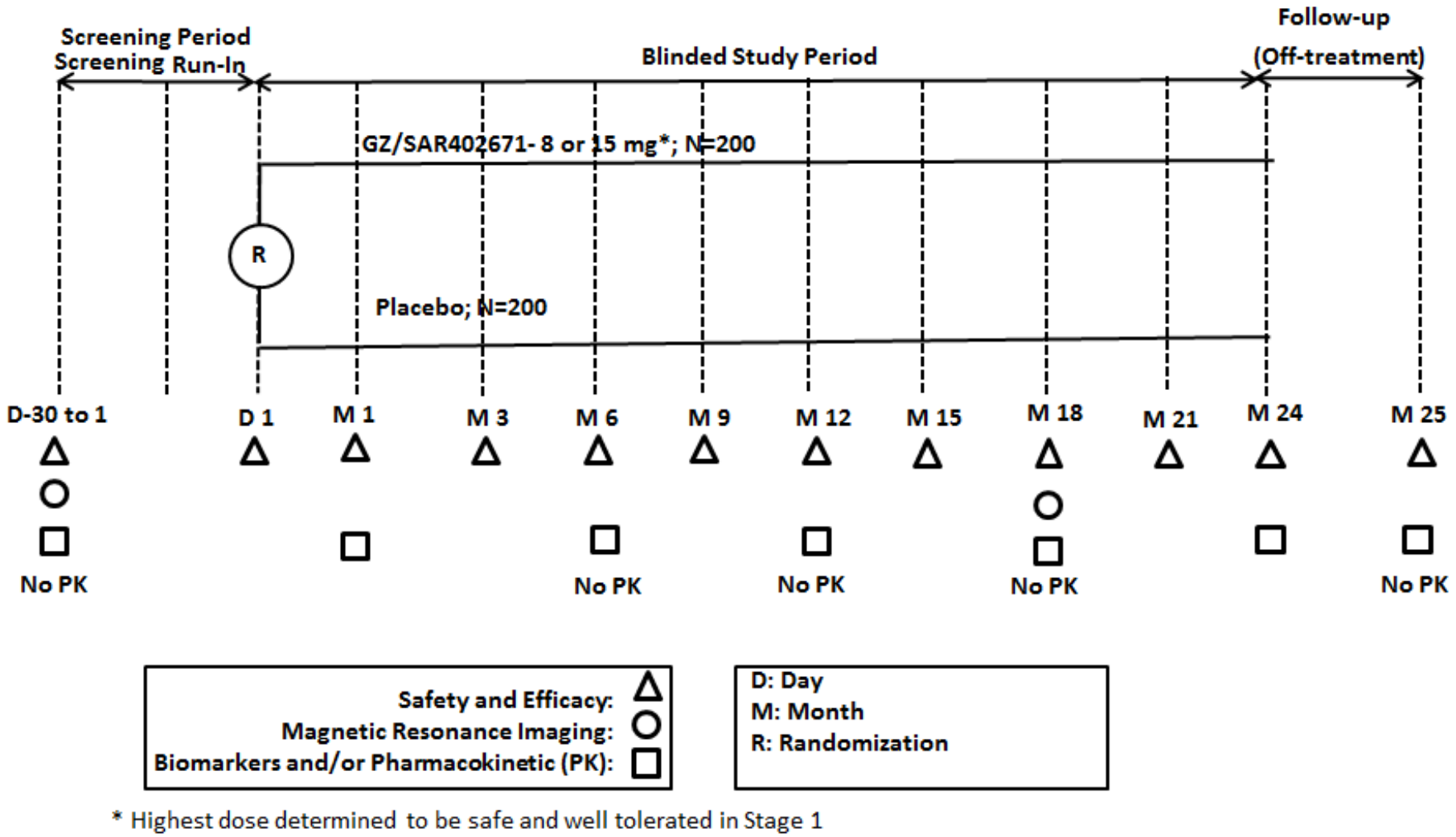
	Stage 2 Total study duration: 26 months (maximal). • Screening period: - Initial screening: up to 15 (+3) days. - Placebo run-in period: 15 days ±3 days. • Core treatment period: 24 months. • Follow-up: 30 days after final dose of IMP. Not applicable for patients who may be eligible for a potential long-term extension study after completion of 24 months of treatment

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN FOR STAGE 1



1.2 GRAPHICAL STUDY DESIGN FOR STAGE 2



* Highest dose determined to be safe and well tolerated in Stage 1

1.3 STUDY FLOW CHART FOR STAGE 1

	Screening period		Blinded treatment period[a]										Follow-up (off-treatment)
	Initial screening	Run-in											
Visit	**1**	**2**	**3 (Baseline)**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[a, w] (End of treatment)**	**13[b]**
Months	**-1**	**-0.5**	**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-30 to -16[u] (+3)**	**-15 (±3)**	**1 (±3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (-7 to +21)**
Informed consent (for Stage 1)	X												
Inclusion criteria	X	X	X										
Exclusion criteria	X	X	X										
Demographics	X												
Medical/surgical history	X												
Medication history	X												
Body weight, height[c]	X	X						X					X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination Complete	X									X		X	
Physical examination Abbreviated[e]		X	X	X	X	X	X	X	X		X		X
Laboratory testing[f]													
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X	X	X	X	X	X	
Pregnancy test (WOCBP)[g]	X	X	X	X	X	X	X	X	X	X	X	X	
FSH and/or estradiol as needed[g]	X												
Viral serology[h]	X												

	Screening period		Blinded treatment period[a]										Follow-up (off-treatment)
	Initial screening	Run-in											
Visit	**1**	**2**	**3 (Baseline)**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[a, w] (End of treatment)**	**13[b]**
Months	**-1**	**-0.5**	**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-30 to -16[u] (+3)**	**-15 (±3)**	**1 (±3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (-7 to +21)**
Urinalysis w/microscopy[i]	X			X	X	X	X	X	X	X	X	X	
GSL markers	X			X		X		X		X		X	X
Serum/plasma biomarkers	X			X		X		X		X		X	X
venglustat plasma concentration (PK)[j]			X	X		X				X			
Urinary markers, urine spot[k, l]			X	X	X	X	X	X	X	X	X	X	X
Collection of home urine based on 24 h collection[l]			X	X	(X)	X	(X)	X		X		X	
12-lead ECG[m]		X				X						X	
MRI[n]	X[o]			X			X			X			
BDI-II		X			X	X	X	X	X	X	X	X	
Ophthalmological examination[p]		X				X		X		X		X	
Diaries													
Dispense diary		X	X	X	X	X	X	X	X	X	X		
Collect/review diary			X	X	X	X	X	X	X	X	X	X	
Complete daily symptom diary[q]		X (7 days prior to baseline visit)	X (daily)					X (7 days prior to visit)		X (14 days prior to visit)		X (14 days prior to visit)	
Randomization			X										

	Screening period		Blinded treatment period[a]										Follow-up (off-treatment)
	Initial screening	Run-in											
Visit	**1**	**2**	**3 (Baseline)**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[a, w] (End of treatment)**	**13[b]**
Months	**-1**	**-0.5**	**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-30 to -16[u] (+3)**	**-15 (±3)**	**1 (±3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (-7 to +21)**
PRO[r]													
BPI			X	X	X	X	X	X	X	X	X	X	
BFI			X	X	X	X	X	X	X	X	X	X	
PGIS		X	X		X			X		X		X	
PGIC					X			X		X		X	
EQ-5D-5L			X		X	X		X		X		X	
Dispense IMP/placebo		X[v]	X	X	X	X	X	X	X	X	X		
Call IXRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP accounting & compliance			X	X	X	X	X	X	X	X	X	X	
Biobanking[s]			X					X				X	
Pharmacogenetic sample			X										
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAE[t]	X	X	X	X	X	X	X	X	X	X	X	X	X

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 = Brief Pain Inventory; CT = computed tomography; ECG = electrocardiogram; EQ-5D-5L = EuroQoL 5-dimension 5-level; FSH = follicle stimulating hormone; GSL = glycosphingolipid; IMP = investigational medicinal product; MRI = magnetic resonance imaging; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PRO = Patient Reported Outcome; SAEs = serious AEs; TKV = total kidney volume; US = ultrasonography; WHO = World Health Organization; WOCBP = women of childbearing potential.

a If a patient discontinues treatment with IMP early during the core treatment period, the patient 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. In addition, every effort will be made to have the patients return to the site at the time corresponding to their scheduled visits, particularly the Month 18 Visit and the Month 24 Visit. If the patient does not agree to a site visit, they will be contacted by telephone to inquire about safety status.

b 30 days after the last dose of IMP will be evaluated. Not applicable for patients screening for the long-term extension study within 30 days after Month 24 (Visit 12). For patients to be screened for the long-term extension study after Month 24 (Visit 12) and prior to Month 13 (Visit 13), the last visit in Study EFC15392 should coincide with the first visit in the long-term extension study.

c Height to be measured only at Visit 1.

d 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 should be used for all subsequent BP measurements.

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

f All laboratory assessments occur prior to intake of double-blind IMP. Samples should be collected in fasting conditions. Some assessments done at the beginning of screening may have to be repeated, Investigator will need to receive and evaluate results of repeated tests prior to Visit 3.

g Serum pregnancy testing only at Visit 1; urine pregnancy testing subsequently. Serum pregnancy test results must be reviewed prior to the run-in phase for all WOCBP unless there is documented history of menopause (based on documented FSH and estradiol levels - if results not documented then FSH and estradiol will be tested at screening) or they are surgically sterile. Any positive urine test results must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations. Patients will perform monthly urine pregnancy at home and report to the site.

h Viral serology (central lab) includes hepatitis B surface antigen (HBs Ag), hepatitis B core antibody (HBc Ab) anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency Virus 1 and 2 antibodies (anti-HIV1 and anti-HIV2 Ab).

i 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 lab) 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.

j Plasma samples for PK to be collected on Day 1 (3 ±1 hours, post dose), Month 1 (pre-dose and 3 ±1 hours post dose), Months 6 and 18 (pre-dose). At visits when a post-dose PK sample is to be collected, patients should take the study drug on site.

k Spot urine will be collected based on 3 samples from the Day -2, morning of the day of the site visit and from 24 hour urine sample (or sample provided for urinalysis on the day of the visit - for visits when collection of 24 hour sample is not required) (see Section 9.4.3).

l Urine will be collected to evaluate exploratory biomarkers, albumin, total protein, creatinine, electrolyte and osmolality. At selected sites, urinary exosomes will be isolated from the urine at Visits 3, 4, 5, and 7. Please refer to laboratory manual for collection instructions. Collection of 24-hour urine sample at Visits 5 and 7 will be performed only at selected sites that participate in isolation of urinary exosomes.

m The 12-lead ECG recordings should be performed before blood samplings. Investigator should evaluate V2 ECG reading prior to run-in medication administration; V2 ECG central reader's assessment should be evaluated prior to IMP administration at Visit 3. The ECG will be evaluated as "normal" or "abnormal".

n 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 patients.

o If a patient has documented CT/MRI/US kidneys imaging test results obtained prior to the study, Investigator may use this data for preliminary evaluation of a patient`s eligibility based on massively enlarged kidneys at Visit 1. First study MRI for confirmation of TKV Imaging Classification Class will be performed at Visit 2 (Run-in visit). If a patient has no documented CT/MRI/US kidneys imaging test results obtained prior to the study, Investigator will perform MRI for confirmation of TKV Imaging Classification Class at Visit 1 (initial screening visit). TKV volume must be confirmed by a central reader prior to Visit 3.

p The patient is required to have an ophthalmological examination with pupil dilation before randomization, at Month 6 (Visit 6), Month 12 (Visit 8), Month 18 (Visit 10), and at Month 24 (Visit 12) (or upon withdrawal or discontinuation). Ophthalmological examinations at Visit 2, Month 12 (Visit 8), Month 18 (Visit 10), and Month 24 (Visit 12) will also include measurement of the corneal thickness (or endothelial cell density) and measurement of intraocular pressure. If at any time during study participation a patient experiences a decline of ≥2 lines in BCVA compared with that at baseline or previous assessment, a slit-lamp examination with pupil dilation should be performed. Observed lens opacities must be graded with the WHO simplified cataract grading system. A slit-lamp examination with pupil dilation must be performed again in 3 months. If no new cataract is seen during this examination, a normal schedule of ophthalmological examinations with pupil dilation can be resumed. If patient had change of WHO Grade ≥1 in any of the 3 features (nuclear, cortical, and posterior subcapsular opacification) of the lens, the next scheduled ophthalmological examination (in 3 months) in this patient must include pupil dilation and evaluation of observed cataract(s) and observations graded with the WHO simplified cataract grading system. If no new change of WHO Grade ≥1 is seen during this examination, a normal schedule of ophthalmological examinations with pupil dilation can be resumed. Pupil dilation and full ophthalmological examination can be performed at any time if deemed medically necessary; observed lens opacities must be graded with the WHO simplified cataract grading system (see Section 9.4.10).

q The daily diaries will be filled out by patients at home for 7 days prior to baseline visit and after that at home for consecutive days for the specified administration period before the study visits and will be collected at the time of visit.

r The PROs will be administered to patients at study visit according to the listed schedule.

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

t All SAEs, AEs and AEs of special interest (AESIs) will be collected starting with signing informed consent and 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 patient is lost to follow-up. All patients should be followed to collect safety information up to 30 days after the last IMP administration or up to the first visit of the long-term extension study, whichever occurs first. For patients enrolled or screened into the long-term extension study prior to 30 days after the last dose of IMP, all SAEs, AEs, and AESIs will be collected up to the last visit in Study EFC15392, which will coincide with the first visit in the long-term extension study. Details of ongoing AEs and ongoing medications at the time of the last visit in Study EFC15392 will be duplicated as such into the long-term extension study.

u The initial screening period (Visit 1) can last up to 15 days (+3 days). Visit 2 can be performed as soon as results of all assessments performed at Visit 1 are available.

v During the run-in period the patient will receive single-blind placebo.

w At Visit 12 patients may be offered to enter long-term extension study. For patients who will agree and will be eligible to enter into a potential long-term extension study without any discontinuation between the EFC15392 and the LTS15823 studies, Visit 12 (end of treatment visit) of EFC15392 study will correspond to Visit 1 of LTS15823 study including all planned evaluations to be performed at Visit 12 of EFC15392 study and an additional MRI that will be performed in the frame of Visit 1 of the LTS15823 study.

1.4 STUDY FLOW CHART FOR STAGE 2

	Screening period		**Blinded treatment period**[a]										**Follow-up (off-treatment)**
	Initial screening	**Run-in**											
Visit	**1**	**2**	**3 (Baseline)**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**[a, y] **(End of treatment)**	**13**[b]
Months	**-1**	**-0.5**	**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-30 to -16**[w] **(+3)**	**-15 (±3)**	**1 (±3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (-7 to +21)**
Informed consent (for Stage 2)	X												
Inclusion criteria	X	X	X										
Exclusion criteria	X	X	X										
Demographics	X												
Medical/surgical history	X												
Medication history	X												
Body weight, height[c]	X	X						X					X
Vital signs[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination Complete	X									X		X	

	Screening period		Blinded treatment period[a]										Follow-up (off-treatment)
	Initial screening	Run-in											
Visit	**1**	**2**	**3 (Baseline)**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[a, y] (End of treatment)**	**13[b]**
Months	**-1**	**-0.5**	**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-30 to -16[w] (+3)**	**-15 (±3)**	**1 (±3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (-7 to +21)**
Physical examination Abbreviated[e]		X	X	X	X	X	X	X	X		X		X
Laboratory testing[u]													
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology	X		X	X	X	X	X	X	X	X	X	X	
Pregnancy test (WOCBP)[f]	X	X	X	X	X	X	X	X	X	X	X	X	
FSH and/or estradiol as needed[f]	X												
Viral serology[g]	X												
Urinalysis w/microscopy[h]	X			X	X	X	X	X	X	X	X	X	
GSL markers	X			X		X		X		X		X	X
Serum/plasma biomarkers[i]	X					X		X		X		X	X
venglustat plasma concentration (PK)[j]				X								X	
Urinary markers, urine spot[i, k, l]			X	X	X	X	X	X	X	X	X	X	X
Collection of home urine based on 24 h collection[l]			X	X	(X)	X	(X)	X		X		X	
mGFR[v]			X					X				X	
12-lead ECG[m]		X				X						X	
MRI[n]	X[o]									X			

	Screening period		Blinded treatment period[a]										Follow-up (off-treatment)
	Initial screening	Run-in											
Visit	**1**	**2**	**3 (Baseline)**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[a, y] (End of treatment)**	**13[b]**
Months	**-1**	**-0.5**	**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-30 to -16[w] (+3)**	**-15 (±3)**	**1 (±3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (-7 to +21)**
BDI-II		X			X	X	X	X	X	X	X	X	
Ophthalmological examination[p]		X				X		X		X		X	
Diaries													
Dispense diary		X	X	X	X	X	X	X	X	X	X		
Collect/review diary			X	X	X	X	X	X	X	X	X	X	
Complete daily symptom diary[q]		X (7 days prior to baseline visit)	X (daily)					X (7 days prior to visit)		X (14 days prior to visit)		X (14 days prior to visit)	
Randomization			X										
PRO[r]													
BPI			X	X	X	X	X	X	X	X	X	X	
BFI			X	X	X	X	X	X	X	X	X	X	
PGIS		X	X		X			X		X		X	
PGIC					X			X		X		X	
EQ-5D-5L			X		X	X		X		X		X	
Dispense IMP/placebo		X[x]	X	X	X	X	X	X	X	X	X		
Call IXRS/IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X
IMP accounting & compliance			X	X	X	X	X	X	X	X	X	X	
Biobanking[s]			X					X				X	
Pharmacogenetic sample			X										

	Screening period		Blinded treatment period[a]										Follow-up (off-treatment)
	Initial screening	Run-in											
Visit	**1**	**2**	**3 (Baseline)**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12[a, y] (End of treatment)**	**13[b]**
Months	**-1**	**-0.5**	**0**	**1**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**25**
Day (window [days])	**-30 to -16[w] (+3)**	**-15 (±3)**	**1 (±3)**	**30 (±7)**	**90 (±7)**	**180 (±7)**	**270 (±7)**	**360 (±7)**	**450 (±7)**	**540 (±7)**	**630 (±7)**	**720 (±7)**	**750 (-7 to +21)**
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
AEs/SAEs[t]	X	X	X	X	X	X	X	X	X	X	X	X	X

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 = Brief Pain Inventory; CT = computed tomography; ECG = electrocardiogram; EQ-5D-5L = EuroQoL 5-dimension 5-level; FSH = follicle stimulating hormone; GSL = glycosphingolipid; IMP = investigational medicinal product; mGFR = measured GFR; MRI = magnetic resonance imaging; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic; PRO = Patient Reported Outcome; SAEs = serious AEs; TKV = total kidney volume; US = ultrasonography; WHO = World Health Organization; WOCBP = women of childbearing potential.

a If a patient discontinues treatment with IMP early during the core treatment period, the patient 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. In addition, every effort will be made to have the patients return to the site at the time corresponding to their scheduled visits, particularly the Month 24 Visit. If the patient does not agree to a site visit, they will be contacted by telephone to inquire about safety status.

b 30 days after the last dose of IMP will be evaluated. Not applicable for patients screening for the long-term extension study within 30 days after Month 24 (Visit 12). For patients to be screened for the long-term extension study after Month 24 (Visit 12) and prior to Month 13 (Visit 13, the last visit in Study EFC15392 should coincide with the first visit in the long-term extension study.

c Height to be measured only at Visit 1.

d 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 should be used for all subsequent BP measurements.

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

f Serum pregnancy testing only at Visit 1; urine pregnancy testing subsequently. Serum pregnancy test results must be reviewed prior to the run-in phase for all WOCBP unless there is documented history of menopause (based on documented FSH and estradiol levels - if results not documented then FSH and estradiol will be tested at screening) or they are surgically sterile. Any positive urine test results must be confirmed based on serum pregnancy test. The Investigator may perform additional tests at their discretion or as required by local regulations. Patients will perform monthly urine pregnancy at home and report to the site.

g Viral serology (central lab) includes hepatitis B surface antigen (HBs Ag), hepatitis B core antibody (HBc Ab) anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency Virus 1 and 2 antibodies (anti-HIV1 and anti-HIV2 Ab).

h 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 lab) 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.

i Serum/plasma and urine samples for exploratory biomarkers analysis collected in Stage 2 of the study, will be analyzed only if results of this analysis during Stage 1 are considered as useful for further investigation.

j PK sample collection time for Month 1 (pre-dose and 3[±1] hours post dose, Month 24 [pre-dose]). At visits when a post-dose PK sample is to be collected, patients should take the study drug on site.

k Spot urine will be collected based on 3 samples from the Day -2, morning of the day of the site visit and from 24 hour urine sample (or sample provided for urinalysis on the day of the visit - for visits when collection of 24 hour sample is not required) (see Section 9.4.3).

l Urine will be collected to evaluate exploratory biomarkers (except at Month 1 visit), albumin, total protein, creatinine, electrolyte and osmolality. At selected sites, urinary exosomes will be isolated from the urine at Visits 3, 4, 5, and 7. Please refer to laboratory manual for collection instructions. Collection of 24-hour urine sample at Visits 5 and 7 will be performed only at selected sites that participate in isolation of urinary exosomes.

m The 12-lead ECG recordings should be performed before blood samplings. Investigator should evaluate V2 ECG reading prior to run-in medication administration; V2 ECG central reader's assessment should be evaluated prior to IMP administration at Visit 3. The ECG will be evaluated as "normal" or "abnormal".

n 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 patients.

o If a patient has documented CT/MRI/US kidneys imaging test results obtained prior to the study, Investigator may use this data for preliminary evaluation of a patient`s eligibility based on massively enlarged kidneys at Visit 1. First study MRI for confirmation of TKV Imaging Classification Class will be performed at Visit 2 (Run-in visit). If a patient has no documented CT/MRI/US kidneys imaging test results obtained prior to the study, Investigator will perform MRI for confirmation of TKV Imaging Classification Class at Visit 1 (initial screening Visit). TKV volume must be confirmed by a central reader prior to Visit 3.

p The patient is required to have an ophthalmological examination with pupil dilation before randomization, at Month 6 (Visit 6), Month 12 (Visit 8), Month 18 (Visit 10), and at Month 24 (Visit 12) (or upon withdrawal or discontinuation). Ophthalmological examinations at Visit 2, Month 12 (Visit 8), and Month 24 (Visit 12) will also include measurement of the corneal thickness (or endothelial cell density) and measurement of intraocular pressure. If at any time during study participation a patient experiences a decline of ≥2 lines in BCVA compared with that at baseline or previous assessment, a slit-lamp examination with pupil dilation should be performed. Observed lens opacities must be graded with the WHO simplified cataract grading system. A slit-lamp examination with pupil dilation must be performed again in 3 months. If no new cataract is seen during this examination, a normal schedule of ophthalmological examinations with pupil dilation can be resumed. If patient had change of WHO Grade ≥1 in any of the 3 features (nuclear, cortical, and posterior subcapsular opacification) of the lens, the next scheduled ophthalmological examination (in 3 months) in this patient must include pupil dilation and evaluation of observed cataract(s) ad observations graded with the WHO simplified cataract grading system. If no new change of WHO Grade ≥1 is seen during this examination, a normal schedule of ophthalmological examinations with pupil dilation can be resumed. Pupil dilation and full ophthalmological examination can be performed at any time if deemed medically necessary; observed lens opacities must be graded with the WHO simplified cataract grading system (see Section 9.4.10).

q The daily diaries will be filled out by patients at home for 7 days prior to baseline visit and after that at home for consecutive days for the specified administration period before the study visits and will be collected at the time of visit.

r The PROs will be administered to patients at study visit according to the listed schedule.

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

t All SAEs, AEs and AEs of special interest (AESIs) will be collected starting with signing informed consent and 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 patient is lost to follow-up. All patients should be followed to collect safety information up to 30 days after the last IMP administration or up to the first visit of the long-term extension study, whichever occurs first. For patients enrolled or screened into the long-term extension study prior to 30 days after the last dose of IMP, all SAEs, AEs, and AESIs will be collected up to the last visit in the Study EFC15392, which will coincide with the first visit in the long-term extension study. Details of ongoing AEs and ongoing medications at the time of the last visit in EFC15392 study will be duplicated as such into the long-term extension study.

u All laboratory assessments occur prior to intake of double-blind IMP. Samples should be collected in fasting conditions. Some assessments done at the beginning of screening may have to be repeated, Investigator will need to receive and evaluate results of repeated tests prior to Visit 3.

v A subset of patients will be evaluated with iohexol for mGFR.

w The initial screening period (Visit 1) can last up to 15 days (+3 days). Visit 2 can be performed as soon as results of all assessments performed at Visit 1 are available.

x During the run-in period the patient will receive single-blind placebo.

y At Visit 12 patients may be offered to enter long-term extension study. For patients who will agree and will be eligible to enter into a potential long-term extension study without any discontinuation between the EFC15392 and the LTS15823 studies, Visit 12 (end of treatment visit) of EFC15392 study will correspond to Visit 1 of LTS15823 study including all planned evaluations to be performed at Visit 12 of EFC15392 study and an additional MRI that will be performed in the frame of Visit 1 of the LTS15823 study.

2 TABLE OF CONTENTS

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3 LIST OF ABBREVIATIONS

ADMA:	asymmetric dimethylarginine
ADPKD:	autosomal dominant polycystic kidney disease
AE:	adverse event
AEs:	adverse events
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
anti-HCV:	anti-hepatitis C
anti-HIV1:	anti-human immunodeficiency virus 1 antibody
anti-HIV2 Ab:	anti-human human immunodeficiency virus 2 antibody
AST:	aspartate aminotransferase
AUC:	area under the concentration-time curve
BCVA:	best corrected visual acuity
BDI-II:	beck depression inventory II
BFI-SF:	brief fatigue inventory short form
BPI-SF:	brief pain inventory short form
BUN:	blood urea nitrogen
CDMS:	clinical data management system
CI:	confidence intervals
CKD:	chronic kidney disease
CKD-EPI:	Chronic Kidney Disease Epidemiology Collaboration
CL_{ss}:	clearance at steady state
C_{max}:	maximum observed concentration
CNS:	central nervous system
COR-2:	cortical cataract-2
DBP:	diastolic blood pressure
DMC:	Data Monitoring Committee
DNA:	deoxyribonucleic acid
eCRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EOT:	end-of-treatment
EQ-5D-5L:	European quality of life 5-dimension 5-level
EU:	European Union
FD:	Fabry disease
fe:	mean fraction of dose excreted unchanged in urine
FGF23:	fibroblast growth factor 23
FSH:	follicle stimulating hormone
GBA:	glucocerebrosidase
GBA-PD:	Parkinson's disease with a confirmed acid-β-glucosidase gene mutation, glucocerebrocidase in Parkinson Disease
GCP:	Good Clinical Practice

GCS:	glucosylceramide synthase
GD:	Gaucher disease
GD3:	Gaucher Disease Type 3
GGT:	gamma-glutamyl transferase
GI:	gastrointestinal
GL-1:	glucosylceramide
GL-2:	lactosylceramide
GL-3:	globotriaosylceramide
GM3:	monosialodihexosylganglioside
GSL:	glycosphingolipids
GSL:	glycosphingolipid
HBcAb:	hepatitis C core antibody
HBsAb:	hepatitis B surface antibody
HBsAg:	hepatitis B surface antigen
hERG:	human ether-a-go-go-related gene
HLGT:	high-level group term
HLT:	high level term
IB:	investigator's brochure
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
INR:	International Normalized Ratio
IRB:	Institutional Review Board
IRT:	interactive response technology
ITT:	Intent-to-treat
LC-MS/MS:	liquid chromatography tandem mass spectrometry
LLOQ:	lower limit of quantification
MCP-1:	monocyte chemoattractant protein-1
MedDRA:	Medical Dictionary for Regulatory Activities
mGFR:	measured glomerular filtration rate
MMRM:	mixed effect model with repeated measures
MMSE:	mini mental state examination
MRI:	magnetic resonance imaging
NOAEL:	no observed adverse effect level
NRS:	numeric rating scale
NYHA:	New York Heart Association
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PGIC:	patient global impression of change
PGIS:	patient global impression of severity
PK:	pharmacokinetic(s)
PR interval:	the time from the onset of the P wave to the start of the QRS complex
PRO:	patient reported outcome
PSC-2:	posterior subcapsular cataract-2
PT:	prothrombin time, preferred term
PTT:	partial thromboplastin time
QD:	once daily

QRS interval:	time from ECG Q wave to the end of the s wave corresponding to ventricular depolarization
RAAS:	renin-angiotensin-aldosterone system
SA:	statistical analysis plan
SAEs:	serious adverse events
SAR:	suspected adverse reaction
SBP:	systolic blood pressure
SC:	Steering Committee
SE:	standard errors
SMQ:	standardized MedDRA query
SOC:	system organ class, system organ class
SRT:	substrate reduction therapy
ST deviation:	ECG ST-segment deviation
SUSAR:	Suspected Unexpected Serious Adverse Reaction
TEAE:	treatment-emergent adverse event
TKV:	total kidney volume
t_{max}:	time to maximum observed concentration
ULN:	upper limit of normal
US:	United States
WHO:	World Health Organization
WOCBP:	women of childbearing potential
β-hCG:	beta human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

4.1 BACKGROUND: VENGLUSTAT AND AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

4.1.1 Venglustat

GZ402671, also referred to as venglustat, SAR402671 is a glucosylceramide synthase (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 glycosphingolipids 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 autosomal dominant polycystic kidney disease (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 glycosphingolipids (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.

[redacted]

4.1.2 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 (US), 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 3.2 in 10 000 people. This is below the EU ceiling for orphan designation 5 in 10 000 (1).

Tolvaptan is approved in Japan, EU, US, 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 adverse events (AEs).

The completion of the HALT-PKD study provided important insights to the management of hypertension in ADPKD (5). The HALT-PKD study, a US multicenter trial conducted on more than 1000 ADPKD patients with up to 8 years of follow-up, advised strict blood pressure control. In patients with estimated glomerular filtration rate (eGFR]) above 60 mL/min/1.73 m^2, a target blood pressure of 110/70 mmHg was suggested, especially in young patients with a high progression risk. In chronic kidney disease (CKD) Stage 3, the target blood pressure should be below 120/80 mmHg. Double renin-angiotensin-aldosterone system (RAAS) blockade with a target blood pressure of 120/80 mmHg or less had no beneficial effects but did increase complications among older ADPKD patients (6). There is a significant variation in the local standard of care for blood pressure target and the use of therapeutic agent to achieve that.

It is generally advised to reduce dietary sodium intake to within limits recommended for the general healthy population, and general CKD population (<100 mmol/d). Increased fluid intake has been hypothesized to reduce the progression of ADPKD, but there is no direct evidence to

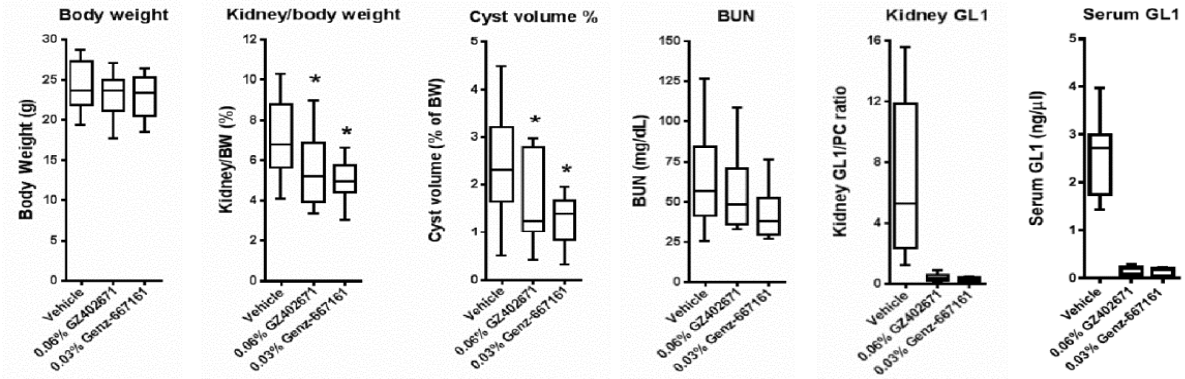
support this as a conclusive recommendation for use in clinical practice (7). In addition, since urinary osmolality is an endpoint in this trial, increase in fluid intake has not been recommended beyond normal daily fluid intake.

4.1.3 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 (Figure 1). 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 (BUN) 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.

Figure 1 - Dose-dependent glucosylceramide synthase lowering and efficacy in the jck mouse model of polycystic kidney disease



BUN = blood urea nitrogen; BW = body weight; GL-1 = glucosylceramide; K/BW = kidney/body weight; SEM = standard error of the mean.
Jck mice were administered venglustat or the reference compound Genz-667161 in feed ad libitum from 26 days of age until sacrificed at 64 days of age. Data shown are mean +/- SEM.
Percentage of glucosylceramide lowering is indicated above the corresponding bars.
*p <0.05.

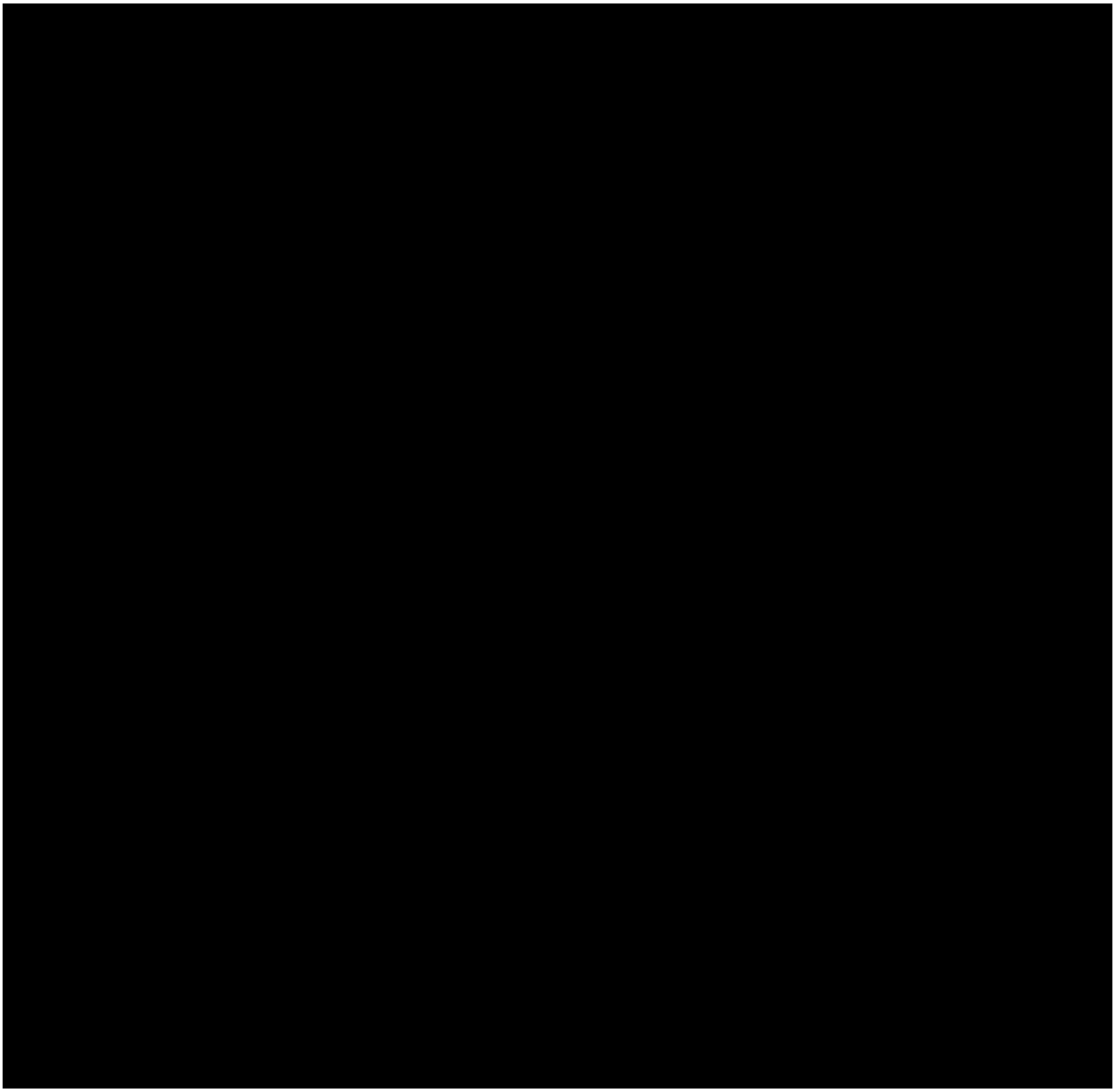
4.2 CLINICAL TRIALS OF VENGLUSTAT IN HUMANS

[redacted]

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 subjects.
- TDR12768 was a Phase 1, double-blind, randomized, placebo-controlled, sequential, ascending repeated oral dose study in healthy male and female subjects. 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 subjects. 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 patients with FD. The primary endpoint was the change from baseline in GL-3 scores as evaluated by light microscopy in superficial skin capillary endothelium. Secondary endpoints included plasma GL-3, plasma lyso-GL-3, plasma GL-1, scoring of GL-3 from other cell types in skin biopsy using LM, and urine GL-3 and lyso-GL-3.
- LTS14116 was an open-label Phase 2 extension study that assessed the long-term safety, PD, and exploratory efficacy of venglustat in FD patients who completed ACT13739 study.
- [redacted]
- POP14499 was a Phase 1, single-center, open-label, single dose study in subjects with mild, moderate and severe RI, and in matched subjects with normal renal function, to study the effect of RI 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. [redacted]

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



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

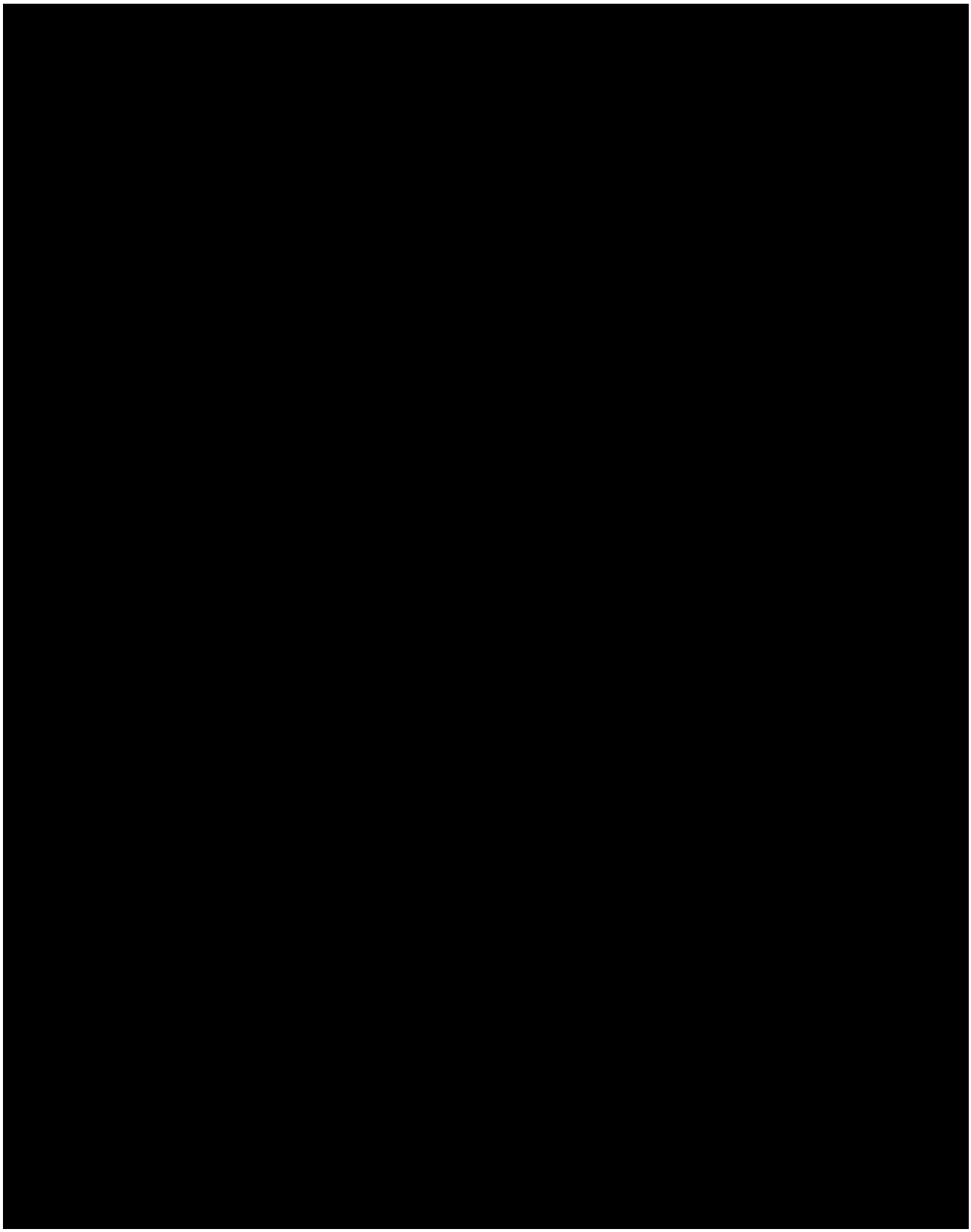
4.3 BENEFIT/RISK OF VENGLUSTAT

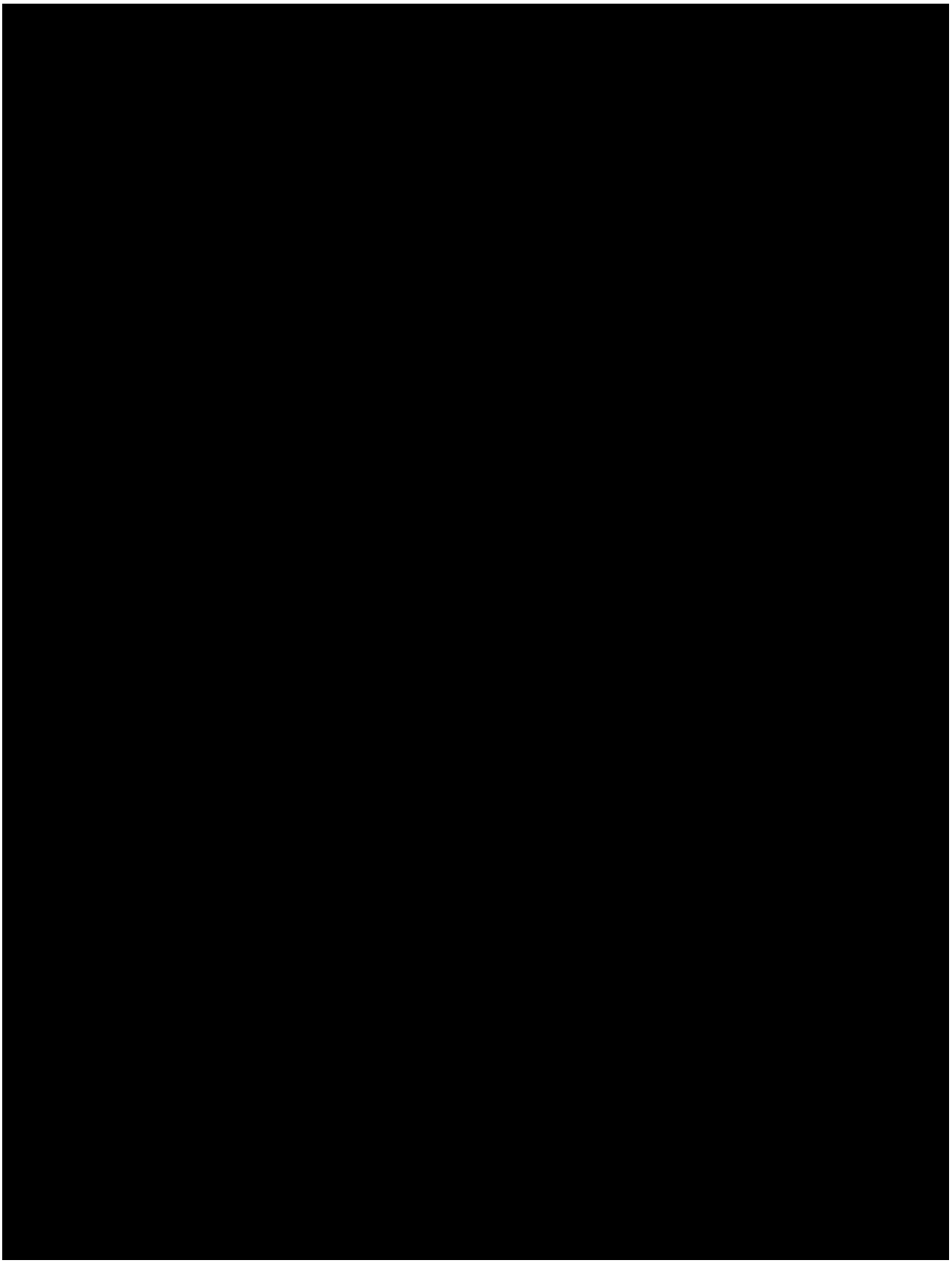
Venglustat significantly reduced GSL levels, reduced cyst growth, and preserved renal function in 3 different preclinical ADPKD models (8, 9, 10). These results strongly support the hypothesis

that GCS inhibition using venglustat could be a viable treatment to slow cyst growth and preserve renal function in individuals with ADPKD.

Venglustat is currently being investigated for FD, GD3, GM2, and Parkinson's disease patients with a confirmed acid-β-glucosidase GBA mutation (GBA-PD). Overall, in the clinical program, the majority of reported AEs were assessed as mild to moderate; most of which resolved spontaneously. Serious adverse events (SAEs) and discontinuations due to adverse events (AE) have been limited in Phase 2 studies. Based on an evaluation of the cumulative safety data from the clinical program, venglustat is generally safe and well tolerated.

Potential risks have been identified mostly based on data from the nonclinical toxicology studies (IB).





[redacted]

More detailed efficacy and safety information is provided in the IB.

The anticipated improvement in progression of ADPKD (the rate of total kidney volume [TKV] growth and the rate of renal function [estimated glomerular filtration rate] decline), with its associated reductions in blood pressure, and the tolerability and safety profile of venglustat to date, predict a favorable benefit-risk assessment for venglustat in ADPKD.

5 STUDY OBJECTIVES

5.1 STAGE 1

5.1.1 Primary objective

- To determine the effect of venglustat on the rate of TKV growth in patients at risk of rapidly progressive ADPKD.

5.1.2 Secondary objectives

- To determine the effect of venglustat on the rate of renal function (eGFR) decline.
- To determine the effect of venglustat on pain and fatigue, based on patient reported diary.
- To evaluate the PK of venglustat in ADPKD patients.
- Safety/tolerability objectives:
  - To characterize the safety profile of venglustat,
  - To evaluate the effect of venglustat on mood using BDI-II,
  - To evaluate the effect of venglustat on the lens by ophthalmological examination.

5.1.3 Exploratory objectives

- To explore the impact of venglustat on total liver volume (TLV) (in patients with height-adjusted total liver volume [htTLV] >2 L/m).
- To explore the effect of venglustat on kidney concentrating ability by assessing urine osmolality (in patients not on diuretic).
- To explore the effect of venglustat on nocturia, based on patient reported diary.
- To explore the effect of venglustat on systolic blood pressure (SBP) and diastolic blood pressure (DBP).
- To explore the effect of venglustat on biomarkers associated with ADPKD (eg, Fibroblast Growth Factor 23 [FGF23], Asymmetric Dimethylarginine [ADMA]).
- To explore the effect of venglustat on pain and fatigue based on Brief Pain Inventory [BPI] and Brief Fatigue Inventory [BFI] questionnaires, and general health status (based on EuroQoL 5-dimension 5-level [EQ-5D-5L] questionnaire).
- To explore the effect of venglustat on type, frequency and dosage of analgesic/over-the-counter (OTC) pain medication administration.
- To explore the effect of venglustat on all-cause hospitalization.
- To explore the PD effects of venglustat by measuring downstream metabolites of GCS in plasma and urine.

5.2 STAGE 2

5.2.1 Primary objective

- To determine the effect of venglustat on rate of renal function (eGFR) decline as compared to placebo in patients at risk of rapidly progressive ADPKD.

5.2.2 Secondary objectives

- To determine the effect of venglustat on the rate of TKV growth.
- To determine the effect of venglustat on pain and fatigue, based on patient reported diary
- To evaluate the PK of venglustat in ADPKD patients.
- Safety/tolerability objectives:
  - To characterize the safety profile of venglustat,
  - To evaluate the effect of venglustat on mood using BDI-II,
  - To evaluate the effect of venglustat on the lens by ophthalmological examination.

5.2.3 Exploratory objectives

- To explore the impact of venglustat on TLV (in patients with htTLV >2 L/m).
- To explore the effect of venglustat on kidney concentrating ability by assessing urine osmolality (in patients not on diuretic).
- To explore the effect of venglustat on nocturia, based on patient reported diary.
- To explore the effect of venglustat on SBP and DBP.
- To explore the effect of venglustat on measured GFR (mGFR) (substudy) Appendix L.
- To explore the effect of venglustat on biomarkers associated with ADPKD (eg, FGF23, ADMA).
- To explore the effect of venglustat on pain and fatigue based on Brief Pain Inventory [BPI] and Brief Fatigue Inventory [BFI] questionnaires, and general health status (based on EuroQoL 5-dimension 5-level [EQ-5D-5L] questionnaire).
- To explore the effect of venglustat on type, frequency and dosage of analgesic/over-the-counter (OTC) pain medication administration.
- To explore the effect of venglustat on all-cause hospitalization.
- To explore the PD effects of venglustat by measuring downstream metabolites of GCS in plasma and urine.
- To explore the effect of venglustat on eGFR (CKD-EPI equation) from baseline to 24 months in patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is an international, multicenter, randomized, double-blind, placebo-controlled, two-stage study in adult patients at risk of rapidly progressive ADPKD aged 18 to 50 years in Stages 1 and 2 (and aged 18 to 55 years for patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2 in Stage 2).

The study is divided into 2 stages:

Stage 1: An up to 30-day screening period including a 2-week single-blind placebo run-in (to identify patients who are unlikely to follow the assigned treatment regimen), followed by a randomized double-blind comparative placebo-controlled core treatment period of 24 months duration.

After run-in, eligible patients will be randomized with a 1:1:1 ratio to placebo, 8 mg venglustat, or 15 mg venglustat.

Patients will be stratified based on their predicted ADPKD progression rate (1C versus 1D versus 1E) according to Mayo Imaging Classification and by geographic region (North America, Europe, China, Japan, Republic of Korea, Rest of the World). If after reviewing the unblinded aggregate safety data from Stage 1 (after at least 1 month of treatment of the first 150 randomized patients from Stage 1), the DMC recommends the 8 mg dose for Stage 2, then the DMC may recommend switching patients on 15 mg treatment arm, in Stage 1, to the 8 mg arm.

Stage 2: After the first 150 randomized patients from Stage 1 have completed at least 1 month of treatment (or have prematurely discontinued), the DMC will review in an unblinded fashion the aggregate safety data from Stage 1 and will select the venglustat dose 8 mg or 15 mg for Stage 2 patients. The selected dose will be the highest dose determined to be safe and well tolerated in Stage 1. If after reviewing the unblinded aggregate safety data from Stage 1, the DMC recommends the 8 mg dose for Stage 2, then the DMC may recommend switching patients on the 15 mg treatment arm, in Stage 1, to the 8 mg arm.

Stage 2 will start with an up to 30-day screening period including a 2-week single-blind placebo run-in (to identify participants who are unlikely to follow the assigned treatment regimen), followed by a randomized double-blind comparative core treatment period of 24 months duration.

After run-in, patients will be randomized with a 1:1 ratio to placebo and venglustat (dose to be determined in Stage 1).

Patients will be stratified based on their predicted progression rate (1C versus 1D versus 1E) and by geographic region (North America, Europe, China, Japan, Republic of Korea, Rest of the World).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The maximum study duration per patient will be approximately 26 months.

This will consist of a screening period of up to 30 +3 days (initial screening period of up to 15 +3 days and single-blind placebo run-in period of 15 ±3 days), followed by a blinded study core treatment period of 24 months and a 30-day follow-up visit (for patients not participating in the potential long-term extension study) after the final dose of investigational medicinal product (IMP).

Patients who completed 24 months of treatment in EFC15392 study may be given the option to enroll into an open-label long-term extension study LTS15823 (additional 24 months of treatment with 15 mg venglustat [ie, as specified in the EFC15392 protocol the dose selected for Stage 2 of EFC15392 study during unblinded review by the DMC of the aggregated safety data for 150 patients who have completed at least 1 month of treatment in EFC15392 study]).

The last study visit:

1. for patients who elect to enter the potential long-term extension study upon completion of 24 months of treatment in EFC15392 study will be Visit 12 (Month 24)
2. for patients who complete the treatment in EFC15392 study and elect not to enter this potential extension study will be Visit 13 (Month 25)
3. for patients who permanently discontinue medication and continue for all the remaining visits will be Visit 12 (Month 24) if they continue for all the remaining visits, or it will be their premature follow-up visit.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as being the day the last patient completes his/her last visit planned in the protocol.

The Sponsor reserves the right to discontinue the study at any time.

6.3 INTERIM ANALYSIS

The dose selection safety review will be performed by the DMC when the first 150 patients from Stage 1 have completed 1 month of treatment (or have prematurely discontinued). Based on this safety review, the DMC will select the venglustat dose for Stage 2 (8 mg or 15 mg). The selected dose will be the highest dose determined to be safe and well tolerated.

An interim analysis for futility will be performed when all patients from Stage 1 have completed the first 9 months of treatment and approximately 30% have completed 18 months of treatment with TKV available (or have prematurely discontinued).

Further details are provided in Section 11.5.

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

A DMC, operating independently from the Sponsor and Clinical Investigators, will be responsible for overseeing the safety of patients and the risk/benefit ratio throughout the study. This committee is composed of externally-based individuals with expertise in the disease under study, biostatistics, and/or clinical research. The primary responsibilities of the DMC are to ensure the patients welfare as well as to evaluate and review the safety and other applicable data throughout the course of the study by conducting formal regular reviews of unblinded safety data and make appropriate recommendations to the Sponsor regarding the conduct of the clinical trial.

The DMC will review, in an unblinded fashion, the aggregate safety data from Stage 1 to select the venglustat dose for Stage 2. It will also supervise the interim futility analysis (Section 6.3). The specific responsibilities of the DMC will be described in the DMC charter.

6.4.2 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 until completion of the study.

Among its responsibilities, the SC will receive blinded study status reports from the Sponsor, and will review the recommendations from the DMC throughout the study.

Moreover, the SC will also be responsible for the primary publication(s) emanating from the study. The Principal Investigators (PI) of the study will be selected by the Sponsor and will be the first authors for the primary publication(s). Principal Investigators at the 3 first sites enrolling the most patients will also be included as authors for the primary publication, in addition to the other SC members.

Detailed activities and responsibilities of the SC will be provided in the SC charter.

6.5 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

6.5.1 Rationale for selection of 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. Therefore, 8 mg and 15 mg QD doses of venglustat in ADPKD patients are anticipated to translate into ADPKD efficacy and have been selected for Stage 1 in this study. Since 26.3% to 33.1% of the drug is excreted unchanged in urine, there is a potential for increased exposure in patients with

renal impairment. However, the Sponsor does not anticipate that the renal impairment status of ADPKD patients in Stage 1 of this study (mild to moderate renal impairment with eGFR >45 mL/min/1.73 m^2 baseline) will have any potential implications for patient safety, as indicated by a PBPK model that predicted a mean venglustat plasma steady state exposure in a moderate RI population (GFR 30-60 mL/min/1.73 m^2) following 15 mg QD dose, normal CYP abundance and age (matching the age of ADPKD patients in the current study) to be within the range of steady state exposures observed in Phase 1 (TDR12768 in healthy volunteers) and Phase 2 studies (ACT13739 in FD patients). This was further confirmed with results from a clinical study conducted to assess the impact of renal impairment on venglustat PK (POP14499), where, following a single 15 mg dose, venglustat exposure (AUC) was similar in subjects with mild RI but was estimated to be higher in subjects with moderate and severe RI by as much as 1.33-fold (90% CI: 1.09 to 1.62) and 1.59-fold (90% CI: 1.15 to 2.20), respectively. To provide a conservative estimate of effect of moderate RI on venglustat PK, the upper end of 90% CI (1.62-fold) was taken into account at the lower limit of moderate RI (GFR: 30 mL/min).

Given the current exposure margin from NOAEL in 26-week adult rat toxicology study of approximately 3.7-fold relative to the to human steady state exposure following 15 mg dose (2420 ng.hr/mL obtained from healthy subjects in study TDR12768 and NOAEL exposure of 8890 ng.hr/mL in female rats in adult rat 26-week toxicology study), venglustat exposure in moderate renal impaired subjects with eGFR up to 30 mL/min following a 15 mg QD dose, is anticipated to be below this NOAEL exposures. In addition, venglustat exposure in moderate renal impaired subjects with eGFR up to 30 mL/min following a 15 mg QD dose, is also anticipated to be below the NOAEL exposure estimate for spermatid degeneration from adult mouse precarcinogenicity study (7780 ng.hr/mL). Considering the totality of this information, no dose adjustment is warranted in patients with eGFR ≥30 mL/min.

The patients in Stage 1 will finish 24 months on placebo or 8 mg or 15 mg venglustat. In Stage 2, patients will be randomized to placebo or either 8 mg or 15 mg venglustat. The dose of 8 mg or 15 mg will be selected during unblinded review by the DMC of the aggregated safety data from Stage 1. The selected dose will be the highest dose determined to be safe and well tolerated in Stage 1 (based on DMC review of safety data for 150 patients who have completed at least 1 month of treatment).

If during Stage 1 the 8 mg and 15 mg doses of venglustat have similar safety and tolerability profiles, then the 15 mg dose will be selected. This is because based on the human healthy volunteer plasma PK/PD in the repeat-dose study TDR12768 and rodent ADPKD efficacy studies, better efficacy is anticipated with 15 mg dose due to higher plasma GL-1 reduction as compared to the 8 mg dose. Only minimal safety concerns were observed for the 15 mg dose based on the present safety data of FD patients who have received the 15 mg dose for up to 24 months.

6.5.2 Rationale for study design and control groups

This study is designed to demonstrate the efficacy by slowing the progression of kidney volume and concomitantly evaluate the effect on worsening renal function, patient reported outcome (PRO) and liver volume in patients with ADPKD. Due to the high variability of eGFR, the primary endpoint of Stage 1 is TKV growth rate while the primary endpoint in Stage 2 is the slope

of eGFR. Safety, tolerability, PK, and PD effects of venglustat are supported by Phase 1 and Phase 2 studies and animal toxicology data in rodents up to 26 weeks and dogs up to 39 weeks. In vitro and in vivo genotoxicity studies have been conducted and are negative. Carcinogenicity studies have not yet been conducted.

A prognostic enrichment approach is used to select patients for primary analysis population who will be at risk for rapid progression of disease based on those aged between 18 to 50 years, CKD Stages 2-3A, and Mayo Imaging Classification of ADPKD Class 1C-E. This enrichment allows the detection of treatment benefit on both TKV and GFR in the same population thus circumventing the need for performing separate trials in "early" and "late" ADPKD patients.

Patients with eGFR <45 mL/min/1.73 m^2 aged 18 to 55 years old recruited in Stage 2 of the study will be not included in primary analysis population but the data from these patients will be analyzed separately.

Patients with CKD Stage 3b (eGFR 30 - 45 mL/min/1.73 m^2) aged 18 to 55 years old will be recruited in Stage 2 of the study to permit gathering information on venglustat in this severely affected patient population. However, this patient population will not be included in the Stage 2 primary analysis but will be analyzed separately. The rationale for including these patients in the study is to obtain further information on venglustat exposure, safety and efficacy in patients with lower renal function.

Based on the mode of action of venglustat the benefit of disease modification is expected to decrease whereas the exposures of venglustat increase with declining renal function. For this reason, CKD Stage 4 patients (eGFR <30 mL/min/1.73 m^2) will not be included into the study.

The seamless design of this two-stage trial is based on the similarities of the endpoints of the 2 stages and the identical inclusion/exclusion criteria of the primary analysis population of the 2 stages. This design ensures faster results of the effect of venglustat on TKV with confirmatory results on eGFR so that effective and safe compounds can be provided to the ADPKD patients.

To achieve balanced distribution of factors influencing the progression of the disease between treatment arms, randomization will be stratified based on the Mayo Imaging Classification of progression rate (1C, 1D, and 1E).

The control group will be treated with placebo to allow for an unbiased assessment of treatment effects and safety data. Bias will be minimized by randomizing the patients to treatment groups, blinding the patients, the Investigators, and the Sponsor to the treatment allocations. Tolvaptan, though approved in several regions, is not being used as control due to the following reasons:

- Tolvaptan is not available in all countries due to lack of regulatory approval or market access.
- Even in regions where tolvaptan is available, poor tolerability and safety has led to low levels of uptake of the drug due to patient discontinuation or failure to start therapy.
- Treatment with tolvaptan is associated with acute diuresis which can lead to substantial unblinding resulting in a compromise of the integrity of the trial ie, failure to conduct a randomized controlled trial.

- Even if a blinded study is attempted with tolvaptan by ignoring the effect of acute diuresis, the need for recommending substantially increased water intake to patients in the trial to minimize the risk of dehydration in the blinded tolvaptan arm can lead to an erroneous attribution of excess diuresis in the venglustat arm leading to a suboptimal assessment of treatment benefit.

A parallel-group, randomized, controlled design was selected because trial participants are exposed to a single treatment and assignment to that treatment is based solely on chance. This design is free of the limitations of competing designs such as crossover in which there may be a carryover effect from one treatment to the second treatment. Although this carryover effect can be minimized with a washout period, it is possible that some longer-term effects may persist. While the sample size of the parallel group design is larger to account for more variability when participants cannot serve as their own control, the above-mentioned limitations of the crossover design have led the randomized parallel-group controlled trial design to be the standard for therapeutic trials for regulatory approval such as this trial.

7 SELECTION OF PATIENTS

Note: A patient should not be randomized more than once. One-time rescreening is allowed at the Investigator's medical judgment for any manageable reasons that caused the screening failure and the patient is likely to be eligible before the enrollment completion. For patients agreeing to participate in the mGFR substudy of the Stage 2 of the EFC15392 study, additional eligibility criteria are listed in Appendix L.

7.1 INCLUSION CRITERIA

I 01. Male or female adult with ADPKD with an age at the time the consent is signed:

a) between 18 and 50 years (inclusive) for patients in Stage 1

b) between 18 and 50 years (inclusive) for patients in Stage 2 with an eGFR between 45 and 89.9 mL/min/1.73 m^2 during the screening period*

c) between 18 and 55 years (inclusive) for patients in Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 during the screening period*

Diagnosis of ADPKD in patients with a family history, will be based on unified Pei criteria (12). In the absence of a family history, the diagnosis will be based on the presence of renal cysts bilaterally, totaling at least 20, in the absence of findings suggestive of other cystic renal diseases.

I 02. Mayo Imaging Classification of ADPKD Class 1C, 1D, or 1E** (3).

**TKV volume must be confirmed by a central reader prior to Visit 3.

I 03. Estimated glomerular filtration rate between 45 and 89.9 mL/min/1.73 m^2 during the screening period* (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) for Stage 1.

Estimated glomerular filtration rate between 30 and 89.9 mL/min/1.73 m^2 during the screening period* (CKD-EPI equation) for Stage 2.

*Eligibility will be confirmed by the eGFR value from one of the two first pre-randomization eGFR measurements (Visit 1 or Visit 2 measurements or Visit 1 and an additional measurement performed at the Investigator's discretion between Visit 1 and Visit 2).

I 04. Stable treatment regimen of antihypertensive therapy for at least 30 days prior to the screening visit for hypertensive patient.

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

I 06. Patient has given voluntary written informed consent before performance of any study related procedures not part of standard medical care.

I 07. Patient does not have access to tolvaptan at the time of study start or tolvaptan is not indicated for treatment of patient according to treating physician (patient does not meet recommended criteria for treatment, refuses to initiate or does not tolerate treatment with tolvaptan).

I 08. The patient, if female of childbearing potential, must have a negative blood pregnancy test (β-human chorionic gonadotropin [β-hCG]) at the screening visit and a negative urine pregnancy test at the baseline visit.

I 09. Female patients of childbearing potential and male patients 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 female patients of childbearing potential) for the entire duration of the study and for at least 6 weeks for females and 90 days for males following their last dose of study drug (see contraceptive guidance in Appendix A).

7.2 EXCLUSION CRITERIA

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

7.2.1 Exclusion criteria related to study methodology

E 01. Systolic BP >160 mmHg* at run-in and baseline visits.

*mean value of three or five systolic BP measurements (See Section 9.4.5).

E 02. Administration within 3 months prior to the screening visit of tolvaptan or other Polycystic Kidney Disease-modifying agents (somatostatin analogues).

E 03. The patient, in the opinion of the Investigator, is unable to adhere to the requirements of the study or unable to undergo study assessments (eg, has contraindications to pupillary dilation or unable to undergo magnetic resonance imaging [MRI] [For example: patient's weight exceeds weight capacity of the MRI, ferromagnetic metal prostheses, aneurysm clips, severe claustrophobia, large abdominal/back tattoos, etc]).

E 04. Current participation in another investigational interventional study or use of investigational medicinal product (IMP), within 3 months or 5 half-lives, whichever is longer, before randomization.

E 05. The patient has a 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-HIV1 and anti-HIV2 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 immune due to natural infection (positive HBsAb, negative HBsAg, and positive HBcAb) are eligible if they have a negative HBV DNA test.

E 06. A history of drug and/or alcohol abuse within the past year prior to the screening visit. A history of alcohol dependence within the 5 years prior to the screening visit.

E 07. Any patient who is the Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff, or relative thereof directly involved in the conduct of the study.

E 08. The patient is scheduled for in-patient hospitalization including elective surgery, during the study.

E 09. The patient has a 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 1	hypertensive emergency within 6 months of Visit 1[a]
stroke or transient ischemic attack within 3 months of Visit 1	current malignancy[b]
myocardial infarction within 3 months of Visit 1	tuberculosis (current or untreated[c])
Cushing's disease	uncontrolled diabetes mellitus
Addison's disease	uncontrolled thyroid disorder

a Systolic blood pressure >180 mm Hg or diastolic blood pressure >120 mm Hg, and acute target organ damage. (Aronow WS. Treatment of hypertensive emergencies. Ann Transl Med 2017;5:S5).

b A current malignancy or previous history of cancer in remission for <5 years prior to Visit 1 (localized basal cell or squamous cell carcinoma of the skin that has been resected is not exclusionary).

c Patients with a history of tuberculosis who have received an approved prophylactic treatment regimen or an approved active treatment regimen and who have had no evidence of active disease for a minimum of 2 years may be enrolled (American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Controlling Tuberculosis in the United States. Am J Respir Crit Care Med. 2005;172:1169-27.)

E 10. Any country-related specific regulation that would prevent the patient from entering the study.

For patients in Germany:

- The patient concerned has been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities,
- The patient is an employee of the sponsor or investigator or otherwise dependent on them.

E 11. The patients did not adhere to treatment (<70% compliance rate) in the run-in.

7.2.2 Exclusion criteria related to mandatory background therapies

E 12. The patient has, according to World Health Organization (WHO) Grading (13), a cortical cataract ≥1-quarter of the lens circumference (Grade cortical cataract-2 [COR-2]) or a posterior subcapsular cataract ≥2 mm (Grade posterior subcapsular cataract-2 [PSC-2]). Patients with nuclear cataracts will not be excluded.

E 13. 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 14. The patient has received strong or moderate inducers or inhibitors of CYP3A4 (See Appendix B) within 14 days or 5 half-lives, whichever is longer, prior to randomization. This also includes the consumption of grapefruit, grapefruit juice, or grapefruit containing products within 72 hours of starting venglustat administration.

7.2.3 Exclusion criteria related to the current knowledge of venglustat investigational medicinal product

E 15. The patient is pregnant, or lactating.

E 16. Liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) 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.

E 17. Presence of severe depression as measured by BDI-II >28 and/or a history of a major affective disorder within 1 year of the screening visit.

E 18. Known hypersensitivity to venglustat or any component of the excipients.

If the patient is a screen failure, all data obtained at screening including laboratory results of screening tests must be available in the patient's medical records. For screening failures, the following data obtained during screening will be transferred to the electronic case report form (eCRF) and entered into the database: informed consent date, visit date, patient's demographic data, inclusion and exclusion criteria, AE data (if available), and reason for failure.

Note: Rescreening is possible in this 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 while the screening period is still open to check whether or not they then meet all of the inclusion and none of the exclusion criteria.

Patients who were rescreened in Stage 1 of the study under protocol versions preceding amendment 04 and failed screening because of eGFR <45 mL/min/1.73 m^2, can be screened in Stage 2.

A patient cannot be randomized more than once in the study. Patients who fail screening may be rescreened once during the recruitment period; a different patient identification will be issued. There is no requirement for a waiting period between the screen-failure date and the rescreening date. The interactive response technology (IRT) report will flag rescreened patients. Patients that are rescreened must sign a new consent form and all Visit 1 procedures must be repeated except of certain assessments when for rescreened patients the Investigator may use the initial screening visit results:

- chemistry, hematology, and urinalysis (within 2 weeks of the initial screening visit),
- MRI (obtained within 1 months prior to randomization),
- neurological and ophthalmic exams (obtained within 3 months prior to randomization).

There is no need to repeat collection of already collected at initial screening biomarkers.

To have adequate representation of patients across eGFR spectrum a minimum of 20% of patients will be enrolled within each of the following categories:

- Patients with eGFR at screening from 45.0 to 59.9 mL/min/1.73 m^2.
- Patients with eGFR at screening from 60.0 to 74.9 mL/min/1.73 m^2.
- Patients with eGFR at screening from 75.0 to 89.9 mL/min/1.73 m^2.

In case one of the above categories is over-represented in the study, enrollment of additional patients in this category may be stopped in order to achieve good representativeness of the study population.

7.2.4 Criteria for temporarily delaying of randomization or administration of study treatment

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 proposed in Appendix O should be considered for enrollment, randomization, or administration of study treatment.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Pharmaceutical form

Venglustat or matching placebo will be supplied for oral administration, as opaque hard gelatin capsules:

- Venglustat 4 mg or 15 mg (calculated with reference to the active moiety) or,
- Placebo matching venglustat.

Venglustat and matching placebo will be packaged in blister packs.

8.1.2 Dose of drug per administration

In Stage 1, during the run-in period the patient will receive placebo matching venglustat (2 capsules) once daily for 2 weeks.

During the double-blind core treatment period, the patient will receive once daily doses of venglustat or matching placebo for 24 months:

- Venglustat 8 mg (2 capsules of venglustat 4 mg).
- Venglustat 15 mg (1 capsule of venglustat 15 mg, 1 capsule of placebo).
- Placebo matching venglustat (2 capsules of placebo).

In Stage 2, during the run-in period the patient will receive placebo matching venglustat once daily for 2 weeks (1 or 2 capsules depending on the dose of venglustat selected for Stage 2 during unblinded review by the DMC of the aggregated safety data from Stage 1).

The dose of venglustat determined in Stage 1 or placebo will be administered once per day for 24 months:

- Venglustat 8 mg or 15 mg.
- Placebo matching venglustat.

Venglustat or matching placebo is to be taken daily, around the same time each day throughout the study and can be administered without restriction to food, except for the consumption of grapefruit, grapefruit juice, and/or grapefruit containing products within 72 hours of starting venglustat administration. At visits when a post-dose PK sample is to be collected, patients should take the study drug on site.

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, venglustat may be supplied from the site to the patient via

a Sponsor-approved courier company where allowed by local regulations and approved by the patient. This includes the Direct-to-Patient supply of venglustat during national or regional emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access (See Appendix O).

Both regular on-site IMP dispensation and Direct-to-Patient supply of IMP are not contingent on availability of contemporaneous laboratory results or other study specific assessments.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Not applicable.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Venglustat and placebo to match venglustat will be indistinguishable from one another and be provided in identically matched packaging which includes labeling to protect the blind.
In addition to maintain the blind, the same number of capsules will be taken daily by the patient for each dosing group in Stage 1 and Stage 2.

In Stage 1, patients on 8 mg dosing group will receive 2 capsules of 4 mg. Patients on 15 mg dosing group will receive 1 capsule of 15 mg, plus 1 placebo capsule. Patients on placebo dosing group will receive 2 capsules of placebo. Likewise, in Stage 2, patients on venglustat or on placebo will receive the same number of capsules.

In accordance with the double-blind design, study patients, Investigators and study site personnel will remain blinded to study treatment and will not have access to the randomization list (treatment codes) except under circumstances described in Section 8.3.2. At the assay institutions charged for PK measurements, only samples collected from patients on active drug will be analyzed leading to unblinding of responsible bioanalysts prior to data base lock. Bioanalysts are excluded from the clinical study operation's team and a process will be set up to prevent any potential unblinding ie, no unblinded data will be shared with the clinical study operational team prior to database lock and unblinding of the study. The Investigators and the Sponsor will also be blinded to PK and biomarkers data. A Sanofi Clinical Supplies representative will remain unblinded throughout the study with respect to the study medication kits in order to provide the appropriate study drug to patients; however, sites and study teams must be blinded to PK and biomarker data throughout the study.

Refer to Section 10.5 for suspected unexpected serious adverse drug reaction unblinding by the Sponsor.

8.3.2 Randomization code breaking during the study

In case of an AE, the code must only be broken in circumstances when knowledge of the IMP is required for treating the patient, or when required by local regulatory authorities. If possible, contact should be initiated with the monitoring team before breaking the code.

In case of an emergency, the code breaking can be performed at any time by the Investigator by using the appropriate module of the IRT and/or by contacting any phone number or system provided by the Sponsor for that purpose.

In case of Suspected Unexpected Serious Adverse Reaction (SUSAR), the Pharmacovigilance department of the Sponsor will contact the IRT to reveal the IMP assignment for regulatory reporting requirements for the particular case. The IRT unblinding procedures should be followed as outlined in the IRT manual.

If the blind is broken by the Investigator or designee, the date, time of day, and reason for code breaking must be documented.

If the emergency unblinding transaction is performed by the Investigator (ie, at the site level), then the patient will be withdrawn from treatment. The withdrawal will be discussed on a case-by-case basis. However, if the emergency unblinding transaction is performed by the Sponsor (ie, at the study level), then the patient will not be withdrawn from treatment.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

A randomized treatment kit number list will be generated centrally by the Sponsor. The IMP (venglustat or placebo) will be packaged in accordance with this list.

The Sanofi Clinical Supplies team will provide the randomized list of treatment kit numbers and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system provider. The IRT (centralized treatment allocation system) will generate the patient randomization list and allocates the randomization number and the corresponding treatment kit(s) to the patients accordingly.

Patients who comply with all inclusion/exclusion criteria will be assigned before the IMP administration:

- A patient number according to the chronological order of inclusion.
- A randomization number in a preplanned order following the randomization list.

Randomization will be performed at the baseline visit (Month 0) by the centralized randomization procedure of the IRT.

In Stage 1, patients will be randomized to receive venglustat 8 mg or 15 mg or placebo during the double-blind core treatment period using a ratio 1:1:1.

In Stage 2, patients will be randomized with a 1:1 ratio into placebo, or the selected dose of venglustat.

The treatment kit numbers will be allocated by the centralized treatment allocation system on randomization visit (baseline visit/Month 0), Month 1, Month 3, and every 3 months up to Month 21 in Stage 1 and Stage 2.

A randomized patient is defined as a patient who is registered and assigned with a treatment kit number from the centralized treatment allocation system, as documented from its log file.
A patient cannot be randomized more than once in the study.

The details of the centralized randomization procedure and IRT are provided in a separate manual.

8.5 INVESTIGATIONAL MEDICINAL PRODUCT PACKAGING AND LABELING

Venglustat and matching placebo are packaged and labeled to protect the blind in Stage 1 and Stage 2.

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

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or other authorized persons (eg, pharmacists) are responsible for storing the IMP in a secure and safe place in accordance with local regulations, labeling specifications, policies, and procedures. The IMP should be stored between +2°C and +30°C (36°F and 86°F).

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

Batch and expiry date management will be assisted with IRT.

NOTE: Exceptionally, after discussion between site and Sponsor some IMP kits could be supplied, when feasible, directly from site to patient via a Sponsor-approved courier company. This process would be implemented at selected sites/countries (where certain conditions would be fulfilled, and where permitted locally) and for patients who would consent to such a process. This direct-to-patient process will be described in detail in a separate document and would be implemented after appropriate training of monitoring teams and investigational sites.

8.7 RESPONSIBILITIES

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

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

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 10.4.6).

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 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.

8.7.1 Treatment accountability and compliance

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

Measures taken to ensure and document treatment compliance and IMP accountability include:

- The Investigator or designee will obtain via IRT the treatment kit number(s) and he/she will dispense the treatment kit(s) to the patient.
- Accurate recording of treatment kit number or packaging number as required on appropriate eCRF page for accounting purposes;
- All medication treatment kits (whether empty or unused) are returned by the patient at each visit.
- The Investigator or designee tracks treatment accountability/compliance by diary (by counting missing doses reported by the patient), and by counting the number of used treatment kits and fills in the appropriate page of the patient treatment log.
- The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the patient treatment log form.

A patient diary will be issued to the patient at run-in visit with instructions to record missing doses. A brief explanation should be provided if a dose is missed. The patient should bring their diary and any remaining capsules to each clinic visit.

The site staff will collect and review the patient diary during each clinic visit and record excursions from treatment into the eCRF. The patient diary will be retrieved when the patient finishes their participation in the study.

8.7.2 Return and/or destruction of treatments

Whenever possible all partially used, used, or unused investigational product will be destroyed on-site according to the standard practices and capabilities of the site after reconciliation verification by the monitor.

A detailed treatment log of the destroyed investigational product will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

The Investigator will not destroy any investigational product unless the Sponsor provides written authorization. When destruction at site cannot be performed, all IMPs will be retrieved by the Sponsor or designee for destructions.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient 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 patient's welfare and are unlikely to interfere with the IMP, they may be given as rescue medication at the discretion of the Investigator and must be recorded in the eCRF.

Concomitant medications, including OTC, 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.

8.8.1 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 patients with cataracts.

Venglustat interruptions are permitted for those patients who require temporary use (≤2 weeks) of strong or moderate inhibitors or inducers of CYP3A (per 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 patients 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.
  - Patients 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 other 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.

8.8.2 COVID-19 vaccine

Immunotoxicology-related parameters (e.g., immunophenotyping, total immunoglobulin levels) were not evaluated in the repeat-dose toxicology studies. Based on the available preclinical data (venglustat-related hematological and histopathological changes to immune system tissues/ organs) and data from clinical studies, it is unlikely that venglustat has immunomodulatory properties and would have an impact on the immune system.

The coronavirus disease 2019 (COVID-19) vaccines that have been authorized for use are considered as a concomitant medication with no interaction that requires advice on timing or other aspects of the vaccination.
If the COVID 19 vaccine is authorized, available, and recommended by the local regulatory authority and/or health authority for patients like those in this study, the vaccine can be administered during the study and should be administered according to the label or recommendations of the local regulatory authority and/or health authority.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

Scales and questionnaires should be completed before dosing and before clinical procedures are performed by the study Investigator or other healthcare provider(s). Moreover, if possible, the patient completed instruments should be done prior to clinical interaction in order to try to minimize any influence this may have on the patient (either positive or negative).
The scales/questionnaires will be administered by individuals who will be blinded to study treatment and who are trained in the administration of standardized questionnaires.

The scales/questionnaires are provided in the appendices. Specific instructions for the administration of each scale/questionnaire are provided on each of the scales/questionnaires.

9.1 PRIMARY ENDPOINTS

9.1.1 Stage 1

- Annualized rate of change in TKV based on MRI from baseline to 18 months.

9.1.2 Stage 2

- Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months.

9.2 SECONDARY ENDPOINTS

9.2.1 Stage 1

- Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 18 months.
- Change in Pain (BPI - Item 3) from baseline to 18 months, from the daily symptom diary.
- Change in fatigue (BFI - Item 3) from baseline to 18 months, from the daily symptom diary.
- Plasma venglustat concentrations.

9.2.2 Stage 2

- Annualized rate of change in TKV based on MRI from baseline to 18 months.
- Change in Pain (BPI - Item 3) from baseline to 24 months, from the daily symptom diary.
- Change in fatigue (BFI - Item 3) from baseline to 24 months, from the daily symptom diary.
- Plasma venglustat concentrations.

9.2.3 Safety/tolerability endpoints

- Safety in terms of TEAEs/AEs/SAEs, laboratory parameters, vital signs, electrocardiogram and findings from physical examination will be assessed through the study and will be reported in the eCRF. Adverse event data will be collected throughout the study. Treatment-emergent AEs are defined as AEs that develop, worsen (according to the Investigator opinion), or become serious during the treatment period. The treatment period is defined as the time from first dose of study treatment up to 30 days after last dose of study treatment. Full details of safety reporting and AE monitoring procedures are provided in Section 10.1.
- Change in score of BDI-II during the treatment-emergent period.
- Change in the lens clarity by ophthalmological examination during the treatment-emergent period.

9.3 EXPLORATORY ENDPOINTS

9.3.1 Stage 2 only

- Annualized rate of change in mGFR from baseline to 24 months (substudy).
- Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months in patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2.

9.3.2 Stages 1 and 2

- Annualized rate of change in total liver volume based on MRI (in patients with htTLV >2 L/m) from baseline to 18 months, Change in:
  - Systolic BP during the treatment-emergent period,
  - Diastolic BP during the treatment-emergent period,
  - Pain (BPI), fatigue (BFI), and health status (EQ-5D-5L) from baseline to 18 months in Stage 1 and 24 months in Stage 2,
  - Nocturia from baseline to 18 months in Stage 1 and 24 months in Stage 2, based on patient reported diary,
  - Urine osmolality from baseline to 18 months in Stage 1 and 24 months in Stage 2 (in patients not on diuretic),
  - Type, frequency, and dosage of analgesic/OTC pain medication administration from baseline to 18 months in Stage 1 and 24 months in Stage 2,
  - Biomarkers associated with ADPKD (eg, FGF23 and ADMA) from baseline to 18 months in Stage 1 and 24 months in Stage 2,
  - Glucosylceramide (GL-1) and GM3 from baseline to 18 months in Stage 1 and 24 months in Stage 2.
- Rate of all-cause hospitalization.
- Time to confirmed 30% reduction in eGFR.

- Time to confirmed 40% reduction in eGFR.

9.4 ASSESSMENT METHODS

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix O.

9.4.1 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.

Magnetic resonance imaging will be performed at the following time points:

- Stage 1: During the screening period (at Visit 1 or Visit 2) and at Months 1, 9, and 18.
- Stage 2: During the screening period (at Visit 1 or Visit 2) and at Month 18.

9.4.2 Estimated glomerular filtration rate

Estimated glomerular filtration rate will be calculated from the creatinine result from the general chemistry laboratory assessments according to the study flow charts (Section 1.3 and Section 1.4). The 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 patients (except Japanese patients), the Asian-modified CKD-EPI (aCKD-EPI) equation will be used (14):

$$\text{Female and SCr} \leq 0.7\text{: } 151 \times (SCr / 0.7)^{-0\,328} \times (0.993)^{age}$$
$$\text{Female and SCr} > 0.7\text{: } 151 \times (SCr / 0.7)^{-1.210} \times (0.993)^{age}$$
$$\text{Male and SCr} \leq 0.9\text{: } 149 \times (SCr / 0.9)^{-0.412} \times (0.993)^{age}$$
$$\text{Male and SCr} > 0.9\text{: } 149 \times (SCr / 0.9)^{-1.210} \times (0.993)^{age}$$

- For calculation of eGFR in Japanese patients, CKD-EPI Study equation multiplied by a Japanese coefficient of 0.813 will be used (15).

9.4.3 Urine osmolality

Urine will be analyzed for urine osmolality during the blinded treatment period (Months 0, 1, 3, 6, 9, 12, 15, 18, 21, and 24) and at the final study visit (Month 25).

Procedure for the urine (spot) collection:

1. Patient will fast after 10 pm (Day -3 pm).
2. Sample before the sleep will be discarded (Day -3 pm).
3. First morning void will be discarded (Day -2 am).
4. The second urine void shall be collected as first spot (Day -2 am).
5. First morning void will be discarded (Day -1 am).
6. Collection of 24-hour urine (whole day) - before visits that include 24-hour urine sample collection (Visits 3, 4, 6, 8, 10 and 12).
7. Patient will fast after 10 PM (Day -1 am).
8. First morning void will be included in 24-hour collection (day of the visit) - for visits that include 24-hour urine sample collection (Visits 3, 4, 6, 8, 10 and 12).
9. The second urine void shall be collected as second spot (day of the visit).
10. The third urine spot sample will be collected from 24-hour urine sample at site (Visits 3, 4, 6, 8, 10 and 12) or from urine sample provided by patient for urinalysis during the visit (Visits 5, 7, 9, 11 and 13).

9.4.4 Adverse events

Refer to Section 10.4 to Section 10.7 for details.

The rate of all-cause hospitalization will be assessed as exploratory endpoints.

9.4.5 Vital signs

Vital signs including respiratory rate, heart rate (in bpm), blood pressure (systolic/diastolic in mmHg), and temperature (in Celsius; °C) will be recorded at every visit during the screening and double-blind core treatment periods and at the final visit.

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 (16). Blood pressure will be measured under standardized conditions using the same method for a given patient. 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.

After sitting quietly for at least 10 minutes with the arm resting at heart level, three readings will be obtained at least 1 minute apart. 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.

Body temperature (auricular or oral body temperature [°C]) will be collected using the same method for a given patient. Any hyperthermia should be evaluated by Investigator and if it meets criteria for AE reporting (see Section 10.4.2), it should be recorded as an AE and the Investigator should perform all investigations necessary to rule out infection.

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

Changes from baseline in SBP and DBP will also be assessed as other endpoints.

9.4.6 Physical examination

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 a thorough review of all body systems to collect physical observations/measurements.

A mental status evaluation will be performed as a 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 patient, provided the method covers all the areas assessed by MMSE.

A full standard basic neurological examination will be performed as a 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.

The Investigator will evaluate and access clinical findings as normal, abnormal but not clinically significant, or abnormal and clinically significant.

Complete physical examination will be performed at screening, Months 18 and 24. At screening, height will be measured without shoes and body weight will be measured without shoes or heavy clothing (see Section 1.3 and Section 1.4).

Abbreviated physical examinations will focus on areas important for assessment of AEs if necessary.

Abbreviated physical examinations will be performed at the run-in visit, Months 0, 1, 3, 6, 9, 12, 15, 21, and 25 (see Section 1.3 and Section 1.4).

9.4.7 Laboratory safety variables

All laboratory data listed in this section will be measured at a central laboratory. The laboratory data will be collected at designated visits as shown in Section 1.3 and Section 1.4. The clinical laboratory data consist of blood analysis (including hematology, clinical chemistry, and urinalysis). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

The following laboratory safety variables will be analyzed:

- Hematology: red blood cell count, hematocrit, hemoglobin, white blood cell count with differential count (neutrophils, eosinophils, basophils, monocytes, and lymphocytes), platelets, prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- Chemistry:
  - Plasma/serum electrolytes: sodium, potassium, chloride, calcium, bicarbonate,
  - Liver function: ALT, AST, gamma-glutamyl transferase (GGT), alkaline phosphatase (ALP), total and conjugated bilirubin,
  - Renal function: urea, serum creatinine, serum cystatin C,
  - Metabolism: glucose, albumin, total proteins.
- Urinalysis and microscopy.
- At screening, serum β-HCG test for women of childbearing potential (WOCBP).

9.4.8 Electrocardiogram variables

Heart rate, ECG recordings, including time from ECG Q wave to the end of the S wave corresponding to ventricular depolarization (QRS interval), the time from the onset of the P wave to the start of the QRS complex (PR interval), QT interval, ECG ST-segment deviation (ST deviation), T wave morphology, and U wave presence or absence will be determined per local site procedure using automated and manual readings of all ECGs. All ECG recordings will be centrally read by independent experts. Refer to central ECG reading manual for more details.

Any clinically significant abnormality (eg, corrected QT or QTc >450 msec in males/>470 msec in females) observed at the run-in visit (Day -15 to Day -1) upon Investigator review will be immediately rechecked for confirmation before making a determination regarding patient exclusion from the study. Additional ECGs may be performed if deemed clinically necessary by the Investigator (eg, diagnosis of AE) and will be documented in the eCRF.

A 12-lead ECG will be performed prior to randomization (at Visit 2), at Month 6 and at Month 24.

Electrocardiogram recordings should be performed before blood samplings.

9.4.9 Beck Depression Inventory, second edition

Depression will be monitored during the study by using the BDI-II according to the study flow chart (see Section 1.3 and Section 1.4 and Appendix D) Beck Depression Inventory-II 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 0-3. The two exceptions to this are Questions 16 and 18. Question 16 addresses changes in sleeping pattern, while question 18 addresses changes in appetite. Patients 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.

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

9.4.10 Ophthalmological examination

The effect of venglustat on the lens will be closely monitored throughout the study. The ophthalmological examination will include the measurement of visual acuity with current correction (or without correction as applicable), best corrected distance and near visual acuity after correction for refractive errors using the Snellen chart, and slit-lamp examination including examination of the cornea, lens, and retina after pupil dilation. Details of the ophthalmological examination are described in the study reference manual. When a cataract is detected, it must be graded 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 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.

An ophthalmological examination with pupil dilation will be performed prior to randomization (Visit 2), at Month 6 (Visit 6), Month 12 (Visit 8), Month 18 (Visit 10), and at Month 24 (Visit 12) (or upon withdrawal or discontinuation) of the blinded treatment period.

Prior to randomization (Visit 2), at Month 12 (Visit 8), Month 18 (Visit 10), and Month 24 (Visit 12) in Stage 1, and prior to randomization (Visit 2), at Month 12 (Visit 8), and Month 24 (Visit 12) in Stage 2, ophthalmological examinations will also include measurement of the corneal thickness (or endothelial cell density) and measurement of intraocular pressure.

If at any time during study participation a patient experiences a decline of ≥2 lines in best corrected visual acuity (BCVA) **compared with that at baseline or previous assessment**, a slit-lamp examination with pupil dilation should be performed. Observed lens opacities must be graded with the WHO simplified cataract grading system. A slit-lamp examination with pupil dilation must be performed again in 3 months. If no new cataract is seen during this examination, a normal schedule of ophthalmological examinations with pupil dilation can be resumed.

If patient had change of WHO Grade ≥1 in any of the 3 features (nuclear, cortical, and posterior subcapsular opacification) of the lens, the next scheduled ophthalmological examination (in 3 months) in this patient must include pupil dilation and evaluation of observed cataract(s) graded with the WHO simplified cataract grading system. If no new change of WHO Grade ≥1 is seen during this examination, a normal schedule of ophthalmological examinations with pupil dilation can be resumed.

Pupil dilation and full ophthalmological examination can be performed at any time if deemed medically necessary; observed lens opacities must be graded with the WHO simplified cataract grading system.

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.

9.4.11 Patient reported outcomes

Table 1 shows the concepts of measurement and their related PRO questionnaires to be used in the trial. Patient reported outcomes performed on site will be completed prior to any procedures or discussions about the treatment and disease.

Table 1 - Patient reported outcome (PRO) concepts and questionnaires

Concept	PRO questionnaire
Overall pain	BPI-SF (Appendix E)
Overall fatigue	BFI- (Appendix F)
Global impression of severity	PGIS (Appendix G)
Global impression of change	PGIC (Appendix H)

Concept	PRO questionnaire
Health status	EQ-5D-5L (Appendix I)
Daily symptoms of ADPKD (worst pain: BPI, Item 3, worst fatigue: BFI, Item 3, nocturia)	Daily diary

ADPKD = Autosomal dominant polycystic kidney disease; BFI = Brief Fatigue Inventory: BPI-SF = Brief Pain Inventory short-form; EQ-5D-5L = EuroQoL 5-dimension 5-level; PGIC = Patient global impression of change; PGIS = Patient global impression of severity; PRO = Patient reported outcome.

9.4.11.1 Overall pain

Overall pain will be measured using the BPI short-form (BPI-SF [17]); one of the most widely used instruments for measuring pain in clinical trials (Appendix E). 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, 3, 6, 9, 12, 15, 18, 21, and 24 visits.

9.4.11.2 Overall fatigue

The Brief Fatigue Inventory- (BFI [18]) has been used widely in clinical research in both drug development and observational studies (Appendix F). 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; two recalling the past 24 hours, one "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, 3, 6, 9, 12, 15, 18, 21, and 24 visits.

9.4.11.3 Global impression of severity

Patient global impression of severity (PGIS) is a single item scale in which patients indicate an overall assessment of their APKD symptoms (none, mild, moderate, and severe). The PGIS will be administered at the run-in visit, baseline visit, and Months 3, 12, 18 and 24 visits (Appendix G).

9.4.11.4 Global impression of change

The Patient Global Impression of Change (PGIC) consists of one item adapted to the patient that evaluates all aspects of patients' health and assesses if there has been an improvement or decline in clinical status since they started taking the study medication (7-category scale from "very much better" to "very much worse"). The PGIC will be administered at Months 3, 12, 18 and 24 visits (Appendix H).

9.4.11.5 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 3, 6, 12, 18 and 24 visits (Appendix I).

9.4.11.6 Daily symptoms of autosomal dominant polycystic kidney disease

A daily diary will be included in the study to measure pain, fatigue and nocturia with a 24-hour recall. The diary will be completed for 7 days prior to baseline visit and for the specified administration period before the study visits (see Section 1.3 and Section 1.4). The diary will be comprised of 3 items plus an additional item that will direct to the medication entry log:

- A nocturia item: “Last night, how many times did you wake up because you had to urinate? (if you did not wake up, please write 0)”.
- Item 3 of the BFI-SF to measure worst fatigue in the past 24 hours; “Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue in the last 24 hours”. Response options are given on an 11-point NRS from 0 (No Fatigue) to 10 (As bad as you can imagine).
- Item 3 of the BPI-SF to measure worst pain in the past 24 hours; “Please rate your pain by marking the box beside the number that best describes your pain at its worst in the last 24 hours”. Response options are given on an 11-point NRS from 0 (no pain) to 10 (pain as bad as you can imagine).
- Medication log entry item; "Have you taken any medication for your pain in the past 24 hours? Yes/No".

If the response to the medication log entry item is *"Yes"* patients will enter the pain medication log.

An average score for each item will be taken for each administration period.

9.4.12 Analgesic/over the counter pain medication administration

Analgesic use will be captured at baseline and at each pain assessment period using a medication log. Patients will report pain medication use in their daily diary.

9.4.13 Pharmacodynamic and exploratory biomarkers

Plasma, serum, and urine samples will be collected at the times specified in the study flow chart (see Section 1.3 and Section 1.4). Based on collection from an anticipated 640 patients at 7 time points, up to 4480 samples are expected per assessed biomarker.

9.4.13.1 Biomarkers associated with autosomal dominant polycystic kidney disease

Pharmacodynamic biomarkers associated with ADPKD such as FGF23 and ADMA in plasma will be analyzed using appropriate bioanalytical platforms at the Sponsor's laboratory or at a subcontracted laboratory. Other analytes may also be assessed if available data during the course of the study suggest a relationship to disease course in ADPKD patients or to venglustat.

Urine samples (24-hour urine collections) will be analyzed for markers of kidney injury such as monocyte chemoattractant protein-1 (MCP-1) using an appropriate bioanalytical platform at the Sponsor's laboratory or at a subcontracted laboratory. Additional exploratory biomarkers in urine (eg, Kidney Injury Molecule-1 [KIM-1], neutrophil gelatinase-associated lipocalin [NGAL], or GL-1, GM3) may be assessed.

9.4.13.2 Glycosphingolipids: glucosylceramide, monosialodihexosylganglioside

Plasma samples for GL-1 and GM3 will be analyzed using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) methods at the Sponsor's laboratory or at a subcontracted laboratory.

9.4.14 Pharmacokinetics

9.4.14.1 Sampling time

Blood samples for plasma venglustat assessment will be collected from all patients according to the time points described below and as shown in the study flow charts (see Section 1.3 and Section 1.4):

Based on collection of PK samples from an anticipated 640 patients (5 samples per patient in Stage 1 for 240 patients and 3 samples per patient in Stage 2 for 400 patients), approximately 2400 PK samples are expected from the study.

- Stage 1:
  - Day 1: 3 (±1) hours post dose,
  - Month 1: Pre-dose and 3 (±1) hours post dose,
  - Months 6 and 18: Pre-dose.
- Stage 2:
  - Month 1: Pre-dose and 3 (±1) hours post dose,
  - Month 24: Pre-dose.

At visits when a post-dose PK sample is to be collected, patients should take the study drug on site.

For PK sample collected at end-of-treatment visit in case of premature treatment discontinuation, time of last dose and time of PK sample collected should be accurately recorded.

9.4.14.2 Pharmacokinetics handling procedure

Special procedures for collection, storage, and shipment of plasma samples collected for venglustat concentrations will be provided in a separate laboratory manual provided by the central laboratory. An overview of PK sample handling procedure is provided in Table 2.

Table 2 - Summary of plasma pharmacokinetics samples handling for venglustat

Sample type	venglustat
Matrix	Plasma
Blood sample volume	See study specific laboratory manual
Anticoagulant	K2EDTA
Blood handling procedures	See study specific laboratory manual
Aliquot split	See study specific laboratory manual
Storage conditions	Keep in upright position at -70°C
Shipment conditions	Frozen, on dry ice

K2EDTA = dipotassium ethylenediamine tetraacetic acid.

9.4.14.3 Bioanalytical method

Venglustat plasma concentrations will be determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method (DMPK15-R012) with a lower limit of quantification (LLOQ) of 0.5 ng/mL under the responsibility of QPS, Newark, Delaware, USA.

9.4.14.4 Pharmacokinetics parameters

Only sparse plasma pharmacokinetic samples will be collected at clinical visits (see study flowchart in protocol Section 1.1). As a result, no pharmacokinetic parameters will be generated. Pharmacokinetic variables will include plasma venglustat concentrations.

Exploratory venglustat metabolite profiling and/or metabolite exposure analysis may be conducted in the collected plasma samples.

9.4.15 Pharmacogenetic assessment

9.4.15.1 Optional stored deoxyribonucleic acid sample

Once enrollment is confirmed, patients will be asked if they are willing to consent to long-term storage of deoxyribonucleic acid (DNA) samples for future use. For those patients who provided written consent to the collection of the optional pharmacogenetic samples, blood samples for exploratory genetic analysis of DNA will be collected at Day 1 (Section 1.3 and Section 1.4) for the purpose of pharmacogenetic analysis and this sample will be stored. This sample may be used for genetic analysis related to ADPKD and/or to venglustat.

This blood sample will be transferred to a Sanofi site (or a subcontractor site) which could be located outside of the country where the study is conducted. Sanofi or its subcontractor will extract DNA from the sample.

This blood sample, and the DNA that is extracted from it, will be assigned a second number, a Genetic ID that is different from the Patient ID. This "double coding" is performed to separate a patient's medical information and DNA data.

The clinical study data (coded by Patient ID) will be stored in the clinical data management system (CDMS), which in a distinct database in a separate environment from the database containing the genetic data (coded by Genetic ID). The key linking Patient ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The DNA will be stored for up to 15 years from the completion of the clinical study report.

If a patient, via written request, asks for destruction of his/her samples and the samples have not yet been double coded, the Sponsor will destroy the samples per applicable guidelines; however, any data already generated will not be destroyed. The Sponsor will notify the Investigator in writing that the samples have been destroyed. However, any analyses of the sample(s) that have already been performed or data generated prior to patient's request will continue to be used as part of the research in this project and will be kept by the Sponsor.

Special procedures for collection, storage, and shipping of DNA samples are summarized in Table 3 and will be described in detail in the laboratory manual provided to the study sites.

Table 3 - Summary of handling procedures for stored DNA samples

Sample type(s)	Pharmacogenetics
Blood sample volume	6 mL
Tube type	Tube provided by central laboratory for DNA sample storage
Anticoagulant	See laboratory manual for specific instructions
Blood handling procedures	See laboratory manual for specific instructions
Shipping conditions	See laboratory manual for specific instructions
Blood sample storage conditions	-20°C or colder; See laboratory manual for specific instructions

DNA: deoxyribonucleic acid.

9.4.16 Future use of samples

For patients who have consented to it, serum samples will be collected at Visits 3, 8, and 12 and these samples will be stored (Biobanking).

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For patients who have consented to it, the samples that are unused or left over after

testing and samples collected for Biobanking may be used for other research purposes (excluding genetic analysis) related to ADPKD than those defined in the present protocol.

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

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

9.4.17 Isolation of urinary exosomes

Urinary exosomes will be isolated from the urine of patients at selected sites. Exosomes isolation will be done on the 24-hour samples of urine already collected in the study (Appendix K).

9.5 APPROPRIATENESS OF MEASUREMENTS

For details please refer to Section 4 and Section 6.5.

10 STUDY PROCEDURES

The staff of each study center will include the following physicians: a primary nephrologist and a Subinvestigator. The primary nephrologist, who can serve as the PI, will have overall responsibility to lead the site study team (physicians, pharmacists, technicians, nurses, and clinical coordinators) in all aspects of the study. The Subinvestigator can back up the PI when/if needed.

The clinical coordinator may be a qualified individual who will be responsible for coordinating and assisting all study site staff, including patient scheduling and completion and monitoring of all patients' case report forms. He/she will be responsible for coordinating IMP administration, and collect, process, and send all blood and other forms of biological samples and requests to the central laboratory. Additionally, he/she will be responsible for administering the patient-reported questionnaires and coordinating the conduct of the MRIs.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix O.

10.1 VISIT SCHEDULE

This is an outpatient study consisting of on-site visits. Additional, optional phone-call visits to monitor safety should be scheduled as often as deemed necessary by the Investigator. If a patient does not attend a scheduled visit, the study site personnel should contact the patient by telephone as soon as possible for rescheduling.

Scales and questionnaires should be completed before dosing and before clinical assessments by the Study Investigator or other healthcare provider(s).

Before any screening assessment is performed, information regarding the aims and methods of the study, its constraints and risks will be explained to the patient and a written summary in the form of an informed consent will be provided. The patient must sign and date the informed consent before screening and before patient demography is recorded.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for these to be performed over more than one site visit if necessary, as long as the screening visit window prior to Day -15 (run-in/Visit 2) is respected. Rescreening is possible in this study.

The study visits occur on the planned dates (relative to the first administration of IMP), as scheduled. The visit schedule should be adhered to within ±3 days for the run-in period, ±7 days for the double-blind core treatment period, and -7 to +21 days for the follow-up (off-treatment) period. If one visit date is skipped/missed/changed, the next visit should take place according to the original schedule.

Further details of procedures/assessments listed in the following sections are captured in the study flow charts (Section 1.3 and Section 1.4).

10.1.1 Screening period

10.1.1.1 Visit 1: screening from Day -30 to Day -16

The initial screening period (Visit 1) can last up to 15 days (+3 days). Visit 2 can be performed as soon as results of all assessments performed at Visit 1 are available.

The following activities will be performed:

- An explanation of the purpose, procedures, potential risks, and benefits of this study will be provided to the patient.
- Informed consent signature and date will be collected.
- Patient demography will be recorded.
- Confirmation of eligibility by the Investigator.
- MRI (if the patient has no documented CT/MRI/US kidneys imaging test results obtained prior to the study)
  - If the patient has documented CT/MRI/US kidneys imaging test results obtained prior to the study, the Investigator may use this data for preliminary evaluation of the patient`s eligibility (massively enlarged kidneys) at Visit 1. First study MRI for confirmation of TKV Imaging Classification Class will be performed at Visit 2 (run-in visit).
- Medical/surgical history.
- Review of current medical conditions, with AE/SAE reporting (if any).
- Review of current and prior medications.
- Complete physical examination.
- Record of height and body weight measurements.
- Vital signs.
- Laboratory assessments.
  - Chemistry and hematology.
- Viral serology (to be performed by a central laboratory: HBsAg, HBcAb, anti-HCVAb, anti-HIV1 Ab and anti-HIV2 Ab).
- Blood sampling for GSL marker analysis.
- Blood sampling for biomarker analysis in Stage 1. In Stage 2, only if to be done following analysis of Stage 1 samples.
- Urinalysis (local dipstick test) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leukocyte esterase. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urinalysis with microscopy (to be performed by a central laboratory).

- Serum β-HCG pregnancy test (for women of childbearing potential [WOCBP]).
- Blood sampling for follicle stimulating hormone (FSH)/estradiol levels (in post-menopausal females, if not previously documented).

10.1.1.2 Visit 2: run-in Day -15

Visit window: The run-in visit (Day -15) can be performed up to 15 (±3) days after the initial screening visit or as soon as results of all assessments performed at Visit 1 are available.

The following activities will be performed:

- Whenever possible, the BDI-II (Appendix D) and PGIS (Appendix G) should be done prior to clinical interaction with the Investigator. At screening, patients with BDI-II of 20 to 28, inclusive, should be evaluated by a mental health specialist before the Investigator can determine if the patient would be able to fully participate in the trial. Patients with a BDI-II of >28 (severe depression) at screening will be excluded.
- Review of current medical conditions, with AE/SAE reporting (if any).
- Review of current medications.
- Abbreviated physical examination (focus on areas important for assessment of AEs if necessary).
- Record of body weight measurement.
- Vital signs.
- 12-lead ECG (print out of ECG recording should be evaluated by Investigator prior to IMP administration).
- Laboratory assessments (Chemistry only).
- Urine pregnancy test (for WOCBP).
- Ophthalmological examination with pupil dilation including measurement of the corneal thickness (or endothelial cell density) and measurement of intraocular pressure.
- MRI (if MRI for confirmation of TKV Imaging Classification Class was not performed at Visit 1).
- Confirmation of eligibility by the Investigator.
- Issue daily symptom diary and remind the patient that this should be completed for the 7 days before the next visit.

Following confirmation of eligibility (based on results of assessments performed at the screening visit, including evaluation of liver enzymes at the screening visit and blood pressure at the run-in visit), patients will receive once daily, 2 placebo capsules for 2 weeks in Stage 1 (1 or 2 placebo capsules in Stage 2).

A patient diary will be issued with instructions to record any missing doses of IMP and pain medication used. The patient should bring their diary and any remaining capsules to the next clinic visit. The site staff will review the patient diary during the clinic visit and record excursions from treatment into the eCRF.

The patient should be given suitable containers in which to collect the 24-hour urine and the urine spot, required prior to the next visit and to be returned at that visit.

10.1.2 Treatment period - Month 0 to Month 24

Visit window: The randomization visit (Day 1) should be performed 15 days after Visit 2 with the acceptable window of ±3 days. Using Day 1 as reference, a time frame of ±7 days is acceptable for Visits 4 to 12. (If one visit date is skipped/missed/changed, the next visit should take place according to the original schedule.)

10.1.2.1 Visit 3: randomization at Month 0/Day 1

Screening assessments will be completed within the 30-day screening period. Eligibility will be reconfirmed prior to randomization/first dose IMP administration on Day 1 (based on results of assessments performed during the screening period, including evaluation of liver enzymes at the run-in visit and blood pressure at the baseline visit).

Patients will receive either placebo or venglustat, orally, at the clinic.

Patients will be instructed to record any missing doses of IMP and pain medication used in their patient diary. The patient should bring their diary and any remaining capsules to each clinic visit. The site staff will review the patient diary during each clinic visit and record excursions from treatment into the eCRF. The patient diary will be retrieved when the patient finishes their participation in the study.

The Randomization visit (Day 1) will include assessments and activities as listed in the study flow chart, Section 1.3 and Section 1.4, which should be done in the following order:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
  - BPI (Appendix E),
  - BFI (Appendix F),
  - PGIS (Appendix G),
  - EQ-5D-5L (Appendix H).
- Review of concomitant medications.
- Review of current medical conditions, with AE/SAE reporting (if any).
- Collection of spot urine sample.
- Collection of home urine based on 24-hour collection.
- Reconfirmation of eligibility by the Investigator.
- Review daily symptom diary for completeness.
- Review of missed dose log for eligibility compliance.

- Abbreviated physical examination (focus on cardiac and respiratory systems, as well as any areas important for assessment of AEs if necessary).
- Vital signs.
- Laboratory assessments.
  - Chemistry and hematology.
- Biobanking blood sample (optional) collected prior to the start of IMP.
- Pharmacogenetic sample (optional).
- Urine pregnancy test (for WOCBP).
- Randomization via IRT.
- Dispense study medication.
- Blood sampling for PK analysis 3 hours post dose (Stage 1 only).
- If the patient is participating in the mGFR substudy, perform iohexol infusion and collect blood samples according to Appendix L.
- Issue daily symptom diary and remind the patient that this should be completed daily until Visit 5.

Remind patient to return to the clinic for next visit, bring their diary and any remaining capsules.

Remind patient to not take the dose at home on the next clinic visiting day.

The patient should be given suitable containers in which to collect the 24-hour urine and the urine spot (see Section 9.4.3), required prior to the next visit and to be returned at that visit.

10.1.2.2 Visit 4, 6, 8, 10, 12/Month 1, 6, 12, 18, 24 (Day 30, 180, 360, 540, 720)

Patients will receive either placebo or venglustat, orally, at the clinic.

Patients will be instructed to record any missing doses and pain medication used in their diary. The patient should bring their diary and any remaining capsules to each clinic visit. The site staff will review the patient diary during each clinic visit and record excursions from treatment into the eCRF.

The following activities will be performed:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
  - BDI-II (Visits 6, 8, 10, 12),
  - BPI (Visits 4, 6, 8, 10, 12),
  - BFI (Visits 4, 6, 8, 10, 12),
  - PGIS (Visits 8, 10, 12),

  - PGIC (Visits 8, 10, 12),
  - EQ-5D-5L (Visits 6, 8, 10, 12).
- Review of concomitant medications.
- Review of current medical conditions, with AE/SAE reporting (if any).
- Collection of spot urine sample.
- Collection of home urine based on 24-hour collection.
- Review daily symptom diary for completeness.
- Review of missed dose log for compliance.
- Abbreviated physical examination (focus on areas important for assessment of AEs if necessary; Visits 4, 6, and 8).
- Complete physical examination at Visits 10 and 12.
- Record of body weight measurement at Visit 8.
- Vital signs.
- 12-lead ECG at Visits 6 and 12.
- Laboratory assessments.
  - Chemistry and hematology.
- Blood sampling for GSL markers.
- Blood sampling for biomarker analysis (not collected at Month 1 in Stage 2).
- Blood sampling for PK analysis:
  - Stage 1: pre-dose and 3 hours post-dose at Visit 4; pre-dose at Visits 6 and 10,
  - Stage 2: pre-dose and 3 hours post-dose at Visit 4; pre-dose at Visit 12.
- Biobanking blood sample (optional) at Visits 8 and 12.
- Urinalysis (local dipstick test) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leukocyte esterase. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urinalysis with microscopy; (to be performed by a central laboratory).
- Ophthalmological examination
  - At Month 6 (Visit 6), Month 12 (Visit 8), Month 18 (Visit 10), and Month 24 (Visit 12): ophthalmological examination with pupil dilation
  - At Month 12 (Visit 8), Month 18 (Visit 10) and Month 24 (Visits 12) in Stage 1, and at Month 12 (Visit 8) and Month 24 (Visits 12) in Stage 2, ophthalmological examination will also include measurement of the corneal thickness (or endothelial cell density) and measurement of intraocular pressure.

- MRI at:
  - Stage 1: Visits 4 and 10,
  - Stage 2: Visit 10.
- Urine pregnancy test (for WOCBP).
- If the patient is participating in the mGFR substudy, perform iohexol infusion and collect blood samples according to Appendix L, at Visits 8 and 12.
- Dispense study medication at Visits 4, 6, 8, and 10.
- Remind the patient that the patient daily symptom diary should be completed daily until Visit 5 and for 7 days before Visit 8.

Remind patient to return to the clinic for next visit, bring their diaries and any remaining capsules.

Provide WOCBP with at-home pregnancy tests and remind them to administer the pregnancy test monthly between visits.

Remind patient to not take the dose at home on the clinic visiting day at Visits 6 and 10 during Stage 1, and at Visit 12 during Stage 2.

The patient should be given suitable containers in which to collect the spot urine, to be returned at that visit (see Section 9.4.3).

10.1.2.3 Visit 5, 7, 9, 11/Month 3, 9, 15, 21 (Day 90, 270, 450, 630)

Patients will receive either placebo or venglustat, orally, at the clinic.

Patients will be instructed to record any missing doses and pain medication used in their diary. The patient should bring their diary and any remaining capsules to each clinic visit. The site staff will review the patient diary during each clinic visit and record excursions from treatment into the eCRF.

The following activities will be performed:

- Whenever possible, the following scales and questionnaires should be done prior to clinical interaction with the Investigator:
  - BDI-II (Appendix D),
  - BPI (Appendix E),
  - BFI (Appendix F),
  - PGIS (Visit 5 only; Appendix G),
  - PGIC (Visit 5 only; Appendix H),
  - EQ-5D-5L (Visit 5 only; Appendix I).
- Review of concomitant medications.

- Review of current medical conditions, with AE/SAE reporting (if any).
- Collection of spot urine sample.
- Review daily symptom diary for completeness.
- Review of missed dose log for compliance.
- Abbreviated physical examination (focus on areas important for assessment of AEs if necessary).
- Vital signs.
- Laboratory assessments.
  - Chemistry and hematology.
- Urinalysis (local dipstick test) including glucose, protein, bilirubin, urobilinogen, pH, specific gravity, blood, ketones, nitrite, and leukocyte esterase. Central urinalysis will be performed if any abnormality is observed in the urinalysis dipstick test.
- Urinalysis (microscopy; to be performed by a central laboratory).
- Urine pregnancy test (for WOCBP).
- MRI (at Visit 7 of Stage 1).
- Dispense study medication.
- Remind the patient that the patient daily symptom diary should be completed for the 14 days before Visit 10 and Visit 12.

Remind patient to return to the clinic for next visit, bring their diaries and any remaining capsules.

Provide WOCBP with at-home pregnancy tests and remind them to administer the pregnancy test monthly between visits.

The patient should be given a suitable container in which to collect the 24-hour urine and the spot urine, required prior to the next visit and to be returned at that visit.

10.1.3 Follow-up visit - Visit 13/Month 25 (Day 750)

Not applicable for patients who may be eligible for a potential long-term extension study after completion of 24 months of treatment.

Visit window: The Follow-up Visit (Day 750) can be performed within a -7 to +21 days window.

The following activities will be performed:

- Review of current medical conditions, with AE/SAE reporting (if any).
- Review of current and prior medications.
- Collection of spot urine sample.

- Abbreviated physical examination (focus on areas important for assessment of AEs if necessary).
- Record of body weight measurement.
- Vital signs.
- Laboratory assessments (Chemistry only).
- Blood sampling for GSL markers.
- Blood sampling for biomarker analysis in Stage 1. In Stage 2, only if to be done following analysis of Stage 1 samples.

10.2 DEFINITION OF SOURCE DATA

Source data are defined as original documents, data, and records. This includes, but is not limited to the following: hospital records, clinic and office charts, study-specific source document worksheets, phone logs, memoranda, evaluation checklists, laboratory requisitions and reports, ECG tracings, ophthalmological images and results and reports, local laboratory reports (if applicable), medication dispensing records, patient questionnaires, MRI images, computer printouts, electronic data/information sources including IRT notifications, and any other documentation regarding the patient.

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

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation must be fully documented in the eCRF. In any case, the patients who permanently discontinue IMP during the double-blind treatment period should complete an end-of-treatment visit and have selected assessments performed at Month 18 and Month 24 (refer to Section 10.3.4).

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment 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 O). After close and appropriate clinical and/or laboratory monitoring, once the Investigator considers, according to his/her best medical judgment that the occurrence of the concerned event was unlikely due to the IMP, the safety of the patient is not affected, and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2), treatment with the IMP may be re-initiated.

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator not to re-expose the patient to the IMP at any time during the study, or from the patient not to be re-exposed to the IMP, whatever the reason.

10.3.3 List of criteria for permanent treatment discontinuation

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

The patients 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 DMC (if DMC will decide that benefit/risk ratio is not favorable for this patient).

If a patient 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 study treatment will be discontinued and alternative therapy will have to be discussed by the Investigator.

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

If a patient experiences a reduction in eGFR below 25 mL/min/1.73 m^2, a repeated test must be performed after 30 days:

- If the result of the eGFR test (repeated in 30 days) is below 30 mL/min/1.73 m^2, the study treatment will be discontinued.

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

Patient specific:

- The patient experiences two similar SAE or one life-threatening SAE (assessed as related by the Investigator and/or the Sponsor).
- The patient meets criteria for Hy's law (confirmed ALT >5 × upper limit of normal (ULN) range or confirmed ALT >3 × ULN and bilirubin >2 × ULN).
- The patient becomes pregnant.

Trial specific:

- Any AEs, per Investigator judgment, that may jeopardize the patient's safety.
- Any unblinding of the study treatment by the Investigator.

Any use of prohibited concomitant treatment (see Section 8.8).

- At patient's request, ie, withdrawal of the consent for treatment.

After the company representatives have been made aware of the suspected adverse reactions (SARs), relevant safety/laboratory data will be submitted to the DMC within 72 hours by Global Pharmacovigilance, Clinical, and other related departments as designated by the Company.

Any abnormal laboratory value or imaging reports will be immediately rechecked by the Sponsor and the central reader, respectively, for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

The DMC will also review data if applicable to assist in determining if AEs should preclude continued treatment with venglustat.

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

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the Month 18 and Month 24 Visits.

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

10.3.4 Handling of patients after permanent treatment discontinuation

Patients 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.

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

Patients who prematurely and permanently discontinue study medication should complete rapidly (within 7 days) an end-of-treatment (EOT) assessment visit.

Stage 1: EOT visit should include all procedures of Visit 12 and additionally a PK sample should be collected. In 30 days, a premature Follow-up visit (all procedures of Visit 13) should be performed.

Stage 2: EOT visit should include all procedures of Visit 12. In 30 days, a premature Follow-up visit (all procedures of Visit 13) should be performed.

In addition, for both Stage 1 and Stage 2:

1. Investigator should ask patient who prematurely and permanently discontinued study medication to continue study visits for safety and efficacy assessments (including PRO questionnaires) up to and including the last scheduled visit, if possible.

2. If the patient refuses to attend all scheduled visits and to continue answering all PRO questionnaires, Investigator should ask the patient to continue answering questions of "Daily symptoms of ADPKD" diary and to return to the site at 18 months (to have at least an MRI, blood sample for eGFR evaluation, urine analysis [for urine protein and osmolality], as well as safety assessments performed) and at 24 months (to have blood sample for eGFR evaluation, urine analysis [for urine protein and osmolality], and safety assessments performed).

For patients participating in mGFR substudy of the Stage 2, mGFR measurement should be performed at 24 months.

Patients who withdraw from the study due to pregnancy should be followed 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 one year after the birth of the baby, due to potential risk of abnormalities not present at birth. See Appendix A for guidance.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason without any effect on their care. However, if patients 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.

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

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

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

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator must make the best effort to recontact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

All data collected up to the patient's withdrawal will be included in the analyses. The statistical analysis plan (SAP) will specify how early withdrawals from treatment will be accounted for in the analyses of efficacy endpoints.

Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.3.6 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.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

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

10.4.1.2 Serious adverse event

A **SAE** is any untoward medical occurrence that at any dose:

- Results in death, or

- Is life-threatening, or

  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event

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

  Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered 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 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN,
  - Suicide attempt or any event suggestive of suicidality,
  - Syncope, loss of consciousness (except if documented as a consequence of blood sampling),
  - Bullous cutaneous eruptions,
  - Cancers diagnosed during the study or aggravated during the study.

10.4.1.3 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. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

The definition of AESI for this study are as follows:

- Pregnancy:
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2),
  - In the event of pregnancy in a female patient, IMP should be discontinued,
  - Follow-up of the pregnancy in a female patient or in a female partner of a male patient is mandatory until the outcome has been determined (See Appendix A).
- 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 patient (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,
  - Of note, asymptomatic overdose has to be reported as a standard AE,
  - The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
- Increase in ALT (see the "Increase in ALT" flow diagram in Appendix C of the protocol).
- Other project specific AESI(s):
  - New or worsening lenticular opacities and cataracts.

For opacities present at baseline/previous visit, changes in WHO Grade ≥1 for nuclear, cortical opacification, or posterior subcapsular opacification compared with baseline or previous assessment will be considered as a worsening.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the eCRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s).
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. At the prespecified study end-date, patients who experience an ongoing SAE or an AESI should be followed until resolution, stabilization, or death and related data will be collected.

- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs, ECG, or ophthalmic examination abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or,
  - Requiring either corrective treatment or consultation, and/or,
  - Leading to IMP discontinuation or modification of dosing, and/or,
  - Fulfilling a seriousness criterion, and/or,
  - Defined as an AESI, and or,
  - Leading to unscheduled full ophthalmological examination with or without WHO simplified cataract grading system evaluation.

Instructions for AE reporting are summarized in Table 4.

10.4.3 Instructions for reporting serious adverse events

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

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF or after a standard delay.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In such a case, care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of a source document provided to the Company. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the eCRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life-threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the eCRF system does not work.
- Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding screens in the eCRF.

Instructions for AE reporting are summarized in Table 4.

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix C.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia.
- Thrombocytopenia.
- ALT increase.
- Acute renal insufficiency.
- Suspicion of rhabdomyolysis.

Table 4 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case report form completion	
			AE form	Other specific forms
Adverse Event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No
Serious Adverse Event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	No
Adverse Event of Special Interest	Expedited (within 24 hours)	New or worsening lens opacities and cataracts	Yes	No
		Pregnancy	Yes	Yes
		Symptomatic overdose	Yes	No
		ALT increase as defined in the protocol	Yes	Yes

AE = adverse event; AESI = adverse event of special interest; ALT = alanine aminotransferase; SAE = serious adverse event.

10.4.6 Guidelines for reporting product complaints (investigational medicinal product)

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.

10.5 OBLIGATIONS OF THE SPONSOR

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

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

Adverse events that are considered expected will be specified by the reference safety information in the IB.

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

10.6 SAFETY INSTRUCTIONS

At any time during the study, patients who develop ≥ Grade 3 cataracts will be discontinued from treatment.

In order to closely monitor the liver function, assessment of total protein, albumin, total bilirubin, AST, ALT, and ALP are measured as part of the clinical laboratory testing. Patients with a positive medical history of hepatitis B or hepatitis C antibody at the screening visit will be excluded from the study.

Guidance for the investigation of elevated liver function tests is provided in Appendix C.

Venglustat is not known to be associated with any renal effect. See Appendix C; this algorithm is provided for informational purposes regarding the assessment of acute renal failure.

Investigator should follow local standards of care if during the study patient will require modification of antihypertensive therapy.

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

In Stage 1, approximately 240 patients will be randomized (with randomization ratio 1:1:1) to placebo (n=80) or venglustat 8 mg (n=80) or venglustat 15 mg (n=80). In Stage 2, approximately 320 patients with an eGFR between 45 and 89.9 mL/min/1.73 m² at screening will be randomized (with randomization ratio 1:1) to placebo (n=160) or venglustat (n=160). In addition, 80 patients with an eGFR between 30 and 44.9 mL/min/1.73 m² at screening will be randomized (with randomization ratio 1:1) to placebo (n=40) or venglustat (n=40). The patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 will not be included in the primary efficacy and safety analyses populations but the data from these patients will be analyzed separately.

This sample size will provide approximately 89% power to detect a 50% reduction in annualized rate of change in TKV at end of Stage 1 and approximately 87% power to detect a 30% reduction in annualized rate of change in eGFR between venglustat and placebo at the end of Stage 2. Overall, the total sample size will provide approximately 87% power to detect an effect on both TKV and eGFR.

Sample size and power calculations were based on simulations, assuming different scenarios regarding the dose-response relationship (see Appendix J for additional details). The following model parameters were estimated based on available databases from a similar patient population (patients aged 18 to 50 years with Mayo Class 1C-1E and baseline eGFR from 45 to 90 mL/min/1.73 m²) in 2 historical studies (Consortium for Radiologic Imaging Studies of Polycystic Kidney Disease (CRISP) and the Polycystic Kidney Disease Treatment Network [HALT-PKD]):

- A slope of $\log_{10}$(TKV) of 0.02591, 0.02832 and 0.03141 in patients from Mayo Class 1C, 1D, and 1E respectively (corresponding to 6.1%, 6.7% and 7.5% increase per year in TKV), resulting in average slope of 0.02764 (6.6%/year) assuming 50% of 1C, 33% of 1D and 17% of 1E.
- Standard deviation for the residual error of TKV (on the $\log_{10}$ scale) of 0.02566 and standard deviation for the random effect of slope of 0.01477.
- A slope of eGFR of -3.16, -3.88 and -4.69 mL/min/1.73 m² per year in patients from Mayo Class 1C, 1D, and 1E respectively, resulting in average slope of -3.66 mL/min/1.73 m² per year assuming 50% of 1C, 33% of 1D, and 17% of 1E.
- Standard deviation for the residual error of eGFR of 6.34 and standard deviation for the random effect of slope of 1.98.

In addition, sample size and power calculations assumed an overall significance level of 0.05 (2-sided), 10% dropout rate and included adjustments for handling of multiplicity of tests and futility analysis (as described in Section 11.4.2.3 and Section 11.5.1). A sample size of 80 patients (40 per arm) with an eGFR between 30 and 44.9 mL/min/1.73 m² at screening will provide

approximately 80% probability to detect a treatment effect in this subgroup at the 0.20 significance level (two-sided), based on a model evaluating the dependence of the treatment effect on baseline eGFR.

11.2 DISPOSITION OF PATIENTS

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

Randomized patients consist of all patients who have been allocated a treatment kit based on a randomization process. It will consist of all patients with a treatment kit number allocated and recorded in the IRT database, and regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent-to-treat population

Stage 1

The Stage 1 Intent-to-treat (ITT) population will be defined as all patients who are randomized in Stage 1, analyzed according to the treatment group allocated by randomization (venglustat 15 mg, venglustat 8 mg, or placebo).

Primary analysis in Stage 1 will include all data from Stage 1 available at the cut-off date (ie, including data reported up to Month 24, if any). The cut-off date will be defined as the date all patients from Stage 1 have completed the Month 18 visit (or have discontinued the study).

Stage 2

The combined Stage 1 and Stage 2 ITT population will include all patients with an eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening who are randomized in Stage 1 or Stage 2, analyzed according to the treatment group allocated by randomization (venglustat 15 mg, venglustat 8 mg, or placebo).

Primary analysis in the combined Stage 1 and Stage 2 will include all data available from baseline to the end of the 24-month double-blind core treatment period. Patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m² at screening will not be included in the primary efficacy analysis population but the data from these patients will be analyzed separately.

11.3.2 Safety population

The Stage 1 Safety population will be defined as all patients who are randomized in Stage 1 and received at least one dose or part of a dose of the double-blind IMP, analyzed according to the treatment actually received (venglustat 15 mg, venglustat 8 mg, or placebo)

The combined Stage 1 and Stage 2 Safety population will be defined as all patients with an eGFR between 45 and 89.9 mL/min/1.73 m² at screening who are randomized in Stage 1 or Stage 2 and received at least one dose or part of a dose of the double-blind IMP, analyzed according to the treatment actually received (venglustat 15 mg, venglustat 8 mg, or placebo). Patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m² at screening will not be included in the primary safety analysis population but the data from these patients will be analyzed separately.

A secondary safety analysis population will include patients who are randomized in Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m² at screening and received at least one dose or part of a dose of the double-blind IMP.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- For patients receiving more than 1 study treatment during the trial, the treatment group allocation for as-treated analysis will be the one to which the patient was treated with the longest duration.

11.3.3 Pharmacokinetics/pharmacodynamics analysis population

The PK and PD populations will be defined as all patients who were randomized, received at least one dose of the double-blind IMP and who have at least one PK or PD assessment, respectively.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

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

11.4.1.1 Extent of investigational medicinal product exposure

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

11.4.1.2 Compliance

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

Treatment compliance will be summarized descriptively (N, mean, SD, median, min, and max). The percentage of patients with compliance <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

11.4.2.1.1 Stage 1

In Stage 1, the primary efficacy endpoint is the annualized rate of change in TKV. TKV will be measured with MRI.

Estimands

The primary estimand will be the difference in mean slope of $\log_{10}$-transformed TKV estimated from baseline to 18 months in all randomized patients, regardless of whether or not patients completed the treatment period. This estimand corresponds to a "treatment policy strategy". This estimand will be considered primary for supporting regulatory decision making.

A secondary estimand will be the difference in mean slope of $\log_{10}$-transformed TKV estimated during the on-treatment period (from baseline to end of treatment). This estimand corresponds to a "while on treatment strategy". This estimand will be considered for describing the effect of treatment as long as patients adhere to their randomized treatment.

Primary analysis

A linear mixed effect model will be fitted to the $\log_{10}$-transformed TKV, which will include fix effects of treatment (venglustat 15 mg, venglustat 8 mg or placebo), Mayo Imaging Classification (as per randomization stratification factor: Class 1C versus 1D versus 1E), time (as continuous variable), treatment * time interaction and Mayo Imaging Classification * time interaction, and will include random intercept and slope. Time will be based on actual TKV assessment date relative to randomization date (in years).

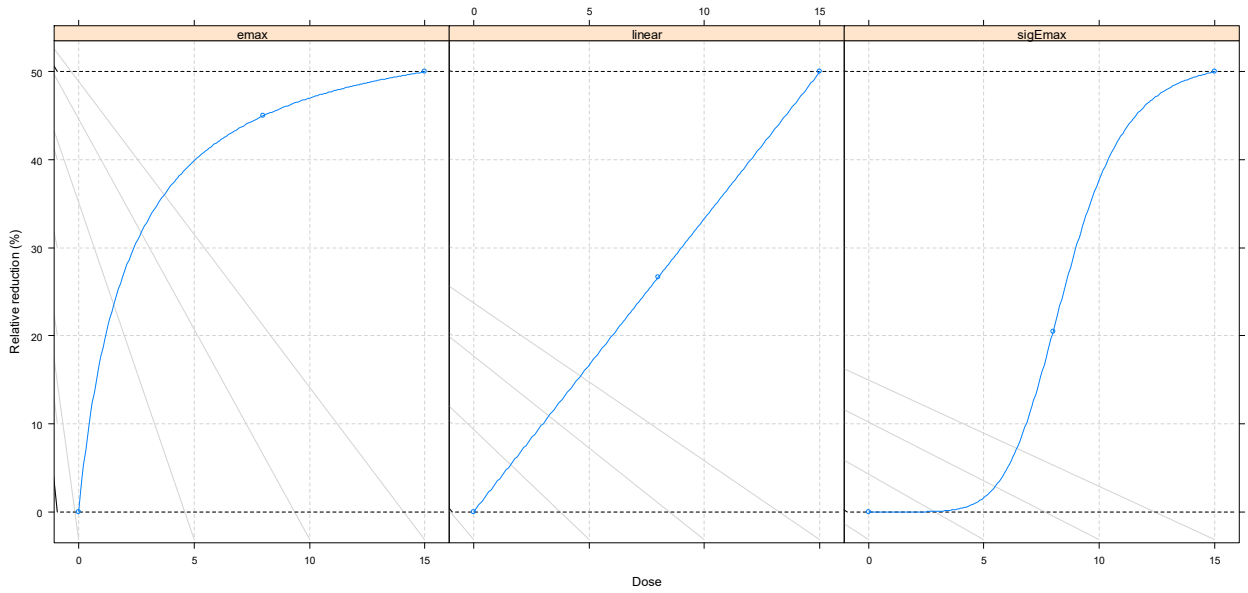
Within group mean slope of $\log_{10}$-transformed TKV will be obtained from the linear mixed effect model, using weights for each stratum (Mayo Class 1C, 1D and 1E) equal to the overall proportion of patients in each stratum in the Stage 1 ITT population (ie, "population weight"). A

back-transformation will be applied to obtain annualized rate of change in TKV (in % per year) within each treatment arm, along with their 95% confidence intervals:

$$\text{Annualized rate of change in TKV (\% per year)} = \left(10^{\text{slope of } \log 10\text{TKV}} - 1\right) \times 100$$

Overall effect of venglustat will be assessed using a Multiple Comparison Procedure (19). Multiple trend tests will be performed using optimal contrasts determined from a set of 3 prespecified candidate models for the dose-response relationship described in Figure 2.

Figure 2 - Prespecified candidate of dose-response models



Optimal contrasts for each candidate model were derived using the R add-on package *DoseFinding* (20) and are presented in Table 5. Contrasts will apply to the treatment * time interaction term in the linear mixed effect model. Multiplicity adjusted p-value will be presented.

Table 5 - Optimal contrasts for the 3 prespecified candidate of dose-response models

Dose	Emax model	Linear model	Sigmoid Emax model
Placebo	-0.8131	-0.7223	-0.6615
venglustat 8 mg	0.3424	0.0314	-0.0838
venglustat 15 mg	0.4707	0.6909	0.7453

Relative reduction in annualized rate of change in TKV will be estimated for each dose of venglustat versus placebo and defined as:

$$\text{Relative reduction (\%)} = \left(1 - \frac{\text{Annualized rate of change in TKV in GZ/SAR402671 arm}}{\text{Annualized rate of change in TKV in placebo arm}}\right) \times 100$$

Relative reduction for each dose of venglustat will be presented with 95% confidence intervals obtained using a first-order Taylor approximation. In addition, p-values for the comparison of each dose of venglustat versus placebo will be presented for descriptive purpose.

Primary analysis in Stage 1 will include all data from Stage 1 available at the cut-off date (including data reported up to Month 24, if any). The cut-off date will be defined as the date all randomized patients from Stage 1 have completed the Month 18 visit (or have discontinued the study).

Handling of missing data

The primary analysis will include all observed TKV data in randomized patients, regardless of whether or not patients completed the treatment period (treatment policy strategy). Patients who prematurely and permanently discontinue study medication will be requested to obtain an MRI scan at 18 months 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.

Missing data will be handled using a multiple imputation method. Missing data will be imputed using a linear mixed effect model that will include separate slopes of $\log_{10}$(TKV) during the on-treatment period and after permanent treatment discontinuation, for each treatment arm (venglustat 15 mg, venglustat 8 mg, or placebo). The imputation model will also include adjustment for Mayo class (1C versus 1D versus 1E) as well as random intercept and slope.

Imputations will be based on the following assumptions:

- Patients with missing data during the on-treatment period will have their data imputed based on the mean slope estimated during the on-treatment period in patients from the same treatment arm.
- Patients with missing data after permanent treatment discontinuation will have their data imputed based on the mean slope estimated during the post-treatment period in patients from the same treatment arm, who discontinued the treatment but had TKV data available during the post-treatment period.

Additional details about the multiple imputation procedure, including a sample SAS code, are included in Appendix J.

If the number of patients who permanently discontinue the treatment but have TKV data available during the post-treatment period is insufficient to estimate the imputation model (less than 3 patients per treatment arm), then the control based multiple imputation (later described as sensitivity analysis) will be used as the primary method to handle missing data.

After multiple imputations, the imputed datasets will be analyzed using the linear mixed effect model described above. Results from the model, including within group mean slopes and contrasts will be combined using Rubin's formula.

Sensitivity analysis

Different sensitivity analyses will be performed, in order to evaluate the robustness of the primary analysis to alternative assumptions about missing data. These sensitivity analyses will target the same estimand as the primary analysis.

Analysis of observed data

In this sensitivity analysis, no imputation of missing data will be performed. The linear mixed effect model described above will be run on all observed data, including data collected after treatment discontinuation. This sensitivity analysis will be based on the assumption that the rate of progression in TKV is the same before and after treatment discontinuation.

Control based multiple imputation

In this sensitivity analysis, missing data will be handled using a control based multiple imputation method. Imputations will be based on a model that will assume that after permanent treatment discontinuation, the slope of $\log_{10}$(TKV) for patients in the venglustat arms will be the same as the slope of $\log_{10}$(TKV) for patients in the placebo arm. The imputation model will also include adjustment for Mayo class (1C versus 1D versus 1E) as well as random intercept and slope.

Imputations will be based on the following assumptions:

- Patients with missing data during the on-treatment period will have their data imputed based on the mean slope estimated during the on-treatment period in patients from the same treatment arm.
- Patients with missing data after permanent treatment discontinuation will have their data imputed based on the mean slope estimated in patients from the placebo arm.

Additional details about the control based multiple imputation procedure are included in Appendix J.

Secondary analysis

A secondary analysis will estimate the difference in mean slope of $\log_{10}$-transformed TKV during the on-treatment period (while on treatment strategy). In this secondary analysis, TKV assessed more than 30 days after the last IMP administration will be excluded from the analysis.
TKV assessed in randomized but not treated patients 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 linear mixed effect model provides valid inference under missing at random assumption.

Another secondary analysis will explore a potential acute hemodynamic effect. In this secondary analysis, only TKV assessed from 1 month to 18 months will be included in the linear mixed effect model. TKV at baseline will be excluded from this secondary analysis.

11.4.2.1.2 Stage 2

In Stage 2, the primary efficacy endpoint is the annualized rate of change in eGFR (CKD-EPI equation).

The analysis of eGFR will be similar to those of TKV, with the exception that no log transformation will be used for eGFR. Baseline eGFR will be defined for each patient as the average of eGFR values assessed prior to randomization.

Primary analysis in Stage 2 will combine all data from Stage 1 and Stage 2 available from baseline to the end of the 24-month double-blind core treatment period. Primary analysis will include all observed eGFR data in randomized patients, regardless of whether or not patients completed the treatment period (treatment policy strategy). Patients who prematurely and permanently discontinue study medication will be requested to obtain eGFR at 24 months. All efforts will be made to minimize the amount of missing data.

Missing data will be handled using methods similar to those of TKV. Additional details are included in Appendix J.

A secondary analysis will estimate the effect of venglustat while patients are still on treatment.

11.4.2.2 Analyses of secondary efficacy endpoints

11.4.2.2.1 Stage 1: Annualized rate of change in eGFR

In Stage 1, the annualized rate of change in eGFR (CKD-EPI equation) is a secondary efficacy endpoint.

The analysis of eGFR in Stage 1 will include all data from Stage 1 available at the cut-off date (ie, including data reported up to Month 24, if any). The cut-off date will be defined as the date all patients from Stage 1 have completed the Month 18 visit (or have discontinued the study).

The analysis of eGFR in Stage 1 will be identical to those of Stage 2 (see Section 11.4.2.1.2)

11.4.2.2.2 Stage 1: Change in pain (BPI- Item 3) from baseline to 18 months

In Stage 1, change in pain from baseline to 18 months is a secondary efficacy endpoint. Pain score will be based on BPI Item 3, assessed from the daily symptom diary.

Daily diaries scores will be averaged over 7 consecutive assessments prior to the baseline, Month 3 and Month 12 visit and over the 14 consecutive days prior to the planned Month 18 visit. At least 50% of the days in the observation period (ie, 4 or more of the 7 days for baseline, Month 3 and Month 12; 7 or more of the 14 days for Month 18) are required to calculate the average score on-missing data.

Change in pain from baseline will be analyzed using a mixed effect model with repeated measures (MMRM). The model will include the fixed categorical effects of treatment (venglustat 15 mg,

venglustat 8 mg, or placebo), Mayo Imaging Classification (as per randomization stratification factor: Class 1C versus 1D versus 1E), time point (Month 3, Month 12, Month 18), treatment-by-time point interaction, randomization strata-by-time point interaction as well as the continuous fixed covariates of baseline and the baseline-by-time point interaction.

This model will be run using SAS Mixed procedure with an unstructured correlation matrix to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method. Denominator degrees of freedom will be estimated using Kenward-Roger approximation. This model will provide baseline adjusted least-squares means estimates at Month 18 for each treatment groups with their corresponding standard errors (SE) and 95% confidence intervals (CI). Within group mean change in pain will be obtained from the MMRM, using weights for each stratum (Mayo Class 1C, 1D and 1E) equal to the overall proportion of patients in each stratum in the Stage 1 ITT population (ie, “population weight”).

Overall effect of venglustat will be assessed using a Multiple Comparison Procedure similar to those of the primary endpoint (see Section 11.4.2.1). In addition, p values for the comparison of each dose of venglustat versus placebo will be presented for descriptive purpose.

11.4.2.2.3 Stage 1: Change in fatigue (BFI- Item 3) from baseline to 18 months

In Stage 1, change in fatigue from baseline to 18 months is a secondary efficacy endpoint. Fatigue score will be based on BFI Item 3, assessed from the daily symptom diary.

Change in fatigue will be analyzed using the same method as change in pain.

11.4.2.2.4 Stage 2: Annualized rate of change in TKV

In Stage 2, the annualized rate of change in TKV is a secondary efficacy endpoint.

The analysis of TKV in Stage 2 will combine all data from Stage 1 and Stage 2 available from baseline to the end of the double-blind core treatment period.

The analysis of TKV in Stage 2 will be identical to those of Stage 1 (see Section 11.4.2.1.1).

11.4.2.2.5 Stage 2: Change in pain (BPI- Item 3) from baseline to 24 months

In Stage 2, change in pain from baseline to 24 months is a secondary efficacy endpoint. Pain score will be based on BPI Item 3, assessed from the daily symptom diary.

Change in pain in Stage 2 will be analyzed using the same method as change in pain in Stage 1, with the exception that an additional time-point at Month 24 will be included.

11.4.2.2.6 Stage 2: Change in fatigue (BFI- Item 3) from baseline to 24 months

In Stage 2, change in fatigue from baseline to 24 months is a secondary efficacy endpoint. Fatigue score will be based on BFI Item 3, assessed from the daily symptom diary.

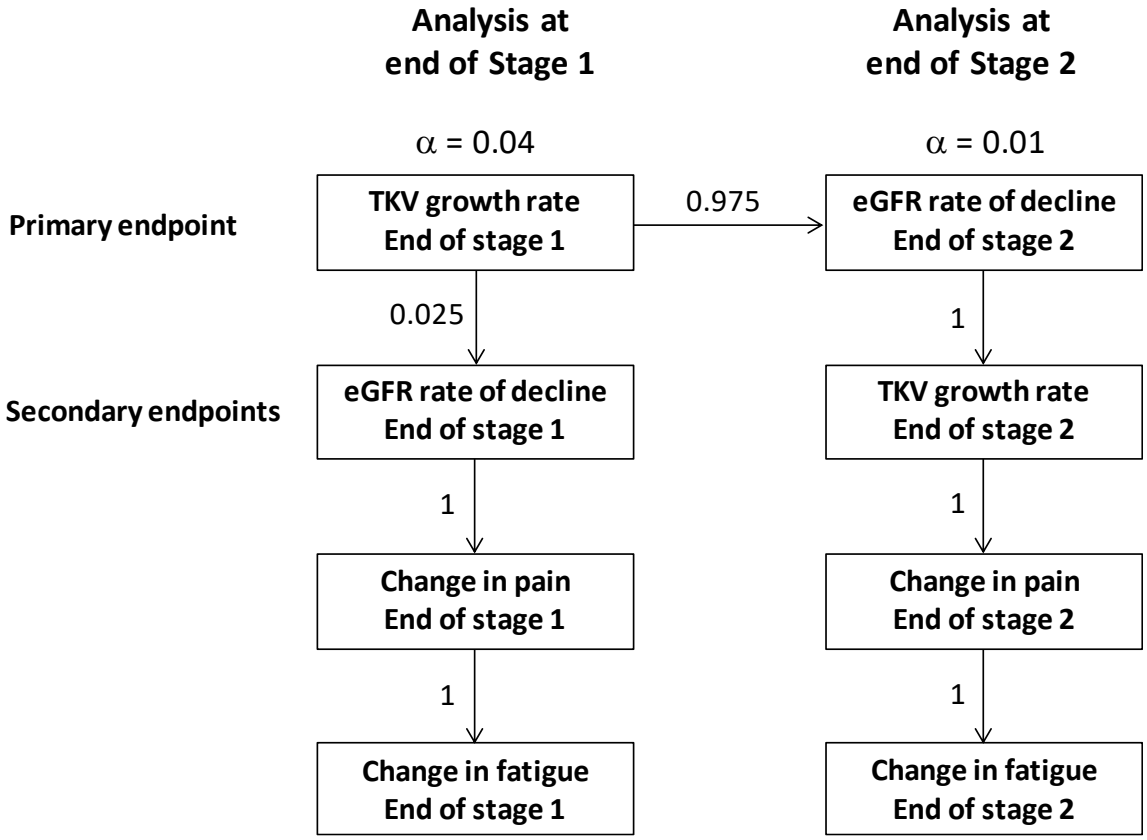
Change in fatigue in Stage 2 will be analyzed using the same method as change in fatigue in Stage 1, with the exception that an additional time-point at Month 24 will be included.

11.4.2.3 Multiplicity considerations

A weighted Bonferroni-based closed test procedure will be used in order to control the Type I error rate for the entire study. This procedure will handle both multiplicity of endpoints (primary and secondary endpoints) and multiplicity of analysis (analysis at end of Stage 1 and analysis at end of Stage 2). Multiplicity of doses will be handled using the Multiple Comparison Procedure described in Section 11.4.2.1.1.

The statistical procedure is illustrated using a graphical approach (19) and is shown in Figure 3. This procedure will ensure a strong control of the overall Type-I error rate at the 0.05 level for the entire study. No further adjustments will be made for sensitivity analyses, secondary analyses or analyses of other secondary efficacy endpoints, for which p-values will be provided for descriptive purpose only. In addition, p-values for the comparison of each dose of venglustat versus placebo will be presented for descriptive purpose.

Figure 3 - Graphical illustration of the procedure for handling multiplicity



Note: Analysis at end of Stage 1 includes all data from Stage 1 available at the cut-off date (defined as the date all patients from Stage 1 have completed the Month 18 visit or have discontinued the study) including data reported up to Month 24, if any. Analysis at end of Stage 2 includes all data from Stage 1 and Stage 2 available from baseline to the end of the 24-month double-blind core treatment period. Analysis of each endpoint is based on a Multiple Comparison Procedure.

11.4.2.4 Secondary analysis including patients from Stage 2 with eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening

A secondary analysis of eGFR will include the following patients:

- Patients from Stage 1 randomized to placebo or to the selected dose of venglustat (N=160)
- Patients from Stage 2 with eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening (N=320)
- Patients from Stage 2 with eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening (N=80)

The purpose of this secondary analysis will be to make model-based inferences about the dependence of the treatment effect on baseline eGFR.

A linear mixed effect model will be fitted to the eGFR, which will include fix effects of treatment (venglustat or placebo), Mayo Imaging Classification (as per randomization stratification factor: Class 1C versus 1D versus 1E), eGFR at screening (as a continuous variable), time (as a continuous variable), treatment * time interaction, Mayo Imaging Classification * time interaction, eGFR at screening * time interaction, as well as the treatment * eGFR at screening * time interaction. The model will also include random intercept and slope.

Mean eGFR slopes within each treatment group (venglustat or placebo), as well as the difference in eGFR slopes, will be estimated for the following patient categories:

- Patients with eGFR at screening of 30 to 44.9 mL/min/1.73 m^2
- Patients with eGFR at screening of 45 to 59.9 mL/min/1.73 m^2
- Patients with eGFR at screening of 60 to 74.9 mL/min/1.73 m^2
- Patients with eGFR at screening of 75 to 89.9 mL/min/1.73 m^2

Estimates within each category will be calculated from the linear mixed effect model, using the center of each category as eGFR at screening in the model. Difference in slopes will be presented with 80% CI.

11.4.3 Analyses of safety data

The observation period will be divided into 4 periods:

- The pretreatment period is defined as the time from the signed informed consent date up to the day prior to the first double-blind IMP administration.

- The on-treatment period is defined as the time from the first administration of the IMP to the last administration of the IMP +1, including any temporary treatment discontinuation period, if any.
- The residual treatment period is defined as the time from the day after the last IMP administration plus 30 days or up to the first visit in the long-term extension study, whichever comes earlier:
  - The treatment-emergent period will include both the on-treatment and the residual treatment periods.
- The post-treatment period is defined as the period of time starting the day after the end of the TEAE period up to the end of the study.

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

The baseline value is defined generally as the last available value before first IMP administration.

The following definitions will be applied to laboratory parameters, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG.
- Potentially clinically significant abnormality criteria will determine which patients had at least 1 PCSA during the treatment-emergent period, taking into account all evaluations performed during the treatment emergent period, including unscheduled or repeated evaluations, local and central evaluations. The number of all such patients will be the numerator for the treatment emergent period PCSA percentage.

11.4.3.1 Adverse events

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The AEs will be classified into predefined standard categories according to chronological criteria:

- Pretreatment AEs: AEs that occurred or worsened during the pre-treatment period.
- Treatment emergent AEs: AEs that occurred or worsened during the treatment-emergent period.
- Post-treatment AEs: AEs that occurred or worsened during the post-treatment period.

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, and the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Death:

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (treatment emergent period, on-study) summarized on the safety population by treatment received.
- Death in nonrandomized patients or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC and PT.

11.4.3.2 Laboratory data and vital signs

The summary statistics (including mean, standard deviation, median, Q1, Q3, minimum, and maximum) of all laboratory variables and all vital signs parameters (raw data and changes from baseline) will be calculated for each visit, last and worst value assessed during the treatment period, and presented by treatment group.

The incidence of PCSAs at any time during the treatment emergent period will be summarized by treatment group whatever the baseline level and/or according to the following baseline categories:

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

For laboratory parameters for which PCSA criterion is not defined, similar table(s) using the normal range could be provided.

Liver tests

The liver function tests, namely ALT, AST, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure for each treatment group.

A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

The normalization (to ≤1 x ULN or return to baseline if baseline > ULN) of elevated liver function tests will be summarized by categories of elevation (3 x ULN, 5 x ULN, 10 x ULN, 20 x ULN for ALT and AST; 1.5 x ULN for alkaline phosphatase; and 1.5 x ULN and 2 x ULN for total bilirubin), with the following categories of normalization: return to baseline PCSA status before last IMP dose, return to baseline PCSA status after last IMP dose, never returned to baseline PCSA status, no assessment after elevation. Note that a patient will be counted only under the maximum elevation category.

The incidence of liver-related AEs will be summarized by treatment group. The selection of preferred terms will be based on standardized MedDRA query (SMQ) Hepatic disorder. Time to liver-related treatment discontinuation and time to liver death may also be provided based on hepatic disorder SMQ.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

Each PD variable will be summarized and compared between venglustat 15 mg, venglustat 8 mg, and placebo using descriptive statistics at each time point, including assessment of observed values and percent change from baseline.

For PK analysis: Trough concentrations (pre-dose) along with other single time point plasma concentration data will be summarized by dose and visit. The data will be reported for individual patients and summarized using descriptive statistics. Plasma concentrations data will be reported separately for Stage 1 and Stage 2.

Exploratory metabolite analysis may be performed on selected plasma samples. If data permit, PK parameters will be estimated for metabolites using noncompartmental methods. These will be summarized using descriptive statistics.

Plasma venglustat concentration data might be used for population PK modeling if considered necessary and the results of population PK modeling will be reported separately from the study report. The population PK analyses will characterize the inter- and intra- subject variability in PK parameters and evaluate the effect of covariates such as, but not limited to, demographics (eg, age, gender, body weight, race), and disease status on oral clearance and volume.

Exploratory PK-PD analyses may be performed as deemed necessary to evaluate exposure-response relationships (in particular TKV, eGFR and safety parameters).

11.4.5 Analyses of patient reported outcomes (health-related quality of life/health economics variables)

Both total scores and subscale scores of PROs will be calculated. Each PRO will be scored according to their scoring guidelines, including handling the missing items. The daily diaries baseline scores and thereafter the average score over 14 days prior to the quarterly visits will be calculated and correlations between these scores and their respected questionnaires will be calculated. The calculation of a diary score requires least 50% of non-missing data (ie, 4 or more of the 7 days for baseline, Month 3 and Month 12; 7 or more of the 14 days for Month 18 and Month 24) (21, 22)

Change from baseline to Month 18 and Month 24 in pain and fatigue is described in Section 11.4.2.2. Change from baseline to Month 18 and Month 24 in other PROs' total score and their subscales will be analyzed using an MMRM similar to pain and fatigue.

11.5 INTERIM AND FINAL ANALYSIS

11.5.1 Dose selection safety review

The dose selection safety review will be performed when the first 150 patients from Stage 1 have completed 1 month of treatment (or have prematurely discontinued).

The dose selection safety review will be performed by the DMC. An unblinded safety report will be prepared by the external independent DMC statistician and will be reviewed by the DMC. Safety data will include AEs (including SAEs and AEs leading to permanent treatment discontinuation), clinical laboratory evaluation, ECG, physical and ophthalmological examination, and BDI-II data.

Based on this safety review, the DMC will select the venglustat dose for Stage 2 (8 mg or 15 mg). The selected dose will be the highest dose determined to be safe and well tolerated.

11.5.2 Interim futility analysis

An interim analysis for futility will be performed when all patients from Stage 1 have completed the first 9 months of treatment and approximately 30% have completed 18 months of treatment with TKV available (or have prematurely discontinued).

The interim analysis will be performed by the external independent statistician and will be reviewed under the supervision of the DMC. The interim analysis will primarily focus on the primary endpoint in Stage 1 (annualized rate of change in TKV) and stopping rules will be based on this primary endpoint. Data monitoring committee will also review secondary efficacy endpoint (annualized rate of change in eGFR) and safety data (AEs, laboratory data, vital signs) available at the time of the interim analysis.

Futility may be declared if the one-sided p-value of the primary endpoint at the interim analysis is >0.30. The one-sided p-value will be determined from the Multiple Comparison Procedure described in Section 11.4.2.1.1. Based on simulations, it is expected that futility may be declared if the relative reduction versus placebo in TKV growth rate estimated at the interim analysis is approximately less than 15%. Probability to declare futility under different scenarios is presented in Appendix J.

Of note, the futility rule is provided as a guideline for the DMC but should not be considered as a strict stopping rule. In case the one-sided p-value observed at the interim analysis is close to the pre-specified threshold, the DMC will review the totality of data available at the time of interim analysis, including safety data (AEs, laboratory data, vital signs), and based on these data, may decide to overrule the futility rule.

In order to protect the global type one error in case the decision is taken to overrule the futility rule, nonbinding futility rules will be used for determination of alpha.

11.5.3 Two-step final analysis

The analysis will be conducted in two steps:

- First step: conducted when all patients from Stage 1 have been randomized and have completed the Month 18 visit (or have discontinued the study). This analysis will be conducted after a partial database lock. First step analysis in Stage 1 will include all collected and validated data from Stage 1 population, up to the cut-off date (including data reported up to Month 24 visit, if any).
- Second step: conducted when all patients from Stage 2 have completed the study and will consist of the final analysis of the combined Stage 1 and Stage 2 study. This analysis will be conducted after the final database lock.

The results of the first step analysis will not be used to change the conduct of the ongoing study in any aspect. This first analysis will be used for the submission of the registration dossier to health authorities accepting TKV growth rate change as a surrogate endpoint reasonably likely to predict changes in eGFR slope.

First step analysis will be conducted before all patients from Stage 1 have completed the 24-month treatment period. However, treatment allocated to each individual patient will not be released to anyone who is directly involved in the conduct of Stage 1 of the study until Stage 1 is fully completed.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and Subinvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practice (GCP), all applicable laws, rules and regulations.

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

12.2 INFORMED CONSENT

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

Prior to a patient’s participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient, and by the person who conducted the informed consent discussion. A separate informed consent form will be used in Stage 1 and Stage 2 of the study. A copy of the signed and dated written informed consent form will be provided to the patient.

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

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix O.

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

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the health authorities (competent regulatory authority) and the appropriate IRB/IEC and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the chairman with IRB/IEC composition.

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

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

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. They should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the IB will be sent to the IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

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

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

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

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

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

13.2 RESPONSIBILITIES OF THE SPONSOR

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

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

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.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the eCRFs (eg, patient's medical file, appointment books, original laboratory records). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

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

It is the responsibility of the Investigator to ensure that the previous use of tolvaptan is documented (physician assessment, intolerant, unwilling or naïve patient with no access) and to maintain adequate and accurate eCRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All eCRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

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

Data are available within the system to the Sponsor as soon as they are entered in the eCRF.

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

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor trial master file.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

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

14.2 RECORD RETENTION IN STUDY SITES

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

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.

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

14.3 CONFIDENTIALITY

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

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

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

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

14.4 PROPERTY RIGHTS

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

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

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

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

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

14.5 DATA PROTECTION

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

Patient race or ethnicity (eg, "American Indian or Alaska Native, Asian, Black/Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported or Unknown") will be collected in this study if permitted by local regulations, because these data are required by several regulatory authorities (eg, on afro American population for FDA or on Japanese population for the PMDA in Japan).

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

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

14.6 INSURANCE COMPENSATION

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

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

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

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

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

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

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

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

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

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

14.8.1 By the Sponsor

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

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.

- Noncompliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients are included earlier than expected.
- If the study no longer meets the development needs of the compound or business needs of the company.

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

14.8.2 By the Investigator

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

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

14.9 CLINICAL TRIAL RESULTS

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

14.10 PUBLICATIONS AND COMMUNICATIONS

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

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within 12 months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

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

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

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

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

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

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

In case of substantial amendment to the clinical trial protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

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

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17 APPENDICES

Appendix A Contraceptive guidance and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:

   NOTE: Documentation can come from the review of patient'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 follicle stimulating hormone (FSH)/estradiol level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH/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 patients

- Male patients 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 study drug:
  - 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 6 for female patients).

- 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 patients:

Female patients 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 study drug as described in Table 6.

Table 6 - 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 patient.*

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 patients 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 study drug.

Male patients with partners of reproductive potential who become pregnant:

- The Investigator will attempt to collect pregnancy information on any female partner of a male study patient who becomes pregnant while participating in this study. This applies only to patients 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 patients who become pregnant:

- The Investigator will collect pregnancy information on any female patient, 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 patient's pregnancy.
- Patient will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on patient 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 10.4.3. While the Investigator is not obligated to actively seek this information in former study patients, he or she may learn of an SAE through spontaneous reporting.
- Any female patient who becomes pregnant while participating in the study will discontinue study treatment and will be withdrawn from the study.

Appendix B List of known CYP3A4 inducers/inhibitors

Please always check/confirm against the Prescribing Information/Summary of Product Characteristics and the most up-to-date information on the FDA site:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling

CYP3A4 inducers

Aminoglutethimide	Nevirapine
Bexarotene	Oxcarbazepine
Bosentan	Phenobarbital
Carbamazepine	Phenytoin
Dexamethasone	Primidone
Efavirenz	Rifabutin
Fosphenytoin	Rifampin
Griseofulvin	Rifapentine
Modafinil	St. John's wort
Nafcillin	

CYP3A4 inhibitors

Amiodarone	Imatinib
Amprenavir	Indinavir
Atazanavir	Isoniazid
Chloramphenicol	Itraconazole
Clarithromycin	Ketoconazole
Conivaptan	Lapatinib
Cyclosporine	Miconazole
Darunavir	Nefazodone
Dasatinib	Nelfinavir
Delavirdine	Posaconazole
Diltiazem	Ritonavir
Erythromycin	Quinupristin
Fluconazole	Saquinavir
Fluoxetine	Tamoxifen
Fluvoxamine	Telithromycin
Fosamprenavir	Verapamil
Grapefruit juice	Voriconazole

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

NEUTROPENIA

Neutrophils < 1500/mm³ or according to ethnic group

Repeat immediately a full blood count if value close to 1500/mm³

Neutrophils < 1500/mm³ confirmed with signs of infection	Neutrophils < 1500/mm³ confirmed with no signs of infection
1. **DISCONTINUE** Investigational Medicinal Product, hospitalization should be considered 2. **PERFORM** biological investigations for infection	1. **DISCONTINUE** Investigational Medicinal Product 2. **INVESTIGATE** for infection

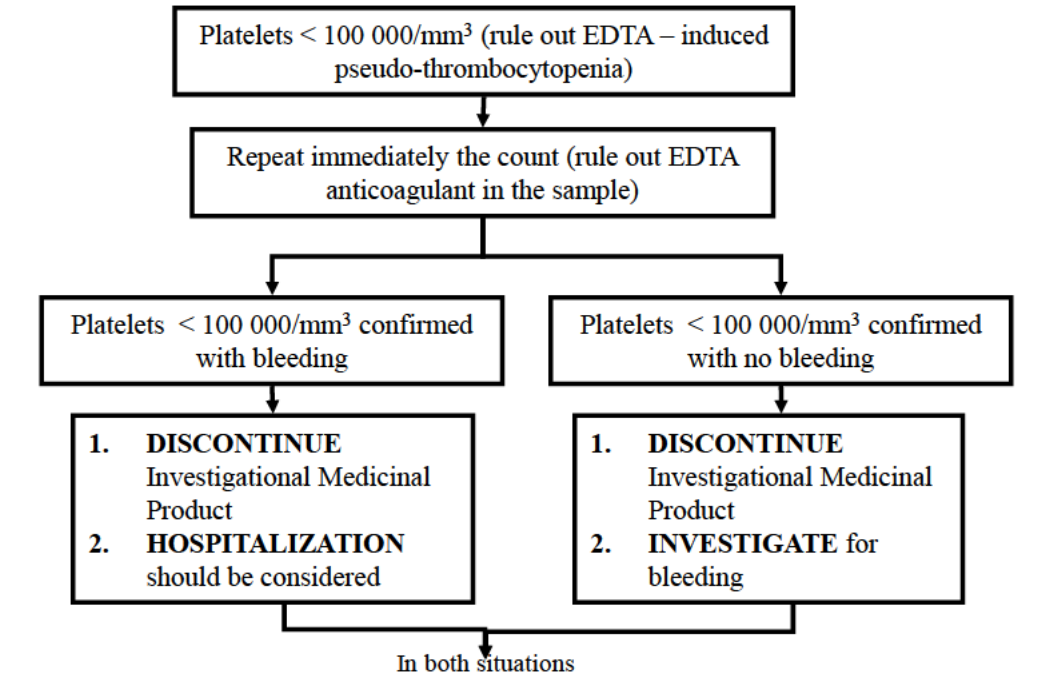
In both situations

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

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

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

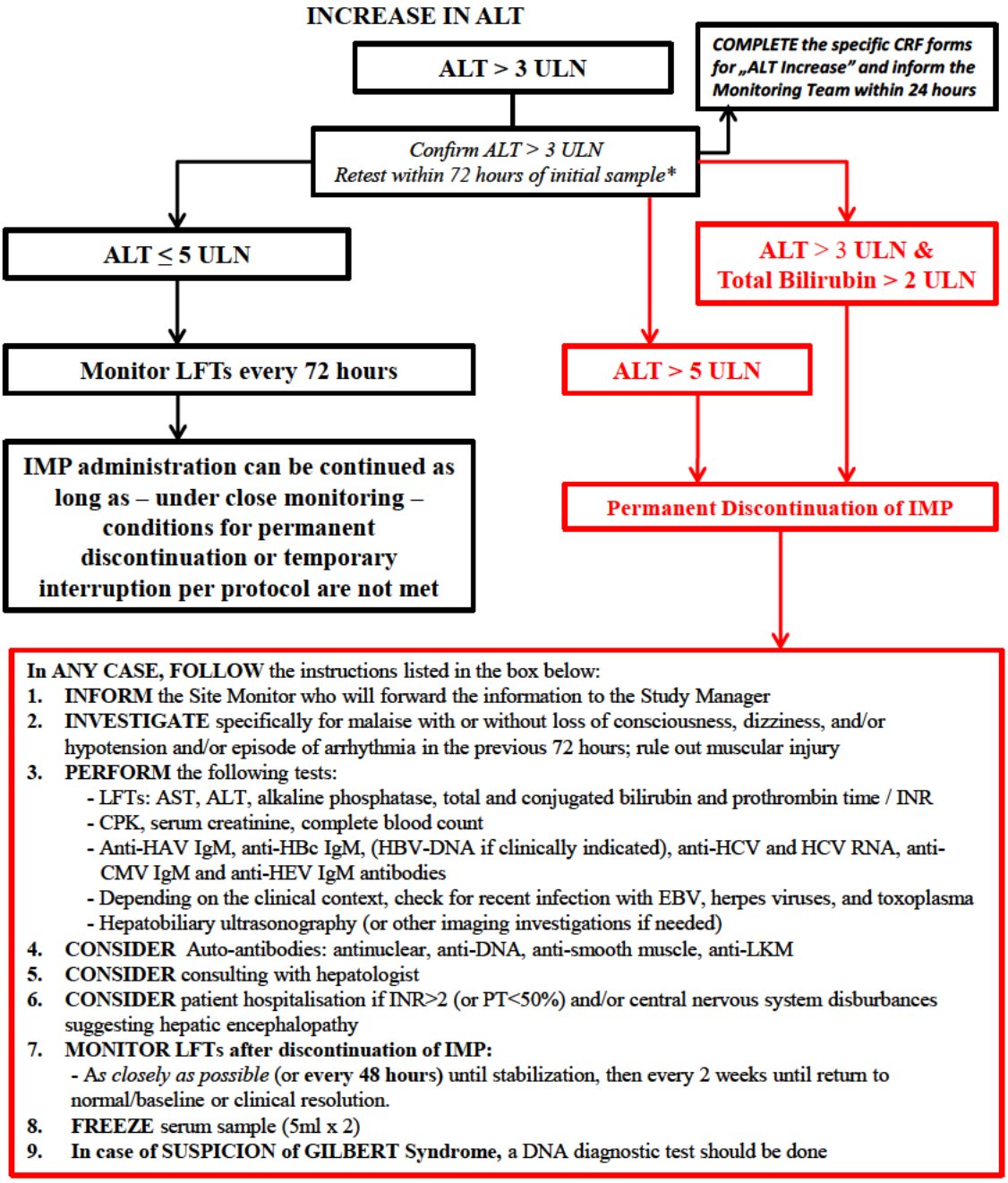
THROMBOCYTOPENIA



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

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

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.



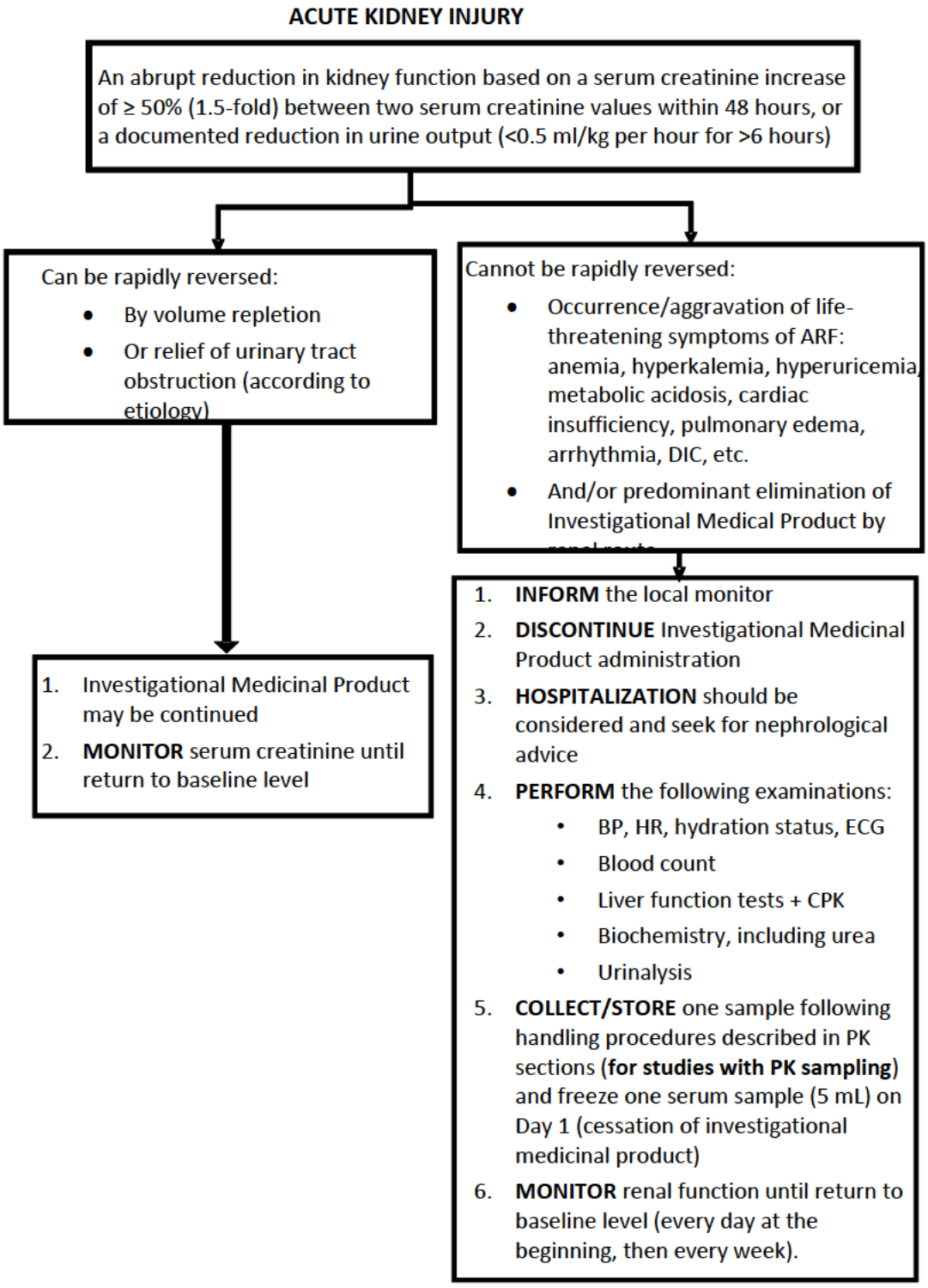
*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

"Baseline" refers to ALT sampled at the 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.

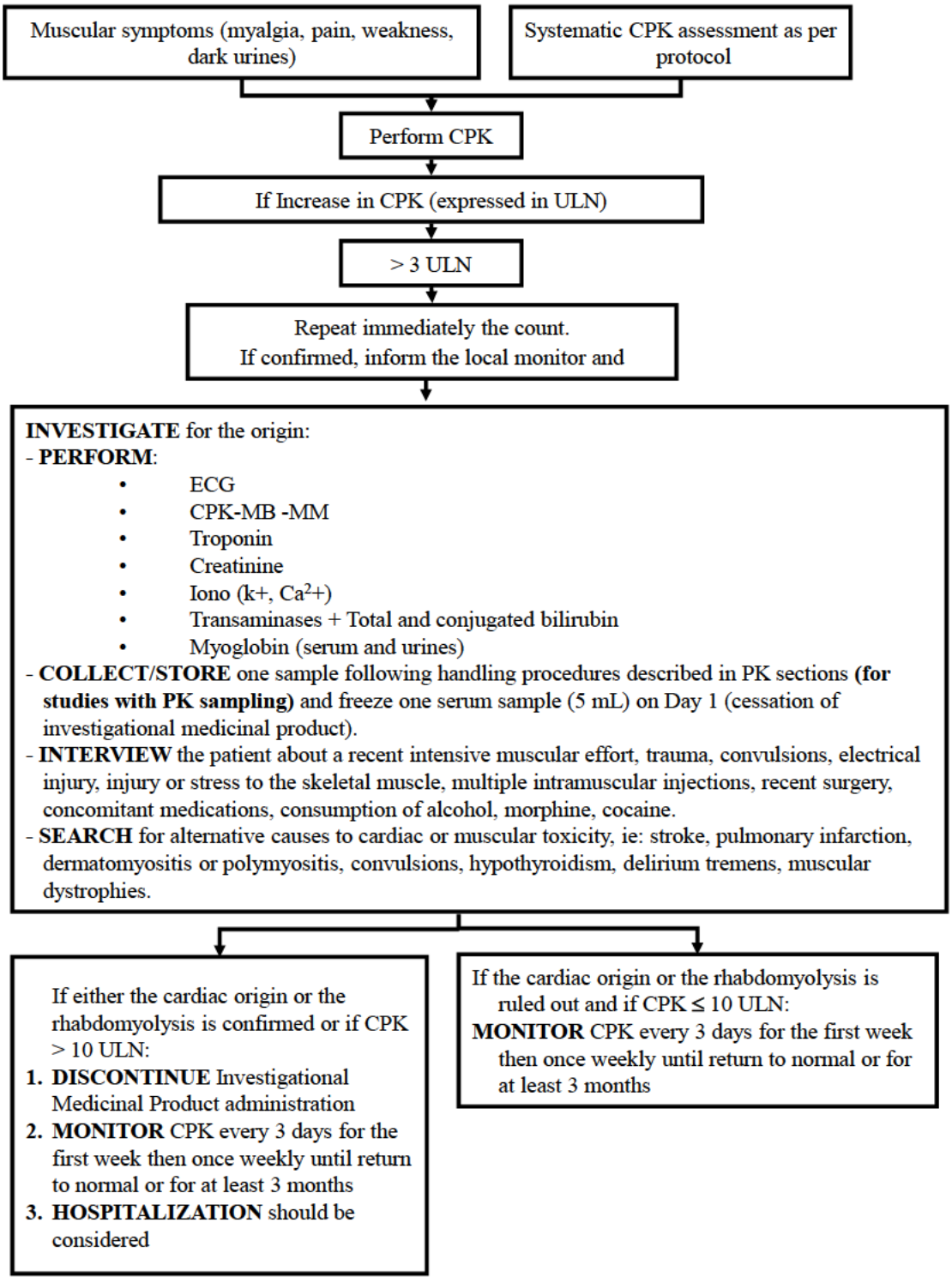
See Section 10.4 for guidance on safety reporting.

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



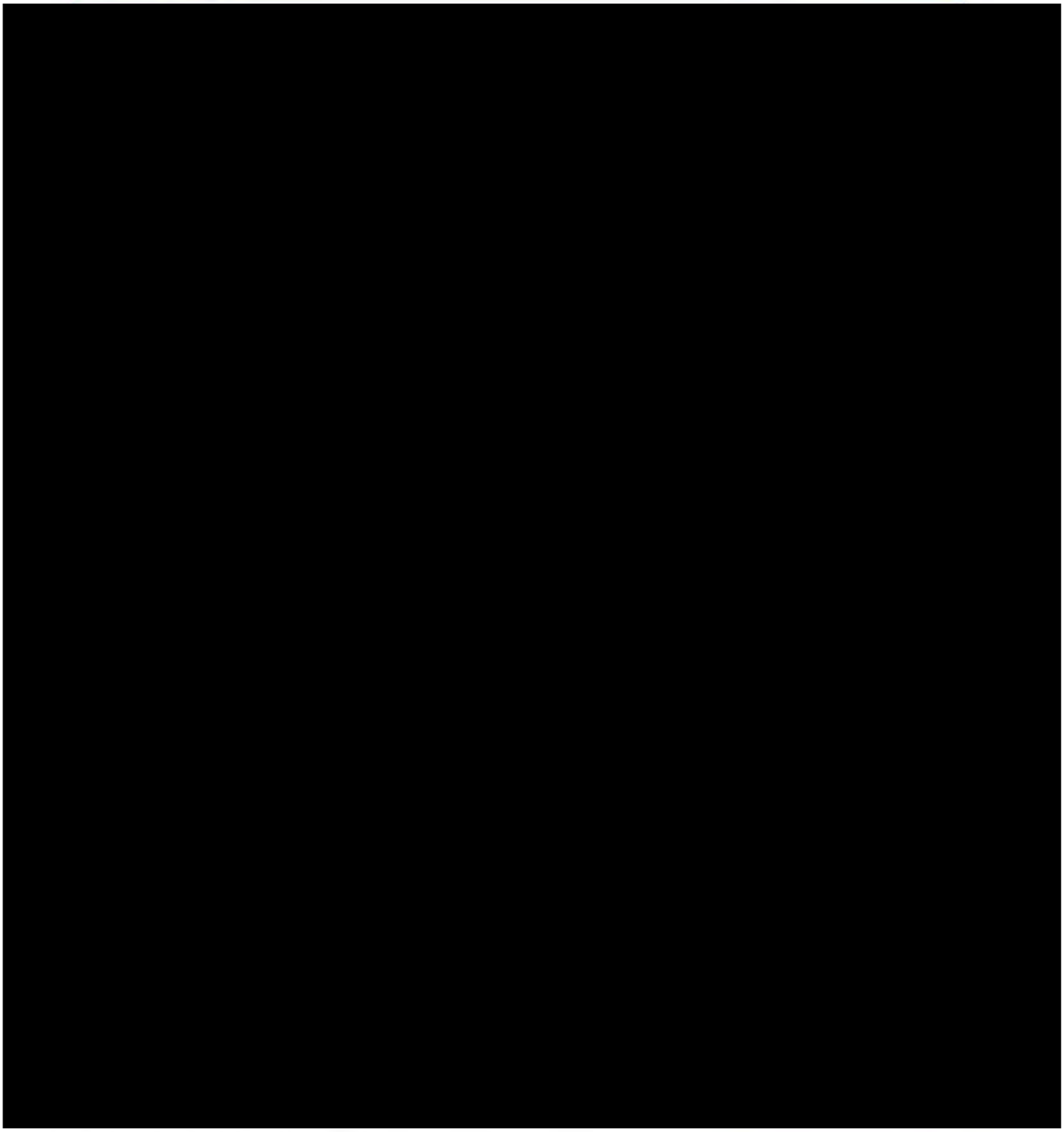
Acute kidney injury is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Section 10.4.2 is met.

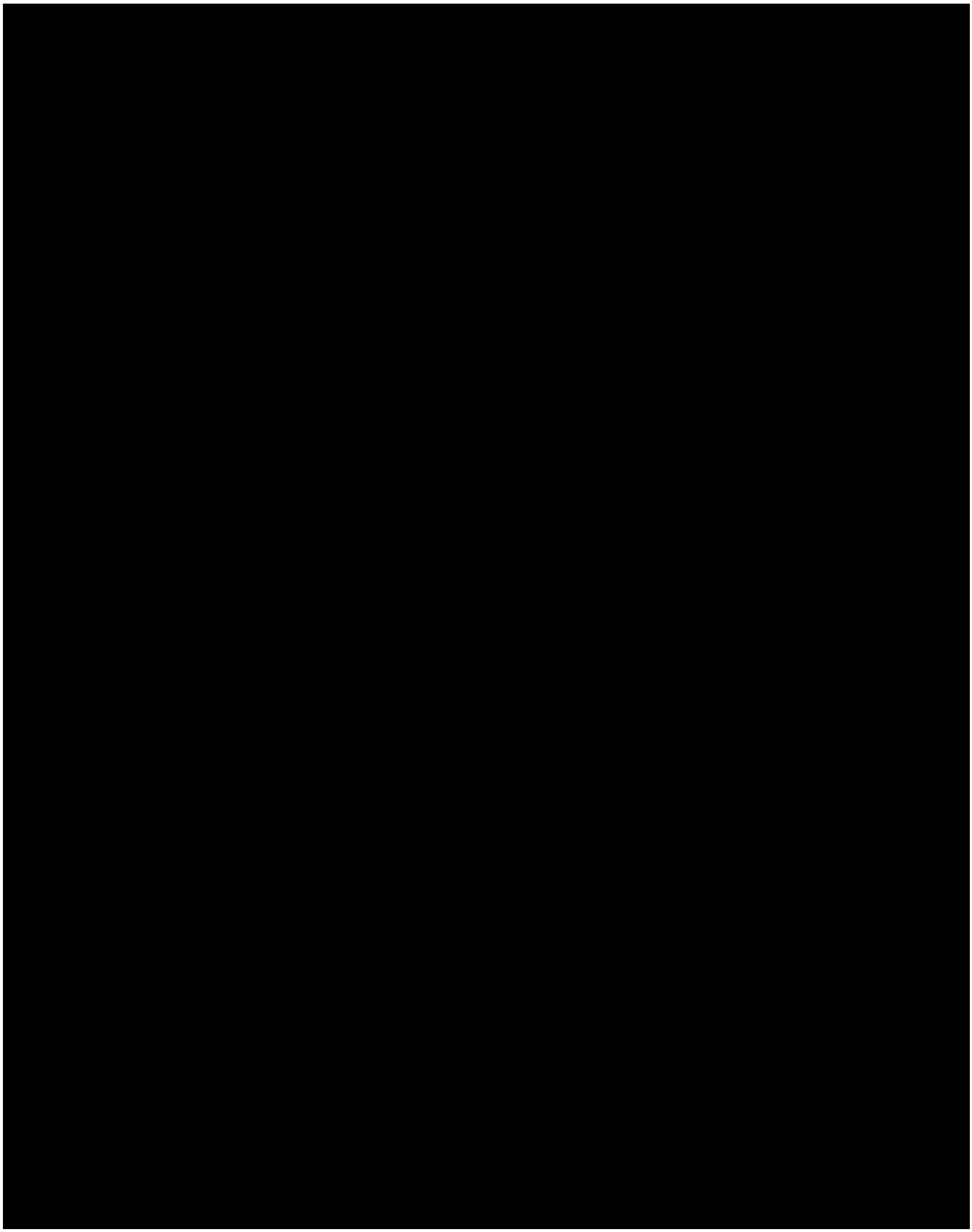
SUSPICION OF RHABDOMYOLYSIS



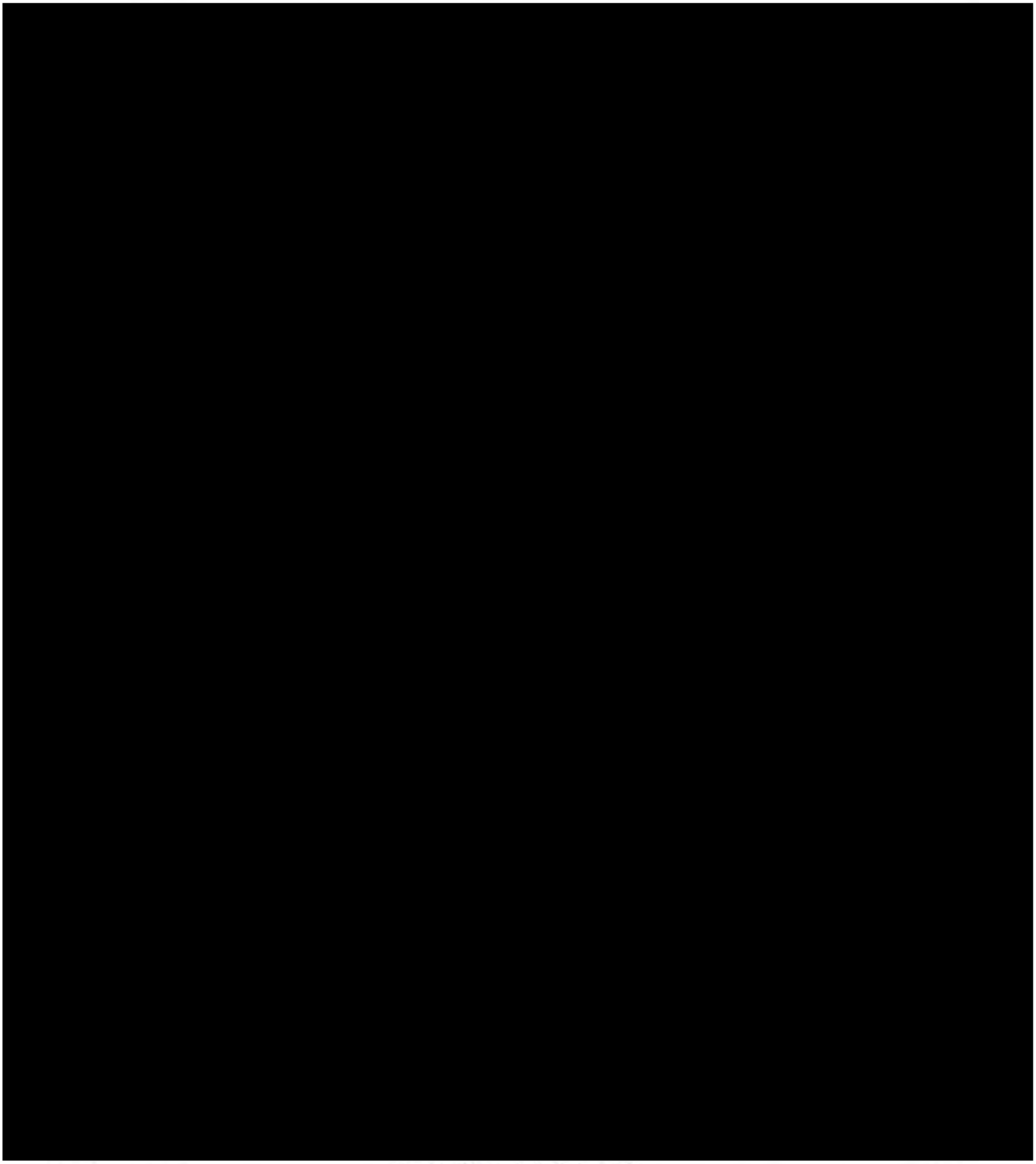
Suspicion of rhabdomyolysis is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in Section 10.4.2 is met.

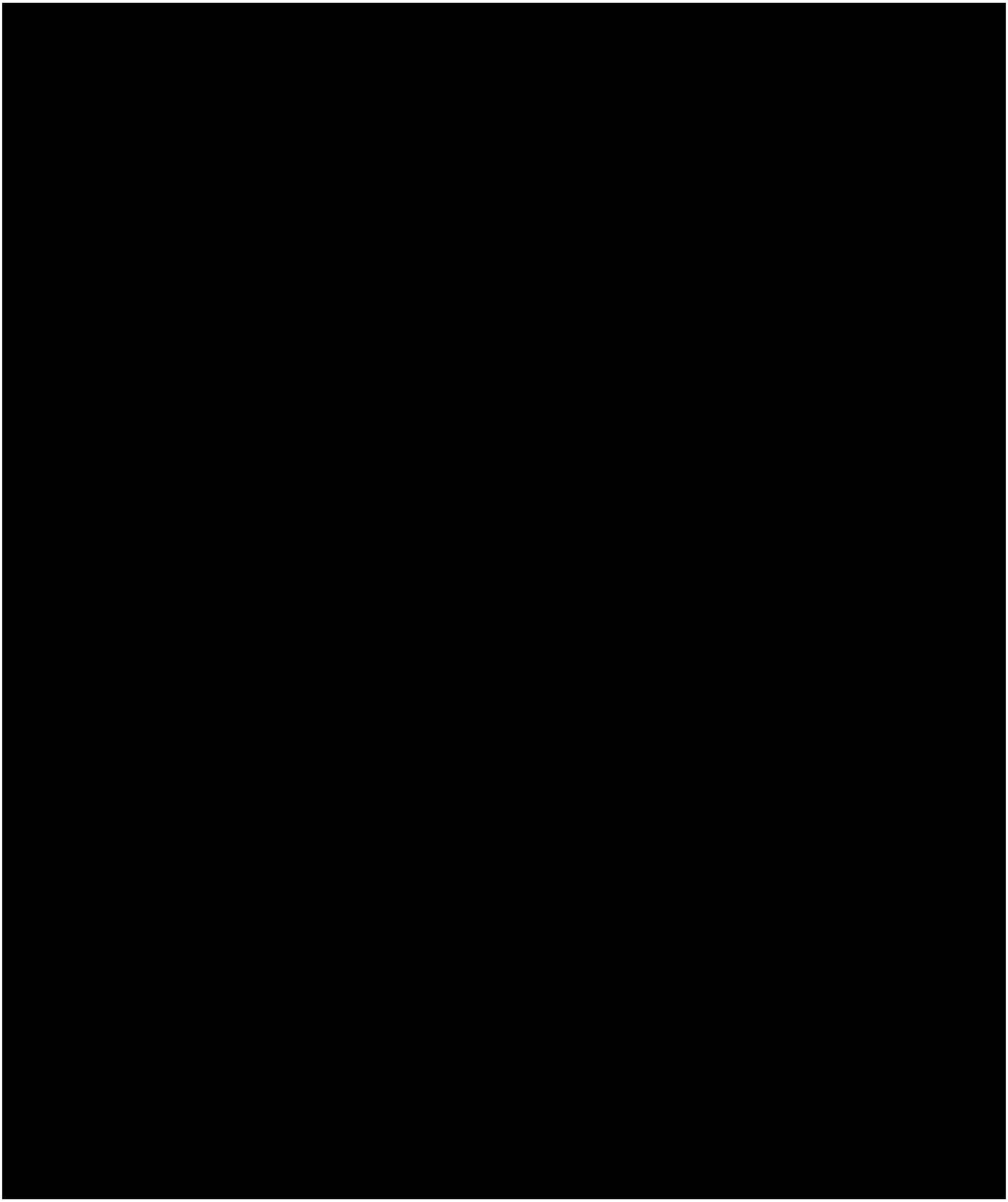
Appendix D Beck depression inventory-II



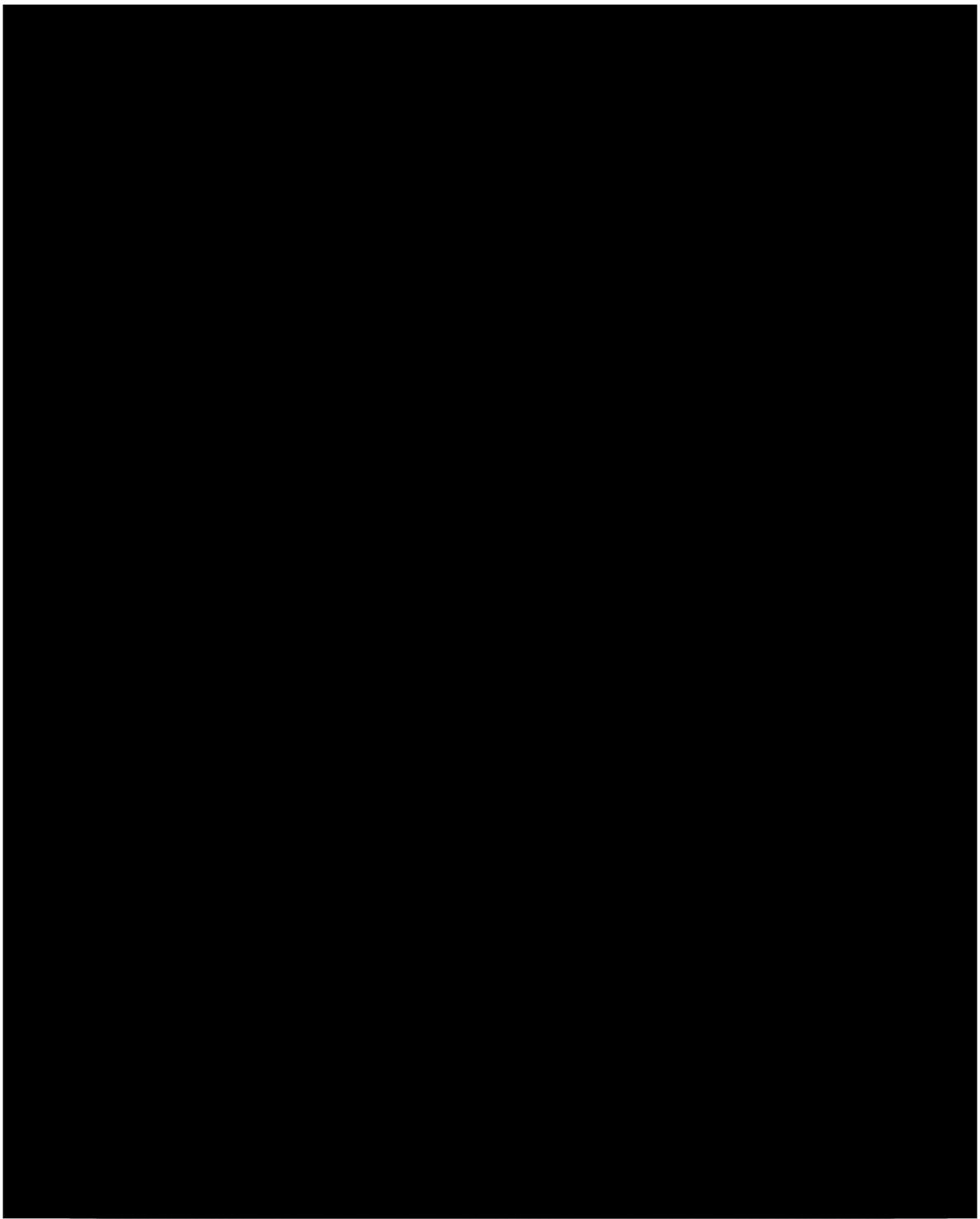


Appendix E Brief pain inventory (short form)





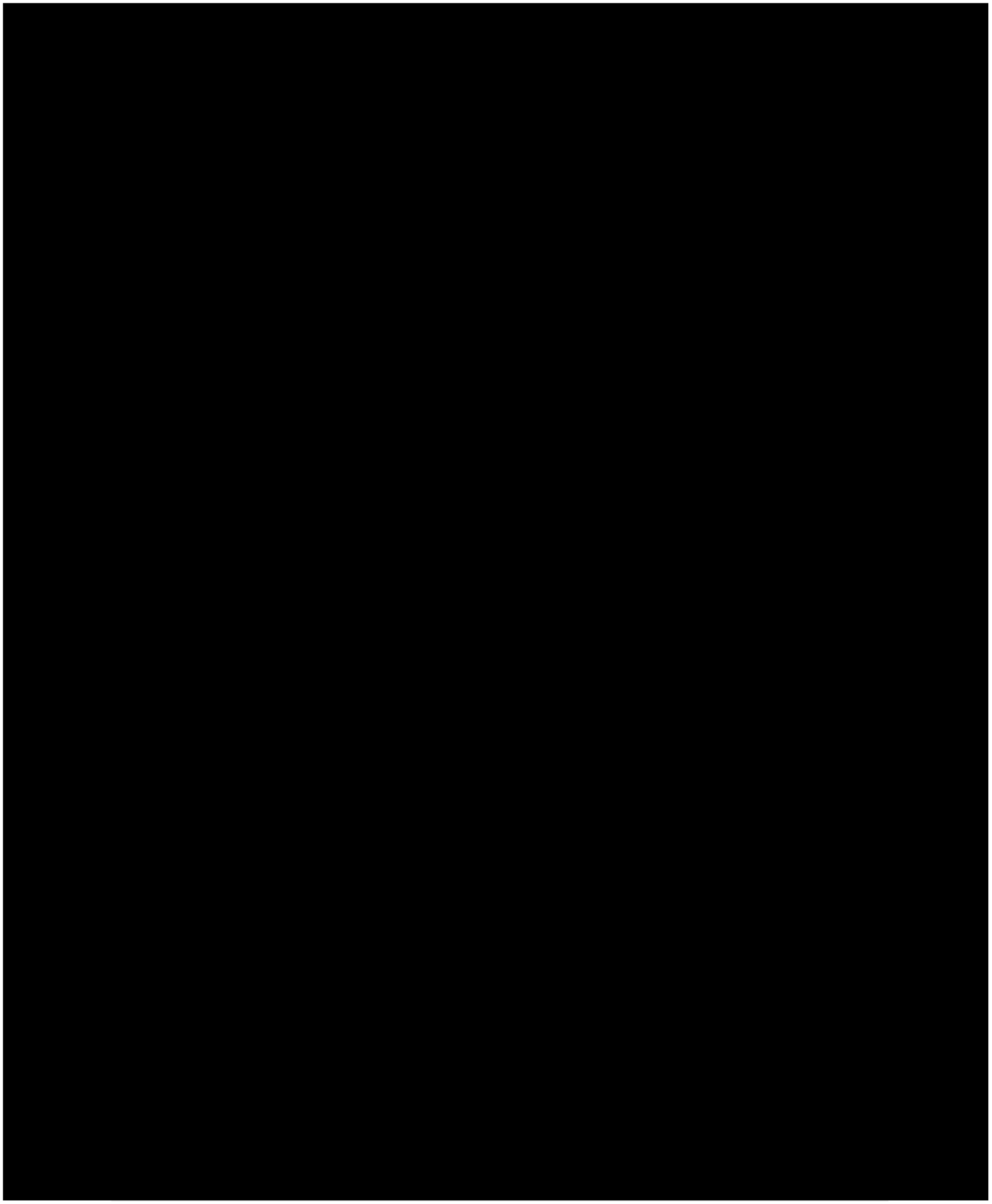
Appendix F Brief fatigue inventory



Appendix G Patient global impression of severity (PGIS)

Appendix H Patient global impression of change (PGIC)

Appendix I EuroQol (EQ-5D-5L)



Appendix J Statistical technical details

Operating characteristics of the study design

Operating characteristics were assessed through extensive simulations. All simulations used the following assumptions on design and parameters:

- Sample size of 80 patients per arm in Stage 1 (randomized 1:1:1 to placebo, venglustat 8 mg or venglustat 15 mg) and of 160 patients per arm in Stage 2 (randomized 1:1 to placebo or venglustat).
- TKV assessed at screening, 1 month, 9 months, and 18 months in Stage 1; at screening and 24 months in Stage 2.
- eGFR assessed at baseline, 1 month, 3 months, and then every 3 months, both in Stage 1 and Stage 2.
- Mean slope of $\log_{10}$(TKV) of 0.02764 (6.6%/year) in the placebo arm.
- Standard deviation for the residual error of TKV (on the $\log_{10}$ scale) of 0.02566 and standard deviation for the random effect of slope of 0.01477.
- Mean slope of eGFR of -3.66 mL/min/1.73 m² per year in the placebo arm.
- Standard deviation for the residual error of eGFR of 6.34 and standard deviation for the random effect of slope of 1.98.
- Correlation between $\log_{10}$(TKV) slope and eGFR slope of -0.35.
- Dropout rate of 10% at 2 years, assuming an exponential distribution for time to dropout.

Simulations were based on different scenarios regarding the true effect of venglustat on TKV and eGFR. Most scenarios assumed a 50% relative reduction in TKV growth rate and a 30% relative reduction in eGFR rate of decline for the venglustat 15 mg, and varying effect of venglustat 8 mg. They also assumed that the 15 mg dose was selected in Stage 2. These scenarios are presented in Table 7. Additional scenarios assuming that the 8 mg dose was selected in Stage 2 were considered and are presented in Table 8.

For each scenario, 10 000 trials were simulated. Each simulated trial was analyzed according to the procedure described in Section 11.4.2.

- An interim analysis was performed when all patients from Stage 1 had TKV at baseline, 1 month and 9 months and 30% of patients also had TKV at 18 months (or had discontinued). Futility was declared at the interim analysis if the one-sided p-value from Multiple Comparison Procedure was >0.30.
- If no futility was declared at interim analysis, the analysis at end of Stage 1 was performed when all patients from Stage 1 had TKV available up to 18 months (or have discontinued). It was also assumed that at the cut-off date, 50% of patients from Stage 1 had eGFR

available at 21 months and 30% had eGFR available at 24 months. According to the procedure for handling multiplicity of test (see Figure 3), the following rules applied:

- A significant effect on TKV at end of Stage 1 was declared if 2 * one-sided p-value from Multiple Comparison Procedure was <0.04.
- If a significant effect on TKV was declared, a significant effect on eGFR at end of Stage 1 was declared if 2 * one-sided p-value from Multiple Comparison Procedure was <0.001.

- Analysis at end of Stage 2 was performed when all patients from Stage 1 and Stage 2 had TKV available up to 18 months and eGFR available up to 24 months (or have discontinued). According to the procedure for handling multiplicity of test, the following rules applied:
  - If a significant effect on TKV was declared at end of Stage 1: A significant effect on eGFR at end of Stage 2 was declared if 2 * one-sided p-value from Multiple Comparison Procedure was <0.049.
  - If no significant effect on TKV was declared at end of Stage 1: A significant effect on eGFR at end of Stage 2 was declared if 2 * one-sided p-value from Multiple Comparison Procedure was <0.01.

The probabilities to detect an effect on TKV and eGFR are presented in Table 7 assuming the 15 mg dose was selected in Stage 2. Under the expected scenario that venglustat 15 mg would provide 50% reduction on TKV growth rate and 30% reduction in eGFR rate of decline, and that the venglustat 8 mg would provide a slightly reduced efficacy of 40% reduction in TKV and 25% reduction in eGFR (scenario 2), the study would have approximately 89% power to detect an effect on TKV and 87% power to detect an effect on eGFR. It is to be noted that thanks to the Multiple Comparison Procedure, the power on TKV and eGFR would remain >80% whatever the efficacy of venglustat 8 mg.

Table 7 - Operating characteristics of the study design assuming the dose 15 mg is selected for Stage 2

Scenario	Probability to detect an effect on TKV at the end of Stage 1	Probability to detect an effect on eGFR at the end of Stage 1	Probability to detect an effect on eGFR at end of Stage 1 and/or end of Stage 2	Probability to declare futility at interim analysis
Scenario 1 15 mg: 50% on TKV, 30% on eGFR 8 mg: 50% on TKV, 30% on eGFR	92.6%	6.4%	90.1%	2.3%
Scenario 2 15 mg: 50% on TKV, 30% on eGFR 8 mg: 40% on TKV, 25% on eGFR	89.0%	5.1%	87.0%	3.1%
Scenario 3 15 mg: 50% on TKV, 30% on eGFR 8 mg: 30% on TKV, 20% on eGFR	86.0%	4.4%	84.6%	3.7%

Scenario	Probability to detect an effect on TKV at the end of Stage 1	Probability to detect an effect on eGFR at the end of Stage 1	Probability to detect an effect on eGFR at end of Stage 1 and/or end of Stage 2	Probability to declare futility at interim analysis
Scenario 4				
15 mg: 50% on TKV, 30% on eGFR 8 mg: 20% on TKV, 15% on eGFR	84.6%	3.9%	83.2%	4.2%
Scenario 5				
15 mg: 50% on TKV, 30% on eGFR 8 mg: 10% on TKV, 10% on eGFR	85.1%	3.7%	83.0%	4.3%
Scenario 6				
15 mg: 70% on TKV, 50% on eGFR 8 mg: 50% on TKV, 30% on eGFR	99.3%	26.4%	99.7%	0.3%

eGFR = estimated glomerular filtration rate; TKV = total kidney volume.

It is expected that venglustat 15 mg would be well tolerated in Stage 1 and therefore selected in Stage 2. However, in case of safety concern, the DMC may recommend the use of venglustat 8 mg for Stage 2. The probabilities to detect an effect on TKV and eGFR in such a case are presented in Table 8. Assuming that venglustat 8 mg would provide 50% reduction on TKV growth rate and 30% reduction in eGFR rate of decline, the power to detect an effect on TKV and eGFR would be >80%.

Table 8 - Operating characteristics of the study design assuming the dose 8 mg is selected for Stage 2

Scenario	Probability to detect an effect on TKV at the end of Stage 1	Probability to detect an effect on eGFR at the end of Stage 1	Probability to detect an effect on eGFR at end of Stage 1 and/or end of Stage 2	Probability to declare futility at interim analysis
Scenario 7				
15 mg: 50% on TKV, 30% on eGFR 8 mg: 50% on TKV, 30% on eGFR	92.6%	6.4%	80.1%	2.3%
Scenario 8				
15 mg: 70% on TKV, 50% on eGFR 8 mg: 50% on TKV, 30% on eGFR	99.3%	26.4%	98.3%	0.3%

eGFR = estimated glomerular filtration rate; TKV = total kidney volume.

Multiple imputation of missing data for TKV - Primary analysis

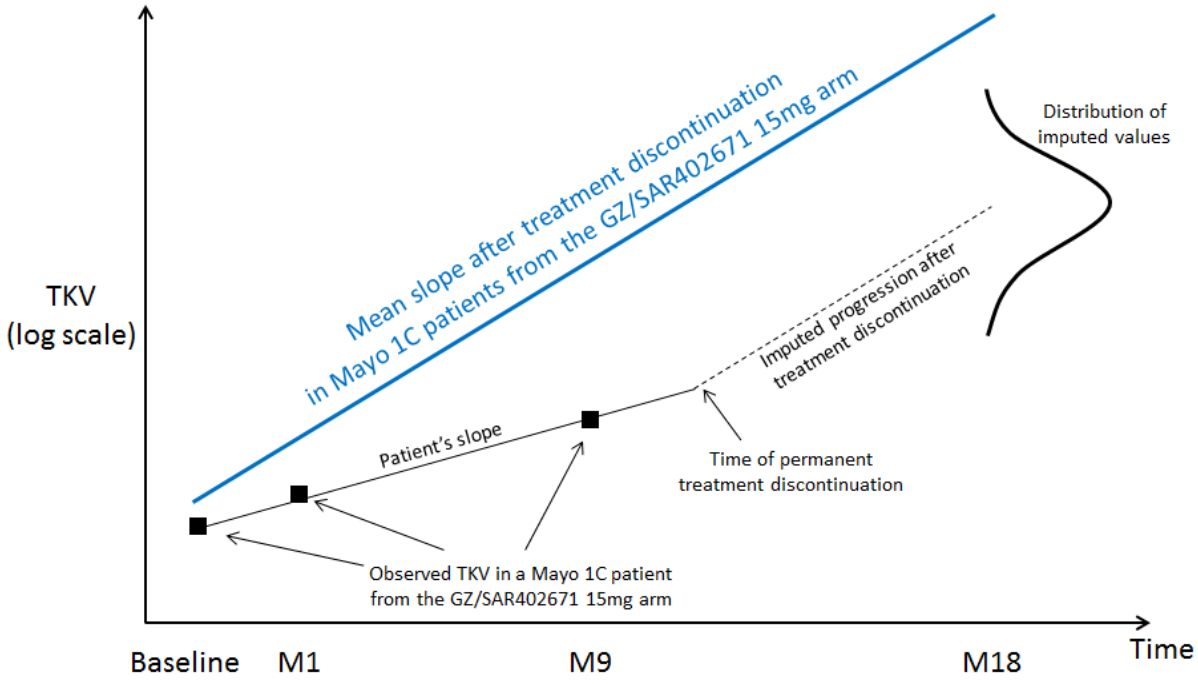
In the primary analysis, missing data will be imputed using a linear mixed effect model that will include separate slopes of $\log_{10}$(TKV) during the on-treatment period and after permanent treatment discontinuation, for each treatment arm (venglustat 15 mg, venglustat 8 mg or placebo). The imputation model will also include adjustment for Mayo class (1C versus 1D versus 1E) as well as random intercept and slope.

Imputations will be based on the following assumptions:

- Patients with missing data during the on-treatment period will have their data imputed based on the mean slope estimated during the on-treatment period in patients from the same treatment arm.
- Patients with missing data after permanent treatment discontinuation will have their data imputed based on the mean slope estimated during the post-treatment period in patients from the same treatment arm, who discontinued the treatment but had TKV data available during the post-treatment period.

In both cases, measurements history of patients with missing data will be accounted for in the imputation process, via within-patients intercept and slope. Imputation model will also be adjusted for Mayo class. Figure 4 provides a schematic representation of imputation of missing data for a Mayo 1C patient randomized to venglustat 15 mg who would permanently discontinue treatment at 12 months, with no TKV available at 18 months. It will be assumed that from 12 to 18 months, TKV would have increased at the same rate as other Mayo 1C patients in the venglustat 15 mg arm who discontinued treatment but had TKV measured after treatment discontinuation. The on-treatment period will be defined as the period from the first IMP administration to the last IMP administration, regardless of temporary treatment discontinuations. The post-treatment period will be defined as the period from last IMP administration +1 day.

Figure 4 - Schematic representation of imputation of missing data - primary analysis



Uncertainty in the imputation model's parameters will be taken into account using a Bayesian approach. A noninformative prior distribution will be used for the parameters of the model. For fixed effects parameters, a normal distribution with mean of 0 and standard deviation of 1000 will

be used as noninformative prior distribution. For variance parameters, the following estimates were obtained from the CRISP and HALT-PKD studies:

- Variance for the random intercept: 0.017647.
- Variance for the random slopes: 0.000218.
- Covariance between random intercept and slopes: 0.000105.
- Variance for the residual error: 0.000658.

These estimates will be used to construct a non-informative prior distribution, corresponding to the distribution that would have been derived if these estimates had been obtained from a sample of 1 patient.

The Bayesian mixed effect model will be fitted using a Markov chain Monte Carlo (MCMC) procedure. Missing values will be treated as unknown parameters and incorporated in the sampling process. A minimum of 100 imputations will be generated for each missing data. The number of imputations may be increased to obtain stable estimates. The number of burn-in iterations and thinning rate may be adjusted in order to improve convergence. The seed will be arbitrarily set to 15392 (study code).

A sample SAS code is provided below.

```
proc mcmc data=datain seed=15392 nbi=100 nmc=1000 thin=10;
 array u[2];
 array S[2,2] (0.017647 0.000105 0.000105 0.000218);
 array mu[2] (0 0);
 array cov[2,2];

 parms int diffint8 diffint15 diffint1D diffint1E slope0ontrt slope8ontrt slope15ontrt slope0posttrt
slope8posttrt slope15posttrt diffslope1D diffslope1E cov Vres;

 prior int   ~ normal(mean=0, sd=1000);
 prior diffint8  ~ normal(mean=0, sd=1000);
 prior diffint15  ~ normal(mean=0, sd=1000);
 prior diffint1D  ~ normal(mean=0, sd=1000);
 prior diffint1E  ~ normal(mean=0, sd=1000);
 prior slope0ontrt ~ normal(mean=0, sd=1000);
 prior slope8ontrt ~ normal(mean=0, sd=1000);
 prior slope15ontrt ~ normal(mean=0, sd=1000);
 prior slope0posttrt ~ normal(mean=0, sd=1000);
 prior slope8posttrt ~ normal(mean=0, sd=1000);
 prior slope15posttrt ~ normal(mean=0, sd=1000);
 prior diffslope1D ~ normal(mean=0, sd=1000);
 prior diffslope1E ~ normal(mean=0, sd=1000);

 prior Vres ~ igamma(1/2, scale=0.000658/2);
 prior cov ~ iwish(2,S);

 random u ~ mvn(mu, cov) subject=subject nooutpost;
```

```
 mean = int + diffint8*arm8 + diffint15*arm15
  + diffint1D*mayo1D + diffint1E*mayo1E
  + slope0ontrt*timeontrt*arm0 + slope0posttrt*timeposttrt*arm0
  + slope8ontrt*timeontrt*arm8 + slope8posttrt*timeposttrt*arm8
  + slope15ontrt*timeontrt*arm15 + slope15posttrt*timeposttrt*arm15
  + diffslope1D*time*mayo1D + diffslope1E*time*mayo1E
  + u[1] + u[2]*time;

 model logtkv ~ normal(mean=mean, var=Vres);

 ods output PosteriorSample=Sample;

run;
```

In the above SAS code:

- Dataset *datain* is the input dataset, with one record per patient and planned assessment. Records will be created for patients with missing TKV at a planned time point.
- Variables *arm0*, *arm8* and *arm15* are dummy variables indicating the randomized treatment arm:
  - *arm0*=1, *arm8*=0 and *arm1*=0 for patients in the placebo arm.
  - *arm0*=0, *arm8*=1 and *arm15*=0 for patients in the venglustat 8 mg arm.
  - *arm0*=0, *arm8*= 0 and *arm15*=1 for patients in the venglustat 15 mg arm.
- Variables *Mayo1D* and *Mayo1E* are dummy variables indicating the Mayo class:
  - *Mayo1D*=0 and *Mayo1E*=0 for Mayo 1C patients.
  - *Mayo1D*=1 and *Mayo1E*=0 for Mayo 1D patients.
  - *Mayo1D*=0 and *Mayo1E*=1 for Mayo 1E patients.
- Variable *time* is a continuous variable indicating the time (in years) of actual assessment (if TKV was observed) or the planned time of assessment (if TKV was missing). For example, for the hypothetical patient described in Figure 4:
  - At Month 0: time=0.
  - At Month 1: time=0.0833.
  - At Month 9: time=0.75.
  - At Month 18: time=1.5.
- Variable *timeontrt* is a continuous variable indicating the cumulative duration of the on-treatment period (in years) at the time of actual assessment (if TKV was observed) or at the planned time of assessment (if TKV was missing). For example, for the hypothetical patient having discontinued treatment after 12 months described in Figure 4:
  - At Month 0: timeontrt=0.
  - At Month 1: timeontrt=0.0833.
  - At Month 9: timeontrt=0.75.
  - At Month 18: timeontrt=1.

- Variable *timeposttrt* is a continuous variable indicating the cumulative duration of the post-treatment period (in years) at the time of actual assessment (if TKV was observed) or at the planned time of assessment (if TKV was missing). For example, for the hypothetical patient having discontinued treatment after 12 months described in Figure 4:
  - At Month 0: timeposttrt=0.
  - At Month 1: timeposttrt=0.
  - At Month 9: timeposttrt=0.
  - At Month 18: timeposttrt=0.5.
- Parameter *int* is the parameters modelling the intercept of $\log_{10}$(TKV) in Mayo 1C patients randomized to placebo.
- Parameters *diffint8* and *diffint15* are the parameters modelling the difference in intercept in patients randomized to 8 mg and 15 mg arms respectively.
- Parameters *diffint1D* and *diffint1E* are the parameters modelling the difference in intercept in Mayo 1D and Mayo 1E patients respectively.
- Parameters *slope0ontrt, slope8ontrt* and *slope15ontrt,* are the parameters modelling the slope of $\log_{10}$(TKV) during the on-treatment period in the placebo, 8 mg and 15 mg arms respectively.
- Parameters *slope0posttrt, slope8posttrt* and *slope15posttrt,* are the parameters modelling the slope of $\log_{10}$(TKV) during the post-treatment period in the placebo, 8 mg and 15 mg arms respectively.
- Parameters *diffslope1D* and *diffslope1E* are the parameters modelling the difference in slope in patients of Mayo Class 1D and 1E respectively (versus Mayo 1C).

Multiple imputation of missing data for TKV - Sensitivity analysis using a control based multiple imputation

In this sensitivity analysis, missing data will be handled using a control based multiple imputation method. Imputations will be based on a model that will assume that after permanent treatment discontinuation, the slope of $\log_{10}$(TKV) for patients in the venglustat arms will be the same as the slope of $\log_{10}$(TKV) for patients in the placebo arm. The imputation model will also include adjustment for Mayo class (1C versus 1D versus 1E) as well as random intercept and slope.

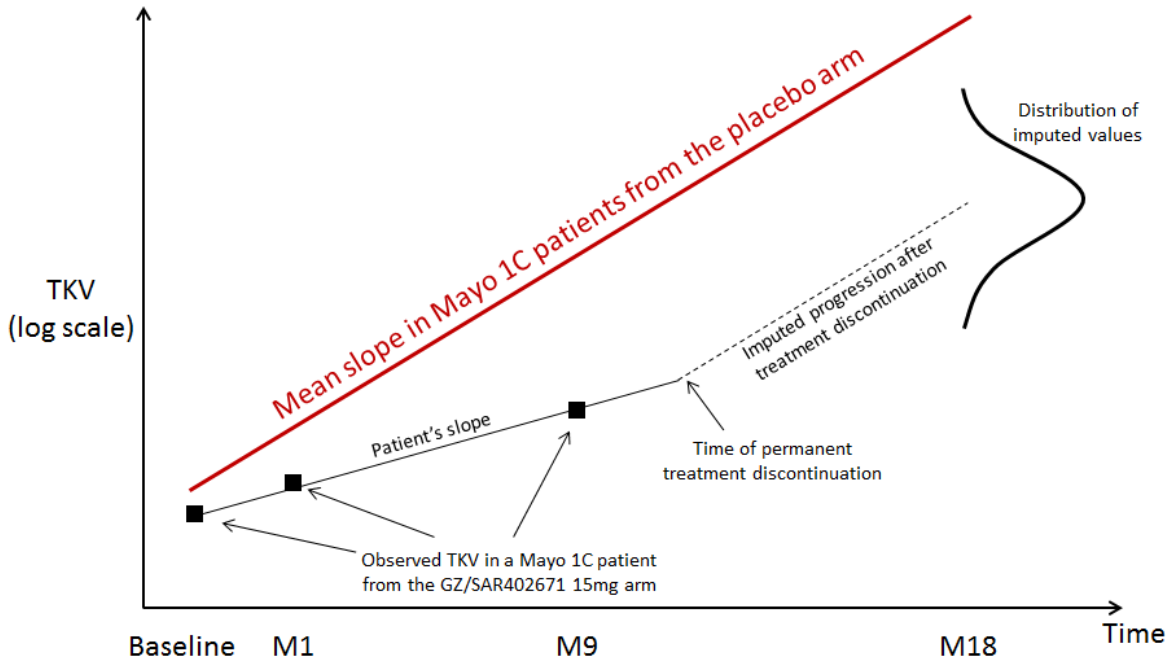
Imputations will be based on the following assumptions:

- Patients with missing data during the on-treatment period will have their data imputed based on the mean slope estimated during the on-treatment period in patients from the same treatment arm.
- Patients with missing data after permanent treatment discontinuation will have their data imputed based on the mean slope estimated in patients from the placebo arm.

Figure 5 provides a schematic representation of imputation of missing data for a Mayo 1C patient randomized to venglustat 15 mg who would permanently discontinue treatment at 12 months, with

no TKV available at 18 months. It will be assumed that from 12 to 18 months, TKV would have increased at the same rate as other Mayo 1C patients in the placebo arm.

Figure 5 - Schematic representation of imputation of missing data - sensitivity analysis using control based multiple imputation



A sample SAS code is provided below.

```
proc mcmc data=datain seed=15392 nbi=1000 nmc=1000 thin=10;
 array u[2];
 array S[2,2] (0.017647 0.000105 0.000105 0.000218);
 array mu[2] (0 0);
 array cov[2,2];

 parms int diffint8 diffint15 diffint1D diffint1E slope0 slope8 slope15 diffslope1D diffslope1E cov Vres;

 prior int   ~ normal(mean=0, sd=1000);
 prior diffint8 ~ normal(mean=0, sd=1000);
 prior diffint15 ~ normal(mean=0, sd=1000);
 prior diffint1D ~ normal(mean=0, sd=1000);
 prior diffint1E ~ normal(mean=0, sd=1000);
 prior slope0  ~ normal(mean=0, sd=1000);
 prior slope8  ~ normal(mean=0, sd=1000);
 prior slope15  ~ normal(mean=0, sd=1000);
 prior diffslope1D ~ normal(mean=0, sd=1000);
 prior diffslope1E ~ normal(mean=0, sd=1000);

 prior Vres ~ igamma(1/2, scale=0.000658/2);
```

```
 prior cov ~ iwish(2,S);

 random u ~ mvn(mu, cov) subject=subject nooutpost;

 mean = int + diffint8*arm8 + diffint15*arm15
  + diffint1D*mayo1D + diffint1E*mayo1E
  + slope0*time*arm0
  + slope8*timeontrt*arm8 + slope0*timeposttrt*arm8
  + slope15*timeontrt*arm15 + slope0*timeposttrt*arm15
  + diffslope1D*time*mayo1D + diffslope1E*time*mayo1E
  + u[1] + u[2]*time;

 model logtkv ~ normal(mean=mean, var=Vres);

 ods output PosteriorSample=Sample;

run;
```

In the above SAS code, variable and parameters have the same interpretation as in the previous model, except:

- Parameters slope0, slope8 and slope15, are the parameters modelling the slope of log10(TKV) during the on-treatment period in the placebo, 8 mg and 15 mg arms respectively. Of note, in the placebo arm, slope is assumed to be the same during the on-treatment and during the post-treatment periods.

A consequence of this model is that after treatment discontinuation, patients from the venglustat arms will have a slope equal to the slope of patients in the same Mayo class treated with placebo. For example, for the hypothetical patient described in Figure 5:

- Between Month 0 and Month 12: the slope will be slope15 (slope of Mayo 1C patients treated with dose 15 mg).
- Between Month 12 and Month 18: the slope will be slope0 (slope of Mayo 1C patients treated with placebo).

Multiple imputation of missing data for eGFR

Missing data for GFR will be handled using a similar approach, with the exception that no log transformation will be used for eGFR. Prior distribution of variance parameters was derived following a similar approach. The following estimates were obtained from the CRISP and HALT-PKD studies:

- Variance for the random intercept: 106.81.
- Variance for the random slopes: 3.90.
- Covariance between random intercept and slopes: 5.36.
- Variance for the residual error: 40.26.

Appendix K Isolation of Urinary Exosomes

1 INTRODUCTION

Exosomes are membrane vesicles, which are secreted from their cells of origin into surrounding body fluids and contain proteins and mRNA which are protected from digestive enzymes by a cell membrane. Exosomes can mediate cell-cell communication and affect signal transduction in recipient cells in both normal and pathological conditions. In the kidney, and other organs, exosomes have been suggested to carry disease-specific biomarkers (23). Analysis of urinary exosomes may therefore provide a method to noninvasively assess disease progression or treatment effects in the kidney.

Urinary exosomes isolation will be done from the 24-hour samples of urine at selected sites.

2 OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives of this substudy are:

- To isolate and study urinary exosomes as a source of kidney dysfunction biomarkers in patients with ADPKD.
- To study the response of kidney dysfunction biomarkers to treatment.

3 PRIMARY ENDPOINTS

Not applicable.

4 STUDY DESIGN

Urinary exosomes will be isolated from the 24-hour samples of urine in patients randomized in the multinational, multicenter, double-blind, placebo-controlled, two stage EFC15392 study at selected sites. 24-hour urine samples of up to 60 patients at Visit 3 (baseline visit) will be screened for expression of the biomarkers of interest.

Urine samples of up to 30 patients that had a high level of expression of the biomarkers of interest at Visit 3 will be further analyzed at Month 1, 3, and 9 to follow changes in biomarker expression.

Samples of urine will be processed and analyzed as noted below.

5 SELECTION OF PATIENTS

Patients who consented to participation in the EFC15392 study at selected sites.

6 STUDY PROCEDURES

A) An aliquot from the 24-hour urine collection will be taken.

B) Study staff will process the urine as follows:

a) Record the date and the total volume of urine for each sample.

b) Thoroughly mix urine prior to aliquoting.

c) Aliquot 100 mL into two 50 mL tubes.

d) Add one protease inhibitor cocktail tablet (Sigma; cat# 4693132001) per 50 mL of urine, dissolve completely.

e) Centrifuge 4 000× g (15 minutes; 4°C) to sediment cells and cellular debris.

f) Using pipette, transfer supernatant into the new 50 mL tube (do not disturb the pellet!).

g) Freeze supernatant at -80°C.

h) Ship frozen on dry ice.

7 WITHDRAWAL OF CONSENT

Patients who wish to withdraw their participation in this additional research may do so at any time. If they do so, they may continue participation in the main study. Patients, who discontinue the main study, must also discontinue participation in this additional research.

8 STATISTICAL ANALYSIS

Not applicable.

9 SAFETY REPORTING

Adverse events and serious adverse events will be captured and reported in accordance with the main EFC15392 study (see Section 10 in the main protocol).

10 ADMINISTRATION

10.1 INFORMED CONSENT

Urinary exosomes are part of ADPKD biomarkers assessment (required tests of the protocol) and are covered by the informed consent of EFC15392 study.

10.2 CONFIDENTIALITY

Data collection and handling by the Sponsor for this substudy will be in accordance with that described in the main EFC15392 protocol (see Section 14.3 in the main protocol), and every effort will be made to protect patient confidentiality. In case the results are published, they will be done so anonymously.

10.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

Urinary exosomes isolation is a required test of the protocol and is covered by the informed consent of EFC15392 study that will be submitted for review and approval to the IRB/EC charged with this responsibility.

10.4 RECORDS RETENTION

Investigators must retain records pertaining to this substudy as described in the main EFC15392 study protocol (see Section 14.2 in the main protocol).

Appendix L Measured glomerular filtration rate substudy

1 INTRODUCTION

The primary endpoint in the Stage 2 of the study EFC15392 is annualized rate of change in estimated glomerular filtration rate (eGFR; CKD-EPI equation) from baseline to 24 months. Estimated glomerular filtration rate may be inaccurate in the nonsteady state and in people in whom non-GFR determinants differ greatly from those in whom the estimating equation was developed. Measured GFR (mGFR) using urinary or plasma clearance of exogenous filtration markers is considered the gold standard for evaluation of kidney function (24). To determine the effect of venglustat on mGFR, GFR will be measured with iohexol in approximately 15% of patients randomized in Stage 2 of the EFC15392 study. Glomerular filtration rate will be calculated by plasma iohexol clearance (25).

2 OBJECTIVE

2.1 PRIMARY OBJECTIVE

The primary objective of this substudy is:

- To determine the effect of venglustat on mGFR.

3 PRIMARY ENDPOINT

The primary endpoint of this substudy is the annualized rate of change in mGFR from baseline to 24 months.

4 STUDY DESIGN

Patients randomized in Stage 2 of the international, multicenter, double-blind, placebo-controlled, two stage EFC15392 study will be asked to participate in this optional substudy. Once written informed consent is obtained, glomerular filtration rate will be measured at Months 0, 12, and 24. Plasma samples will be processed and analyzed as noted below.

5 SELECTION OF PATIENTS

Patients will be selected from those agreeing to participate in Stage 2 of the EFC15392 study, with the additional criteria below.

5.1.1 Additional inclusion criterion

- A written signed acknowledgment for mGFR substudy of EFC15392 protocol in the consent of the Stage 2 of the EFC15392 study indicating patient’s agreement.

5.1.2 Additional exclusion criterion

- Known hypersensitivity to iohexol or other contrast media, known sensitivity to iodine.

Patients who are not eligible for the substudy based on the additional eligibility criteria may still take part in the main study of the EFC15392 protocol.

6 STUDY PROCEDURES

Commercial iohexol will be sourced by the study site for this substudy. Refer to the iohexol Prescribing Information for full information about its properties and the conditions attached to its use.

Iohexol will be stored at the temperature specified in the package insert in a secure location at the site.

Omnipaque 300 mg iodine per milliliter contains 647 mg/mL iohexol. Exactly 5 mL of iohexol solution (drawn in a 5 mL syringe), containing 3.235 g of iohexol will be injected intravenously (IV) through an injection catheter.

The following should be considered prior to performing GFR measurements:

- Patients will have their study visit in the morning in fasted condition (eat nothing and drink only water)
- This procedure should be performed after all other scheduled blood samples for the visit are collected.
- Adequate hydration should be assured before and after administration of iohexol.
- If not obtained within 72 hours of the GFR measurement procedure, the patient's weight and height should be measured and recorded.

6.1 Patient preparation

After a 10-hour fast (eating nothing and drinking only water), 2 IV catheters, one in each arm, will then be placed in the patient's antecubital vein. One line will be used for the single dose injection of nonradioactive iohexol. The second line will be used for intermittent blood sampling.

6.2 Iohexol injection (time -2 to 0 minutes)

Exactly 5 mL of iohexol solution (drawn in a 5 mL syringe), containing 3.235 g of iohexol, will be injected slowly into the injection catheter.

- The 5 mL solution should be injected over a period of 2 minutes.
- The exact time of the injection will be recorded in the eCRF and in the source document. For consistency, the same digital clock should be used throughout the procedure.
- The total, exact, volume of the solution injected must be recorded on the central laboratory requisition form and in the source document.
- Blood samples must not be taken from the arm receiving the iohexol solution.

6.3 Blood collection

Blood samples for the determination of GFR by plasma clearance of iohexol will be collected prior the injection of the iohexol solution as well as during the last 4 hours of the procedure. **Initiation of the GFR procedure will occur at time -2 minutes and is defined as the time at which the iohexol solution is injected. Time 0 represents the end of the iohexol injection. The timing for the blood samples are relative to the end of the iohexol injection (Time 0)**.

Blood samples will be taken at 120, 150, 180, 210, and 240 minutes (2, 2.5, 3, 3.5, and 4 hours) after injection of iohexol. Plasma iohexol concentrations will be measured by a central laboratory. The procedure for measuring mGFR is described in detail in the laboratory manual.

7 WITHDRAWAL OF CONSENT

Patients who wish to withdraw their participation in this substudy may do so at any time. If they do so, they may continue participation in the main study. Patients, who discontinue the main study, must also discontinue participation in the substudy.

Patients, who prematurely discontinue study treatment (regardless of the reason) and continue the main study, should be encouraged to complete the scheduled Month 24 mGFR assessment.

8 STATISTICAL ANALYSIS

8.1 Sample size determination

No formal sample size calculations have been performed for this substudy, sample size was based upon empirical considerations. It is expected that approximately 60 patients (15% of patients randomized in Stage 2) will participate in the mGFR substudy.

8.2 Primary analysis

A linear mixed effect model will be fitted to the mGFR, which will include fix effects of treatment (venglustat or placebo), Mayo Imaging Classification (as per randomization stratification factor: Class 1C versus 1D versus 1E), time (as continuous variable), treatment * time interaction and Mayo Imaging Classification * time interactions, and will include random intercept and slope.

Within group mean slope of mGFR will be obtained from the linear mixed effect model, using weights for each stratum (Mayo Class 1C, 1D and 1E) equal to the overall proportion of patients in each stratum in the Stage 2 population (ie “population weight”). Difference in mean slope will be calculated and presented with its 95% confidence interval. p-value will be presented for descriptive purpose.

No imputation of missing data will be performed. The linear mixed effect model described above will be run on all observed data, including data collected after treatment discontinuation.

9 SAFETY REPORTING

Adverse events and serious adverse events will be captured and reported in accordance with the main EFC15392 study (see Section 10 in the main protocol).

10 ADMINISTRATION

10.1 INFORMED CONSENT

Information about the substudy will be included in the main informed consent for the Stage 2 of EFC15392 study. A separate informed consent where required by local regulations shall be obtained from patients who voluntarily agree to participate in the substudy. A separate informed consent form will be used in Stage 1 and Stage 2 of the study. The informed consent form reflecting this substudy will be submitted for review and approval to the IRB/EC charged with this responsibility.

10.2 CONFIDENTIALITY

Data collection and handling by the Sponsor for this substudy will be will be in accordance with that described in the main EFC15392 protocol (see Section 14.3 in the main protocol), and every effort will be made to protect patient confidentiality. In case the results are published, they will be done so anonymously.

10.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

This substudy, the Informed Consent Form for this substudy, and any advertisement for patient recruitment will be submitted for review and approval to the IRB/EC charged with this responsibility.

10.4 RECORDS RETENTION

Investigators must retain records pertaining to this substudy as described in the main EFC15392 study protocol. (see Section 14.2 in the main protocol).

Appendix M Country-specific requirements

Not applicable.

Appendix N Protocol amendment history

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the clinical trial summary.

The primary reasons for each protocol amendment are summarized below.

AMENDED PROTOCOL 06 (16 December 2020)

This amended protocol 06 (Amendment 06) was considered to be non-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 because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

This amendment was to update Appendix L, which describes the Measured Glomerular Filtration Rate (mGFR) substudy. This substudy is planned to be conducted in selected centers in the USA, the Netherlands, and Canada. This amendment will further clarify inclusion and exclusion criteria and study procedures as described in the summary of changes table.

The full history of protocol amendments is included in Appendix N.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Appendix L, Section 1, Introduction	Added clarification that GFR will be measured with iohexol in patients with the screening eGFR between 45 and 89.9 mL/min/1.73 m^2.	Clarification
Appendix L, Section 5.1.1 Additional inclusion criteria	Added inclusion criterion related to the screening eGFR value in patients eligible for the mGFR substudy.	Clarification
Appendix L, Section 5.1.2, Additional exclusion criteria	Deletion of the exclusion criterion related to the request of the washout periods of 2 weeks for angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) and of 3 days for non-steroidal anti-inflammatory drugs (NSAIDs) prior to the mGFR assessment visit.	To match testing conditions for eGFR and mGFR
Appendix L, Section 6.0, Study Procedures	Added the clarification that “Patients will have their study visit in the morning in fasted condition (eat nothing and drink only water)”. Removed the washout periods related to the temporary discontinuation of ACE inhibitors or ARBs and non-steroidal anti-inflammatory drugs. Added the clarification that “Adequate hydration should be assured before and after administration of iohexol”.	Clarifications

Section # and Name	Description of Change	Brief Rationale
Appendix L, Section 6.1, Patient preparation	Added the clarification that the 10-hour fast means “eating nothing and drinking only water”.	Clarification
Appendix N, Protocol amendment history	Added protocol amendment summary-of-changes table for amended protocol 05	Update

Protocol Amendment 05 Version number 1 (electronic 5.0) Date 17-Aug-2020

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Sections 1.3 Study flow chart for STAGE 1 - footnote p, Section 1.4 Study flow chart for STAGE 2 - footnote p, Section 9.4.10 Ophthalmological examination, Section 10.1.2.2 Visit 4, 6, 8, 10, 12/Months 1, 6, 12, 18, 24 (Day 30, 180, 360, 540, 720), Section 10.4.2 General guidelines for reporting adverse events	Replacement of LOCSIII with WHO simplified cataract grading system.	The LOCSIII requirement of recertification every 6 months renders the utilization of LOCSIII in the study extremely challenging. To ensure continuity of lens changes monitoring and to avoid the risk of losing data related to ophthalmologists potentially not performing the required LOCSIII certification every 6 months during the study, we are replacing LOCSIII with the WHO simplified cataract grading system. Going forward changes in the lens clarity in patients will be evaluated by using the WHO simplified cataract grading system. The replacement of LOCSIII used to grade lens opacities with the WHO simplified cataract grading system in this study will have no impact on the safety monitoring of the lens for the following reasons: 1. The protocol safety rules (increase in the frequency of dilated lens examination or IMP discontinuation) are based on the decrease in BCVA lines and not on the degree of lens opacity progression 2. In the current protocol, pre-treatment opacities detected at Visit 2 (= Run-In) are assessed and characterized with WHO simplified cataract grading system. Therefore, we will be able to compare the future WHO assessments throughout the study (Month 12, 18 & 24) with the WHO grade established at Visit 2 3. Lens opacity progression in small increments with LOCSIII (<1.0 grade) does not trigger the increase of frequency of dilated lens examination.
Clinical Trial Summary - Study objectives, Endpoints Section 5.1 STAGE 1: Section 5.1.2 Secondary objectives Section 5.1.3 Exploratory objectives Section 5.2 STAGE 2: Section 5.2.2 Secondary objectives	Updated the hierarchy of the secondary and exploratory objectives and endpoints: STAGE 1: 1. pain and fatigue are moved from exploratory to secondary objectives and endpoints 2. nocturia is moved from secondary to exploratory objectives and endpoints	Data from venglustat clinical studies do not suggest that venglustat causes urinary frequency or nocturia. For this reason, the change in nocturia was moved from secondary to exploratory endpoints. Pain and fatigue were moved from exploratory to secondary endpoints as they are fit in ADPKD as the concepts for which a positive effect can be shown.

Section # and Name	Description of Change	Brief Rationale
Section 5.2.3 Exploratory objectives Section 9.2 Secondary endpoints Section 9.3 Exploratory endpoints Section 11.4.2.2 Analyses of secondary efficacy endpoints	STAGE 2: 1. pain and fatigue are moved from exploratory to secondary objectives and endpoints 2. urine osmolality and nocturia are moved from secondary to exploratory objectives and endpoints.	
Clinical Trial Summary - Duration of study period (per patient), Section 1.3 Study flow chart for STAGE 1 - footnote b, Section 1.4 Study flow chart for STAGE 2 - footnote b, Section 10.1.3 Follow-up visit -Visit 13/ Month 25 (Day 750)	Added clarification that follow-up visit after V12 (Month 24, end of treatment) visit is applicable for patients who completed the treatment period and elected not to participate in the potential long-term extension study.	Clarification
Section 4.2 Clinical trials of venglustat in humans	Section updated with new and completed clinical trials of venglustat in humans.	Updated information
Section 4.3 Benefit/risk of venglustat	Section updated based on Investigator Brochure ed12 related to new information from nonclinical studies. The toxicity finding in sexually mature dogs was removed based on two external experts' opinions.	Updated information
Section 6.2.1 Duration of study participation for each patient	Added clarification regarding the last study visit in Stage 1 and Stage 2 to allow for patients, upon completion of study EFC15392, to enter into a potential long-term open-label extension (LTS15823).	Clarification
Section 7.2.1 Exclusion criteria related to study methodology - E06	A History of alcohol dependency within the five years prior to the screening visit was added to the exclusion criterion E06.	To exclude cases of potential alcoholic relapse during the study.
Section 7.2.1 Exclusion criteria related to study methodology - E09	Resistant hypertension as an example of clinically significant, uncontrolled medical condition in exclusion criterion E09 was replaced with hypertensive emergency within 6 month of Visit 1.	Correction and clarification.

Section # and Name	Description of Change	Brief Rationale
Section 7.2 Exclusion criteria, Appendix O Contingency Measures for a regional or national emergency that is declared by a governmental agency.	Clarified use of initial screening results for rescreened patients: • MRI (obtained within 1 months prior to randomization), • neurological and ophthalmic exams (obtained within 3 months prior to randomization). • already collected at initial screening biomarkers.	To reduce the burden of assessments on the rescreened patients, certain initial screening exam results that are still clinically actual (no changes are expected during a particular period of time) can be used for rescreening Visit 1 or Visit 2.
Section 7.2.4 Criteria for Temporarily Delaying of Randomization or Administration of Study Treatment	Added section referring to contingency measures proposed in Appendix O for situation if the site is unable to adequately follow protocol mandated procedures during a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access.	Set up of contingency measures for a regional or national emergency that can be declared by a governmental agency.
Section 8.1.2 Dose of drug per administration	Section updated with information that venglustat may be supplied from the site to the patient during national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access.	Clarification.
Section 8.8.1 List of forbidden concomitant medications	Allopurinol was added to the list of medications prohibited during the study. Clarification added that Investigator should consider substituting any concomitant medication that has cataractogenic potential according to its Prescribing Information for noncataractogenic medication.	Link between allopurinol use and cataract development is described in the literature, cataract is reported as adverse event in Prescribing Information for allopurinol. The list of medications with cataractogenic potential in section 8.8.1 is not exhaustive. Investigator should consider substituting any concomitant medication with cataractogenic potential according to its Prescribing Information for noncataractogenic medication.
Section 9.4 Assessments methods, Section 10 Study procedures, Section 10.3.1 Temporary treatment discontinuation with investigational medicinal product(s), Section 12.2 Informed consent	Added reference to the Appendix O.	Set up of contingency measures for a regional or national emergency that can be declared by a governmental agency.

Section # and Name	Description of Change	Brief Rationale
Section 10.3.4 Handling of patients after permanent treatment discontinuation	Added clarification that in patients who prematurely and permanently discontinued study medication, a follow up visit required in 30 days after the premature end-of-treatment visit includes all assessment of the Visit 13.	Clarification.
Section 10.3.6 Lost to Follow-up	Added section describing the actions that must be taken if a participant fails to return to the clinic for a required study visit.	Clarification.
Section 10.4.3 Instructions for reporting serious adverse events	Requirement to send a photocopy of all examinations related to SAE to the representative of the monitoring team was changed to the requirement to send copies of medical records only when they are requested by the Sponsor.	Simplification and standardization of the clinical safety data flow (to minimize risk of non-secured transmission and non-secured storage).
Section 11.3.1.1 Intent-to-treat population	Primary analysis of Stage 1 will include data available at the cut-off date, including data reported up to Month 24, if any	Clarification.
Section 11.3.4 Patient-reported outcome population	PRO population deleted	PRO analysis will be performed on ITT population
Section 11.4.2.1 Analysis of primary efficacy endpoint(s): Section 11.4.2.1.1 Stage 1	Removal of sentence “Time of baseline TKV will be set to 0.”	Time of baseline TKV will be calculated as relative time since randomization date.
Section 11.4.2.2 Analyses of secondary efficacy endpoints	Description of analysis of change in pain and change in fatigue Removal of description of analysis of change in urine osmolality and change in nocturia	Change in pain and fatigue considered as secondary endpoints. Change in urine osmolality and change in nocturia considered as exploratory endpoints
Section 11.4.2.3 Multiplicity considerations	Change in hierarchy of secondary endpoints as illustrated in Figure 3.	Change in pain and fatigue considered as secondary endpoints. Change in urine osmolality and change in nocturia considered as exploratory endpoints
Section 11.4.3 Analyses of safety data	Change in definition of on-treatment period and treatment-emergent period	Clarification.
Section 11.4.3.1 Adverse events	Presentation of statistical tables by SOC and PT	Clarification.
Section 11.4.3.2 Laboratory data and vital signs	Statistical analysis of liver test data was updated	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 11.4.5 Analyses of patient reported outcomes (health-related quality of life/health economics variables)	The text regarding statistical analysis of PRO data using MMRM was updated	Clarification.
Section 11.5.3 Two-step final analysis	Primary analysis of Stage 1 will include data available at the cut-off date, including data reported up to Month 24, if any.	Clarification.
Section 13.2 Responsibilities of the Sponsor	Section supplements with information that monitoring details are located in separate study documents.	Clarification.
Appendix C General guidance for the follow-up of laboratory abnormalities by Sanofi, chart 'Acute Renal Failure'	Definition of acute renal failure was replaced with the definition of acute kidney injury based on the % of change in creatine from baseline.	Study population patients have already increased creatinine at baseline. Definition of acute kidney injury based on the % of change in creatine from baseline and urine output is more suitable for patients with CKD in this study.
Appendix K Isolation of Urinary Exosomes, Section 1.4 Study flow chart for STAGE 2 - footnote l	Urine exosomes sub-study will be performed at selected sites in Stage 1 and Stage 2.	To ensure that site initially selected for this sub-study will have time to complete the substudy.
Appendix O Contingency Measures for a regional or national emergency that is declared by a governmental agency.	Addition of contingency measures for a regional or national emergency that can be declared by a governmental agency.	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 during an emergency that prevents access to the study site.

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Section # and Name	Description of Change	Brief Rationale
Clinical trial summary; study objective(s), 5.2.3 Stage 2, Exploratory objectives	To explore the effect of venglustat on eGFR (CKD-EPI equation) from baseline to 24 months in patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2.	With the inclusion in Stage 2 of the study patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2, this exploratory endpoint has been added.
Clinical trial summary; study design, 6.1 Description of the study	This is an international, multicenter, randomized, double-blind, placebo controlled two stage study in adult patients at risk of rapidly progressive ADPKD aged 18 to 50 years in Stages 1 and 2 (and aged 18 to 55 years for patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2 in Stage 2).	With the inclusion of patients with an eGFR 30 - 44.9 mL/min/1.73 m^2, the upper age limit was increased to 55 years as advanced disease occurs at a more advanced age.

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary; study design; Stage 1	If after reviewing the unblinded aggregate safety data from Stage 1 (after at least 1 month of treatment of the first 150 randomized patients from Stage 1), the Data Monitoring Committee (DMC) recommends the 8 mg dose for Stage 2, then the DMC may recommend switching patients on 15 mg treatment arm, in Stage 1, to the 8 mg arm.	Clarification: Clinical trial summary was supplemented with information already present in Section 6.1 of the protocol.
Clinical trial summary; study design; Stage 2	After the first 150 randomized patients from Stage 1 have completed at least 1 month of treatment (or have prematurely discontinued), the ~~Data Monitoring Committee (~~DMC~~)~~ will review in an unblinded fashion the aggregate safety data from Stage 1 and will select the venglustat dose ~~for Stage 2 (~~8 mg or 15 mg~~)~~ for Stage 2 patients.	Clarification.
Clinical trial summary: study population, inclusion criteria 7.1 Inclusion criteria	Male or female adult with ADPKD ~~diagnosed by unified Pei criteria~~ with an age at the time the consent is signed: between ~~the ages of~~ 18 ~~to~~ and 50 years (~~both~~ inclusive) ~~at screening~~ for patients in Stage 1 between 18 and 50 years (inclusive) for patients in Stage 2 with an eGFR between 45 and 89.9 mL/min/1.73 m^2 during the screening period* between 18 and 55 years (inclusive) for patients in Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 during the screening period* Diagnosis of ADPKD in patients with a family history, will be based on unified Pei criteria. In the absence of a family history, the diagnosis will be based on the presence of renal cysts bilaterally, totaling at least 20, in the absence of findings suggestive of other cystic renal diseases. Mayo Imaging Classification of ADPKD Class 1C, 1D, or 1E**. **TKV volume must be confirmed by a central reader prior to Visit 3. Estimated glomerular filtration rate between 45 ~~to~~ and ~~90~~ 89.9 mL/min/1.73 m^2 ~~at~~ during the screening period*(Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) for Stage 1. Estimated glomerular filtration rate between 30 and 89.9 mL/min/1.73 m^2 during the screening period* (CKD-EPI equation) for Stage 2. *Eligibility will be confirmed by the eGFR value from one of the two first pre-randomization eGFR measurements (Visit 1 or Visit 2 measurements, or Visit 1 and an additional measurement performed at the Investigator's discretion between Visit 1 and Visit 2)	Inclusion in Stage 2 of the study patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2. For confirmation of eligibility, Investigator will use eGFR value from one of the two first pre-randomization eGFR measurements. Criteria for diagnosis of ADPKD was additionally clarified for patients without family history of ADPKD.
Clinical trial summary: study population, inclusion criteria 7.2 Exclusion criteria	Systolic BP >160 mmHg* at run in and baseline visits. *mean value of three or five systolic BP measurements (See Section 9.4.5) The patient has, according to World Health Organization (WHO) Grading, a cortical cataract ~~>~~ ≥1 quarter of the lens circumference (Grade cortical cataract 2 [COR 2]) or a posterior subcapsular cataract ~~>~~ ≥2 mm (Grade posterior subcapsular cataract 2 [PSC 2]). Patients with nuclear cataracts will not be excluded.	Clarification Correction

Section # and Name	Description of Change	Brief Rationale
Clinical trial summary: Total expected number of patients	Stage 2: Approximately ~~320~~ 400 patients (~~160~~ 200 patients on venglustat and 200 patients on placebo ~~per arm~~).	Added information that an additional 80 patients will be enrolled in Stage 2 of the study.
Clinical trial summary: Stage 2 exploratory endpoints 9.3.2 Stage 2 only	Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months in patients with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2	Added to assess exploratory endpoint for Stage 2 patients with eGFR between 25 and 44.9 mL/min/1.73 m^2
Clinical trial summary: assessment schedule, Stage 1, Stage 2	Biomarker assessments: Month -1 and Months 1, 6, 12, 18, 24, and at ~~1 month~~30 days follow-up (Month 25).	Clarification: Adjusted 1 month to 30 days
Clinical trial summary: assessment schedule, PRO assessments; Stage 1	End-of-treatment visit should include all procedures of Visit 12 and additionally a PK sample should be collected. In ~~4 weeks~~30 days, a Follow-up visit should be performed.	Clarification: Adjusted 4 weeks to 30 days.
Clinical trial summary: assessment schedule, PRO assessments: Stage 2	Patients who ~~prematurely and~~ permanently discontinue study medication should complete rapidly (within 7 days) an end-of-treatment assessment visit. End-of-treatment visit should include all procedures of Visit 12. In ~~4 weeks~~30 days, a Follow-up visit should be performed.	Clarification: Adjusted 4 weeks to 30 days.
Clinical trial summary: Statistical considerations; Sample size determination; 11.1 Determination of sample size	In Stage 2, approximately 320 patients with an eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening will be randomized (with randomization ratio 1:1) to placebo (n = 160) or venglustat (n = 160). In addition, 80 patients with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will be randomized (with randomization ratio 1:1) to placebo (n = 40) or venglustat (n = 40). The patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 will not be included in the primary efficacy and safety analyses populations but the data from these patients will be analyzed separately. A sample size of 80 patients (40 per arm) with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will provide approximately 80% probability to detect a treatment effect in this subgroup at the 0.20 significance level (two-sided), based on a model evaluating the dependence of the treatment effect on baseline eGFR.	Added statistical consideration related to probability of detecting a treatment effect in an additional 80 patients with screening eGFR between 25 and 44.9 mL/min/1.73 m^2.
Clinical trial summary: Statistical considerations, Analysis population Stage 2	The combined Stage 1 and Stage 2 ITT population will include all patients with an eGFR 45 and 89.9 mL/min/1.73 m^2 at screening who are randomized in Stage 1 or Stage 2, analyzed according to the treatment group allocated by randomization (venglustat 15 mg, venglustat 8 mg, or placebo). Patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will not be included in the primary efficacy and safety analyses population but the data from these patients will be analyzed separately.	Added information that patients in Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will be described separately from the primary analysis population.
Clinical trial summary: Duration of study period; Stage 1 and Stage 2	Screening period Initial screening: up to 15 (+3) days. Placebo run-in period: 15 days ±3 days ~~2 weeks~~.	Clarified maximum duration of initial screening period; 2 weeks to 15 days clarification for placebo run-in period, and specification of its minimum and maximum duration.

Section # and Name	Description of Change	Brief Rationale
1.2 Graphical study design for Stage 2	New graphical study design for Stage 2 patients with an eGFR between 30 and 44.9 mL/min/1.73 m^2 added	Added revised graphical study design for patients with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening.
1.3 and 1.4 Study flowchart for Stage 1 and Stage 2	Call IXRS/IWRS included in the flowchart for Visits 1-12.	Clarification.
1.3 and 1.4 Study flowchart for Stage 1, Stage 2: footnote "a"	If a patient discontinues treatment with IMP early during the core treatment period, the patient will have an End-of-Treatment/Early Withdrawal (EOT/EW) Visit within 7 days and a Follow-up Visit ~~4 weeks~~ 30 days after the last dose of IMP.	4 weeks to 30-day clarification.
1.3 and 1.4 Study flowchart for Stage 1 and Stage 2: footnote "e"	The abbreviated physical examination should focus on ~~cardiac and respiratory systems, as well as any~~ areas important for assessment of AEs if necessary.	Clarification.
1.3 and 1.4 Study flowchart for Stage 1 and Stage 2: footnote "j" 8.1.2 Dose of drug per administration 9.4.14.1 Sampling time	Plasma samples for PK to be collected on Day 1 (3 ±1 hours post dose), Month 1 (pre dose and 3 ±1 hours post dose), Months 6 and 18 (pre dose). At visits when a post-dose PK sample is to be collected, patients should take the study drug on site.	Clarification that at visits when a PK sample is to be collected, patients should take the study drug on site.
1.3 and 1.4 Study flowchart for Stage 1 and Stage 2: footnote "o"	TKV volume must be confirmed by a central reader prior to Visit 3.	Clarification.
1.3 and 1.4 Study flowchart for Stage 1 and Stage 2: footnote "s"	Prior to the start of IMP at Baseline Visit. In subjects who have consented to it, samples of serum will be collected and archived for future analysis.	Footnote "s" added for clarification
1.3 and 1.4 Study flowchart for Stage 1 and Stage 2: footnote "t"	All SAEs, AEs and AEs of special interest (AESIs) will be collected starting with signing informed consent and continue until 30 days ~~4 weeks~~ 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 ~~4 weeks~~ 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 patient is lost to follow-up. All patients will have a follow-up visit 30 days ~~4 weeks~~ after the last dose of IMP to collect safety information.	4 weeks to 30-day clarification.
1.3 and 1.4 Study flowchart for Stage 1: footnote "u"; Stage 2: footnote "w"; 10.1.1.1 Visit 1: Screening from Day -30 to Day -16	The initial screening period (Visit 1) can last up to 15 days (+3 days). Visit 2 can be performed as soon as results of all assessments performed at Visit 1 are available.	Clarification that initial screening period could last up to 15 days and that it could be completed and V2 could be performed as soon as results of all V1 assessments are available.
4.3 Benefit/risk of venglustat	*Infertility in adult males due to venglustat exposure in childhood (<12 years of age)* ~~Testicular degeneration was observed in juvenile toxicity study in the rat. There were no similar findings in any other nonclinical (adult animal) study. The finding could be related to the development stage of the animals, and is considered to be a potential risk for pediatric patients <12 years of age only. As~~	Described preclinical testicular toxicity findings and theoretical implications. Added clarification that neurological AEs are closely monitored in venglustat studies by means of

Section # and Name	Description of Change	Brief Rationale
	~~pediatric patients are not included in the current study, there will be no measure for clinical monitoring for this risk.~~ The finding of degeneration of testicular germinal epithelium, which was restricted to juvenile rats only, could be related to the development stage of the animals, and is currently considered to be a potential risk only for patients exposed to venglustat below the age of 12 years. Exposure under 12 years of age has a potential to negatively impact male fertility, an effect which would manifest at the time of sexual maturity. There is no measure for clinical monitoring in patients under 12 years of age. The two toxicity findings in sexually mature mice and dogs were of minimal severity and considered likely to be reversible, while there were no findings in any of the adult rat studies. Taken together the relevance of these findings is of unknown clinical significance in adult male patients. The exposures reached in juvenile and adult animal studies are not predicted to be achieved in human when receiving chronic treatment with venglustat at the 15 mg dose. *Theoretical risk of adverse neurological and psychiatric effects given the compound's access to the CNS* Neurological and psychiatric AEs are being closely monitored and evaluated in the clinical trials, and will be monitored in this study, including a complete physical examination that includes a standard neurological examination and the use of BDI-II instrument for assessment of the existence and severity of symptoms of depression. *Concomitant administration with CYP3A inhibitors or inducers* In the completed clinical drug-drug interaction study (INT14339), concomitant administration of venglustat with itraconazole, a strong inhibitor of CYP3A, resulted in an increase in venglustat exposure.	standard neurological examination (part of complete physical examination).
6.1 Description of the study; Stage 2	Stage 1: If after reviewing the unblinded aggregate safety data from Stage 1 (after at least 1 month of treatment of the first 150 randomized patients from Stage 1), the Data Monitoring Committee (DMC) recommends the 8 mg dose for Stage 2, then the DMC may recommend switching patients on 15 mg treatment arm, in Stage 1, to the 8 mg arm. Stage 2: After the first 150 randomized patients from Stage 1 have completed at least 1 month of treatment (or have prematurely discontinued), the DMC will review in an unblinded fashion the aggregate safety data from Stage 1 and will select the venglustat ~~for Stage 2~~ dose 8 mg or 15 mg for Stage 2 patients. The selected dose will be the highest dose determined to be safe and well tolerated in Stage 1. If after reviewing the unblinded aggregate safety data from Stage 1, the DMC recommends the 8 mg dose for Stage 2, then the DMC may recommend switching patients on the 15 mg treatment arm, in Stage 1, to the 8 mg arm~~, if the DMC considers that there is a safety concern with the 15 mg dose~~.	Additionally, described in this section possible course of action with regard to the study drug dose in ongoing patients in Stage 1 that could be recommended by DMC to Sponsor after dose selection for Stage 2.

Section # and Name	Description of Change	Brief Rationale
6.2.1 Duration of study participation for each patient	This will consist of a screening period of up to 30 +3 days (initial screening period of up to 15 +3 days and single-blind placebo run-in period of ~~2 weeks)~~15 ±3 days), followed by a blinded study core treatment period of 24 months and a 30-day follow-up visit after the final dose of IMP.	Clarified maximum duration of initial screening period; 2 weeks to 15 days clarification for placebo run-in period, and specification of its minimum and maximum duration.
6.5.1 Rationale for selection of dose	However, the Sponsor does not anticipate that the renal impairment status of ADPKD patients in Stage 1 of this study (mild to moderate renal impairment with eGFR >45 mL/min/1.73 m^2 baseline) will have any potential implications for patient safety, as indicated by a PBPK model that predicted a mean venglustat plasma steady state exposure in a moderate RI population (GFR 30-60 mL/min/1.73 m^2) following 15 mg QD dose, normal CYP abundance and age (matching the age of ADPKD patients in the current study) to be within the range of steady state exposures observed in Phase 1 (TDR12768 in healthy volunteers) and Phase 2 studies (ACT13739 in FD patients). ~~The patients in Stage 1 will finish 24 months on placebo, 8 mg or 15 mg. In Stage 2, patients will be randomized to placebo and~~ This was further confirmed with results from a clinical study conducted to assess the impact of renal impairment on venglustat PK (POP14499), where, following a single 15 mg dose ~~(8 mg or 15 mg) selected during unblinded review by the DMC of the aggregated safety data from Stage 1. The selected dose will be the highest dose determined~~, venglustat exposure (AUC) was similar in subjects with mild RI but was estimated to be ~~safe and well tolerated~~ higher in ~~Stage~~ subjects with moderate and severe RI by as much as 1.33-fold (90% CI: 1.09 to 1.62) and 1.59-fold (90% CI: 1.15 to 2.20), respectively. To provide a conservative estimate of effect of moderate RI on venglustat PK, the upper end of 90% CI (1.62-fold) was taken into account at the lower limit of moderate RI (GFR: 30 mL/min). Given the current exposure margin from NOAEL in 26-week adult rat toxicology study of approximately 3.7-fold relative to the to human steady state exposure following 15 mg dose (2420 ng.hr/mL obtained from healthy subjects in study TDR12768 and NOAEL exposure of 8890 ng.hr/mL in female rats in adult rat 26-week toxicology study), venglustat exposure in moderate renal impaired subjects with eGFR up to 30 mL/min following a 15 mg QD dose, is anticipated to be below this NOAEL exposures. In addition, venglustat exposure in moderate renal impaired subjects with eGFR up to 30 mL/min following a 15 mg QD dose, is also anticipated to be below the NOAEL exposure estimate for spermatid degeneration from adult mouse precarcinogenicity study (7780 ng.hr/mL). Considering the totality of this information, no dose adjustment is warranted in patients with eGFR ≥30 mL/min. The patients in Stage 1 will finish 24 months on placebo or 8 mg or 15 mg venglustat. In Stage 2, patients will be randomized to placebo or either (8 mg or 15 mg venglustat. The dose of 8 mg or 15 mg will be selected during unblinded review by the DMC of the	Clarification Provided information from the completed study of the assessment of renal impairment on venglustat PK and rationale for no dose adjustment in patients with eGFR ≥30 mL/min.

Section # and Name	Description of Change	Brief Rationale
	aggregated safety data from Stage 1. The selected dose will be the highest dose determined to be safe and well tolerated in Stage 1 (based on DMC review of safety data for 150 patients who have completed at least 1 month of treatment). If ~~both~~ during Stage 1 the 8 mg and 15 mg doses of venglustat have similar safety and tolerability profiles, ~~during Stage 1,~~ then the 15 mg dose will be selected. ~~because,~~ This is because based on the human healthy volunteer plasma PK/PD in the repeat dose study TDR12768 and rodent ADPKD efficacy studies, better efficacy is anticipated with 15 mg dose due to higher plasma GL-1 reduction as compared to the 8 mg dose. ~~There are~~ Only minimal safety concerns were observed for the 15 mg dose based on the present safety data of FD patients who have received the 15 mg dose for up to 24 months.	
6.5.2. Rationale for study design and control groups	A prognostic enrichment approach is used to select patients for primary analysis population who will be at risk for rapid progression of disease based on those aged between 18 to 50 years, CKD stages 2-3A, and Mayo Imaging Classification of ADPKD Class 1C-E. Patients with eGFR < 45 mL/min/1.73 m^2 aged 18 to 55 years old recruited in Stage 2 of the study will be not included in primary analysis population but the data from these patients will be analyzed separately. Patients with CKD stage 3b (eGFR 30 - 45 mL/min/1.73 m^2) aged 18 to 55 years old will be recruited in Stage 2 of the study to permit gathering information on venglustat in this severely affected patient population. However, this patient population will not be included in the Stage 2 primary analysis but will be analyzed separately. The rationale for including these patients in the study is to obtain further information on venglustat exposure, safety and efficacy in patients with lower renal function. Based on the mode of action of venglustat the benefit of disease modification is expected to decrease whereas the exposures of venglustat increase with declining renal function. For this reason, CKD Stage 4 patients (eGFR <30 mL/min/1.73 m^2) will not be included into the study. The seamless design of this two-stage trial is based on the similarities of the endpoints of the 2 stages and the identical inclusion/exclusion criteria of the primary analysis population of the 2 stages.	Clarification.
7.2 Exclusion criteria E1	Systolic BP >160 mmHg* at run in and baseline visits. *mean value of three or five systolic BP measurements (See Section 9.4.5)	Clarification
	The patient has, according to World Health Organization (WHO) Grading, a cortical cataract ~~>~~≥1 quarter of the lens circumference (Grade cortical cataract 2 [COR 2]) or a posterior subcapsular cataract ~~>~~≥2 mm (Grade posterior subcapsular cataract 2 [PSC 2]). Patients with nuclear cataracts will not be excluded.	Correction
7.2 Exclusion criteria E5	The patient has a ~~documented diagnosis~~ positive result of any of the following ~~infections~~ tests: hepatitis B~~, hepatitis C, human immunodeficiency virus 1 or 2 (positive hepatitis B~~ surface antigen (HBsAg), anti-hepatitis C virus (anti-HCV) antibodies, anti-human immunodeficiency virus 1 and 2 antibodies (anti-HIV1	Clarification that patients' immune due to natural infection (positive HBsAb, negative HBs Ag, and positive HBcAb) are eligible

Section # and Name	Description of Change	Brief Rationale
	and anti-HIV2 Ab). Patients with a positive hepatitis B surface antibody (HBsAb) test ~~with a history of prior hepatitis B immunization~~ are eligible if other criteria are met (ie, negative tests for: HBsAg, hepatitis B core antibody [HBcAb]). Patients immune due to natural infection (positive HBsAb, negative HBs Ag, and positive HBcAb) are eligible if they have a negative HBV DNA test.	if they have a negative HBV DNA test.
7.2.3 Exclusion criteria	Patients who were rescreened in Stage 1 of the study under protocol versions preceding amendment 04 and failed screening because of eGFR <45 mL/min/1.73 m^2, can be screened in Stage 2. Patients with eGFR at screening from 75.0 to 89.9 ~~90~~ mL/min/1.73 m^2.	Clarification.
8.8.1 List of forbidden concomitant medication	Alpha-adrenergic receptor agonist glaucoma medications because they can worsen the vision of patients with cataracts. ~~Glaucoma medications.~~	Clarified that among glaucoma medications only alpha-adrenergic receptor agonist glaucoma medications are prohibited during the study treatment period.
9.4.6 Physical examination	A complete physical examination ~~(including full neurological exam)~~ will include a thorough review of all body systems to collect physical observations/measurements. A mental status evaluation will be performed as a 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 patient, provided the method covers all the areas assessed by MMSE. A full standard basic neurological examination will be performed as a part of the complete physical examination. Results will be documented on eCRF pages dedicated to neurological examination. For details, please refer to the Study Reference Manual. Abbreviated physical examinations will focus on ~~cardiac and respiratory symptoms, as well as any~~ areas important for assessment of AEs if necessary.	Provided reference to the Study Reference Manual for details of the full standard neurological examination (including mental status evaluation) that is performed as a part of the complete physical examination.
9.4.10 Ophthalmological examination 10.4.1.3 Adverse event of special interest	For opacities present at baseline/previous visit, changes in LOCSIII score of ≥0.5 for nuclear opalescence, ≥0.8 for cortical opacification, or ≥0.5 for posterior subcapsular opacification compared with baseline or previous assessment will be considered as a worsening.	To specify threshold for minimal significant change in LOCSIII score that will be considered as a worsening of lens opacity.
	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.	Clarification that the Tumbling E distance chart should be based on the Snellen fraction.

Section # and Name	Description of Change	Brief Rationale
10.1.1.2 Visit 2; Run-in Day -15, Visit window	The run-in visit (Day -15) can ~~should~~ be performed up to ~~approximately~~ 15 (±3) days after the initial screening visit or as soon as results of all assessments performed at Visit 1 are available. ~~Visit. Using the date of the initial screening visit (date of the first study procedure) as reference, a time frame of ±3 days is acceptable for this visit.~~ Abbreviated physical examination (focus on ~~cardiac and respiratory systems, as well as any~~ areas important for assessment of AEs if necessary).	Clarification that the run-in visit can be performed up to approximately 15 (+3) days after the initial screening visit or as soon as results of all assessments performed at Visit 1 are available.
10.1.2 Treatment Period - Month 0 to Month 24	Visit window: The randomization visit (Day 1) should be performed ~~30~~ 15 days after Visit 2 ~~the initial screening visit~~ with the acceptable window of ±3 days. Using Day 1 as reference, a time frame of ±7 days is acceptable for Visits 4 to 12. (If one visit date is skipped/missed/changed, the next visit should take place according to the original schedule.)	Clarified that the time of the randomization visit depends on the time frame of Visit 2 and not on the time frame for Visit 1 because the initial screening period could be completed as soon as results of all V1 assessments are available.
10.1.2.1 Visit 3 Randomization at Month 0/Day 1	Biobanking blood sample (optional) collected prior to the start of IMP. Remind patient to not take the dose at home on the next clinic visiting day.	Clarification.
10.1.2.2 Visit 4, 6, 8, 10, 12/Month 1, 6, 12, 18, 24 (Day 30, 180, 360, 540, 720)	Abbreviated physical examination (focus on ~~cardiac and respiratory systems, as well as any~~ areas important for assessment of AEs if necessary; Visits 4, 6, and 8). Biobanking blood sample (optional) at Visits 8 and 12. Remind patient to not take the dose at home on the clinic visiting day at Visits 6 and 10 during Stage 1, and at Visit 12 during Stage 2~~Visits 4, 8, and 10~~.	Correction.
10.1.2.3 Visit 5, 7, 9, 11/Month 3, 9, 15, 21 (Day 90, 270, 450, 630)	Abbreviated physical examination (focus on ~~cardiac and respiratory systems, as well as any~~ areas important for assessment of AEs if necessary).	Clarification.
10.1.3 Follow-up Visit – Visit 13/Month 25 (Day 750)	Abbreviated physical examination (focus on ~~cardiac and respiratory systems, as well as any~~ areas important for assessment of AEs if necessary).	Clarification.
10.3.3 List of criteria for permanent treatment discontinuation	If a patient experiences a reduction in eGFR below 30 mL/min/1.73 m^2 on two visits apart, the patient will be discontinued from the study. If a patient experiences a reduction in eGFR below 25 mL/min/1.73 m^2, a repeated test must be performed in ~~4 weeks~~ 30 days: if eGFR result repeated in ~~4 weeks~~30 days is below 30 mL/min/1.73 m^2, the patient will be discontinued from the study.	Added rules for discontinuation for confirmed decrease in eGFR.
10.3.4 Handling of patients after permanent treatment discontinuation	Stage 1: EOT visit should include all procedures of Visit 12 and additionally a PK sample should be collected. In ~~4 weeks~~ 30 days, a Follow-up visit (Visit 13) should be performed. Stage 2: EOT visit should include all procedures of Visit 12. In ~~4 weeks~~ 30 days, a Follow-up visit (Visit 13) should be performed.	4 weeks to 30-day clarification.

Section # and Name	Description of Change	Brief Rationale
10.4.2 General guidelines for reporting adverse events	Laboratory, vital signs~~, or~~ ECG, or ophthalmic examination abnormalities are to be recorded as AEs only if: Symptomatic and/or, Requiring either corrective treatment or consultation, and/or, Leading to IMP discontinuation or modification of dosing, and/or, Fulfilling a seriousness criterion, and/or, Defined as an AESI, and or, Leading to unscheduled full ophthalmological examination with or without LOCSIII evaluation.	Correction.
11.3.1.1 Intent–to-treat population, Stage 2	The combined Stage 1 and Stage 2 ITT population will include ~~be defined as~~ all patients with an eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening who are randomized in Stage 1 or Stage 2, analyzed according to the treatment group allocated by randomization (venglustat 15 mg, venglustat 8 mg or placebo). Primary analysis in the combined Stage 1 and Stage 2 will include all data available from baseline to the end of the 24-month double-blind core treatment period. Patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will not be included in the primary efficacy analysis population but the data from these patients will be analyzed separately.	Added clarification to the definition of the combined Stage 1 and Stage 2 ITT population will include all randomized patients with eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening and patients from Stage 2 with eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will be analyzed separately.
11.3.2 Safety population	The combined Stage 1 and Stage 2 Safety population will be defined as all patients with an eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening who are randomized in Stage 1 or Stage 2 and received at least one dose or part of a dose of the double-blind IMP, analyzed according to the treatment actually received (venglustat 15 mg, venglustat 8 mg or placebo). Patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will not be included in the primary safety analysis population but the data from these patients will be analyzed separately. A secondary safety analysis population will include patients who are randomized in Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening and received at least one dose or part of a dose of the double-blind IMP.	Added clarification to the definition of the combined Stage 1 and Stage 2 Safety population will be defined as all randomized patients with eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening and patients from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will be analyzed separately.
11.4.2.1.1 Stage 1	Secondary Analysis: In this secondary analysis, TKV assessed more than ~~4 weeks~~ 30 days after the last IMP administration will be excluded from the analysis	4 weeks to 30-day clarification.
11.4.2.4 Secondary analysis including patients from Stage 2 with eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening	New section added; 11.4.2.4 Secondary analysis including patients from Stage 2 with eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening A secondary analysis of eGFR will include the following patients: Patients from Stage 1 randomized to placebo or to the selected dose of venglustat (N = 160) Patients from Stage 2 with eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening (N = 320) Patients from Stage 2 with eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening (N = 80) The purpose of this secondary analysis will be to make model-based inferences about the dependence of the treatment	Described secondary analysis including patients from Stage 2 with eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening.

Section # and Name	Description of Change	Brief Rationale
	effect on baseline eGFR. A linear mixed effect model will be fitted to the eGFR, which will include fix effects of treatment (venglustat or placebo), Mayo Imaging Classification (as per randomization stratification factor: Class 1C versus 1D versus 1E), eGFR at screening (as a continuous variable), time (as a continuous variable), treatment * time interaction, Mayo Imaging Classification * time interaction, eGFR at screening * time interaction, as well as the treatment * eGFR at screening * time interaction. The model will also include random intercept and slope. Mean eGFR slopes within each treatment group (venglustat or placebo), as well as the difference in eGFR slopes, will be estimated for the following patient categories: Patients with eGFR at screening of 30 to 44.9 mL/min/1.73 m^2 Patients with eGFR at screening of 45 to 59.9 mL/min/1.73 m^2 Patients with eGFR at screening of 60 to 74.9 mL/min/1.73 m^2 Patients with eGFR at screening of 75 to 89.9 mL/min/1.73 m^2 Estimates within each category will be calculated from the linear mixed effect model, using the center of each category as eGFR at screening in the model. Difference in slopes will be presented with 80% CI.	
11.4.3 Analyses of safety data	The residual treatment period is defined as the time from the day after the last IMP administration, plus 30 days ~~4 weeks~~ The baseline value is defined generally as the last available value before ~~randomization~~ first IMP administration.	Clarification.
14.2 Record retention in study sites	~~The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.~~ ~~However, applicable regulatory requirements should be taken into account in the event that a longer period is required.~~ ~~The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.~~ 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.	Clarification.
Throughout	Adjusted 4 weeks to 30 days in running text whenever needed	Clarification: Adjusted 4 weeks to 30 days.
Throughout	Minor formatting, consistency, and grammar-related changes done.	For consistency and better readability.

Protocol Amendment 03 Version number: 1 (electronic 3.0) Date: 01 October 2018

Changes made to the protocol are outlined as follows.

- **To change study acronym.**

  In section: Cover Page, Clinical trial summary

  Rationale: change in study acronym.

- **To replace product code with the International Nonproprietary Name venglustat.**

  In section: throughout the document.

  Rationale: introduction of the International Nonproprietary Name.

- **To describe objective of mGFR substudy - to explore the effect of GZ/SAR402671 on measured GFR.**

  In section: Clinical trial summary - Stage 2; Exploratory objectives; 5.2.3 Exploratory objectives.

  Rationale: description of objective of mGFR substudy.

- **To describe endpoint that will be assessed in mGFR substudy: annualized rate of change in mGFR from baseline to 24 months.**

  In section: Clinical Trial Summary - Stage 2; Endpoints; 9.3 Exploratory endpoints; 9.3.2.

  Rationale: description of endpoint that will be assessed in mGFR substudy.

- **To add description of mGFR substudy.**

  In section: Clinical Trial Summary - Stage 2; Assessment schedule; 1.3, footnote v; 10.1.2.1; 10.1.2.2; 10.3.4; Appendix L.

  Rationale: to include details of mGFR substudy.

- **To clarify that collection of 24-hour urine sample at Visits 5 and 7 will take place only at selected sites which participate in isolation of urinary exosomes.**

  In section: 1.3 footnote l; 9.4.17, Appendix K.

  Rationale: clarification of collection of 24-hour urine sample at Visits 5 and 7.

- **To correct spelling of parameter assessed with the urine dipstick.**

  In section: 1.3 footnote i; 1.4 footnote h; 10.1.1.1; 10.1.2.2; 10.1.2.3.

  Rationale: nitrate corrected to nitrite.

- **To clarify timing of evaluation of V2 ECG reading related to run-in medication at V2 and IMP at V3 administration.**

  In section: 1.3; 1.4 footnote m; 10.1.1.2.

  Rationale: clarification added that Investigator should evaluate V2 ECG reading prior to run-in medication administration; V2 ECG central reader's assessment should be evaluated prior to IMP administration at for Visit 3 only.

- **To add information about tolvaptan's approval in US.**

  In section: 4.1.2.

  Rationale: update of the status of tolvaptan's approval.

- **To add clarification that WOCBP should use a highly effective method of contraception during the study.**

  In section: 4.3, 7.1 Inclusion Criteria I09.

  Rationale: clarification of requirement for WOCBP to use a highly effective method of contraception during the study.

- **To clarify the time point of the follow up visit after the final dose of investigational medicinal product.**

  In section: 6.2.1.

  Rationale: clarified that the follow-up visit should occur 30 days after the final dose of investigational medicinal product.

- **To clarify that for patients agreeing to participate in the mGFR substudy of Stage 2, additional entry criteria are listed in Appendix L.**

  In section: 7.

  Rationale: description of additional entry criteria for patients who agree to take part in mGFR substudy of Stage 2.

- **To emphasize that a complete physical examination includes full neurological examination.**

  In section: 9.4.6.

  Rationale: emphasis on the neurological component of the complete physical examination.

- **To establish the plan for handling patients who indicate that they have suicidal thoughts.**

  In section: 9.4.9.

  Rationale: establishing plan for handling patients who indicate that they have suicidal thoughts.

- **To clarify the use of Snellen chart in countries where the Latin alphabet is not used.**

  In section: 9.4.10.

  Rationale: use of Tumbling E distance chart was allowed in countries where Latin alphabet is not used.

- **To remove the phrase that highly effective contraceptive method of birth control may be defined according to the local medical practice and regulations.**

  In section: Appendix A.

  Rationale: "Highly effective contraception" has a specific meaning as defined the Clinical Trial Facilitation Group guidance document on contraception in clinical trials.

Protocol Amendment 02 Version number: 1 (electronic 2.0) Date: 25 May 2018

Changes made to the protocol are outlined as follows.

- **To supplement description of the exploratory objectives of the study.**

  In section: clinical trial summary, 5.1.3, 5.2.3

  Rationale: added description of objective to explore the effect of GZ/SAR402671 on type, frequency and dosage of analgesic/over the counter pain medication administration.

- **To detail settings of the placebo run-in period.**

  In section: clinical trial summary, 6.1, 6.2.1.

  Rationale: single-blind setting added to the description of placebo run-in period in Stage 1 and Stage 2.

- **To add details of stratification of patients by geographic region.**

  In section: clinical trial summary, 6.1.

  Rationale: stratification of patients by region was added to achieve balance between the treatment arms across the different regions.

- **To clarify inclusion criteria.**

  In section: clinical trial summary, 7.1.

  Rationale:

  - Clarification has been made on inclusion criterion I01 related to the timing of evaluation of this criterion;
  - Clarification has been made on inclusion criterion I07 describing situation when patient refuses to initiate treatment with tolvaptan as part of scenario when tolvaptan may not be considered by treating physician as indicated for treatment of patient.

- **To clarify exclusion criteria.**

  In section: clinical trial summary, 7.2.1

  Rationale:

  - Criterion E02 was reworded to emphasize that all Polycystic Kidney Disease-modifying agents should not be administered within 3 months prior to the screening visit;
  - Criterion E05 was supplemented with information when patients with positive hepatitis B core antibody, negative HBsAg and negative hepatitis B surface antibody can be enrolled in the study (to exclude occult HBV infection in isolated anti-HBc positive patients).

- **To apply removal of mGFR substudy to the protocol.**

  In section: clinical trial summary, 1.4, 3, 5.2.3, 9.3.2, 10.1.2.1, 10.1.2.2, 10.3.4, Appendix A.

Rationale: references to mGFR substudy (including collection of blood samples and Appendix A) were removed from the protocol.

- **To clarify adjustment on stratification factors in the analysis.**

  In section: clinical trial summary, 11.4.2.1.1, 11.4.2.2.3, 11.4.5

  Rationale: to clarify that adjustment on stratification factors in the analysis for Mayo imaging classification (Mayo Class 1C, 1D and 1E).

- **To improve the precision and accuracy of the BP measurement.**

  In section: 1.3, 1.4, 9.4.5.

  Rationale: 5-minute rest period was changed to 10-minute rest period; additionally scenario of short-term blood pressure variability between successive measurements was addressed.

- **To clarify screening laboratory assessments.**

  In section: 1.3, 1.4

  Rationale: to clarify that some assessments done at the beginning of screening may have to be repeated prior to randomization.

- **To detail course of actions when any parameter on the locally performed urinary dipstick is abnormal.**

  In section: 1.3, 1.4

  Rationale: to specify that in case if any parameter on the urinary dipstick is abnormal, a urine sample should be sent to the central laboratory for quantitative measurement

- **To expand the justification of placebo selected as the control arm.**

  In section: 6.5.2

  Rationale: Details have been added to justify why tolvaptan is not being used as control arm such as the description of potential discontinuation or failure to initiate the therapy with tolvaptan due to poor tolerability and safety, and possibility of substantial unblinding due to aquaretic effect of tolvaptan.

- **To clarify that enrollment is based on 3 categories of screening eGFR values.**

  In section: 7

  Rationale: to have adequate representation of patients across eGFR spectrum a minimum of 20% of patients within 3 categories of screening eGFR will be enrolled.

- **To clarify blinding measures related to PK measurements.**

  In section: 8.3.1

  Rationale: to clarify that only samples collected from patients on active drug will be analyzed and describe measures to ensure blinding at the assay institutions charged for PK measurements.

- **To clarify forbidden concomitant medications.**

  In section: 8.8.1

  Rationale: to clarify that Polycystic Kidney Disease-modifying agents (eg, somatostatin analogues) are forbidden concomitant medications.

- **To provide details on the method of calculation of eGFR in Asian population of patients and separately in Japanese patients.**

  In section: 9.4.2

  Rationale: to clarify that for calculation of eGFR in Asian population of patients (except Japanese patients) the Asian-modified CKD-EPI equation will be used; the CKD-EPI Study equation multiplied by a Japanese coefficient of 0.813 will be used for eGFR calculation in Japanese patients.

- **To update and clarify instructions for collection of urine spot.**

  In section: 1.3, 1.4, 9.4.3

  Rationale: to clarify instructions for collection of urine spot including collection of third spot sample.

- **To provide details on the frequency and scope of ophthalmic examination, to update the system for grading the type and severity of cataract, to remove requirement for lens photography during each lens assessment and requirement for central reading.**

  In section: clinical trial summary, 1.3, 1.4, 9.4.10, 10.1.1.2, 10.1.2.2, 10.1.2.3

  Rationale: to update the frequency and the scope of ophthalmic exam, to replace LOCSII with LOCSIII, to remove requirement for mandatory lens photography and central reading of lens images.

- **To rename section.**

  In section: 9.4.11

  Rationale: to change the name of section to Patient reported outcomes.

- **To update description of Patient Global Impression of Change questionnaire.**

  In section: 9.4.11.4.

  Rationale: to specify timing of the start of assessment and categories of scales.

- **To update items of the Daily symptoms of autosomal dominant polycystic kidney disease diary.**

  In section: 9.4.11.6.

  Rationale: to regroup pain and nocturia items of the diary and to add an additional item that will direct to the medication entry log.

- **To update information about PK samples collection.**

  In section: clinical trial summary, 1.3, 1.4, 9.4.14.1, 10.1.2.1, 10.1.2.2

Rationale: to remove all pre-dose samples on Day1 in Stage 1; to add a post-dose sample on Day1 in stage 2; to move the PK sampling from Month 6 to month 1 in Stage 2; to specify that the post-dose sample of 3 hours can be collected at 3 + or - 1 hour.

- **To detail stopping rules for individual treatment discontinuation in case of ophthalmic examination findings and reduction in eGFR.**

  In section:10.3.3

  Rationale: To include a stopping rule for individual treatment discontinuation in case of best corrected visual acuity loss due to posterior subcapsular cataract; to modify period between 2 assessments with confirmed reduction in eGFR that should lead to study treatment discontinuation.

- **To clarify visits and assessments that should be performed if patient prematurely and permanently discontinue study medication.**

  In section: clinical trial summary, 10.3.4.

  Rationale: to specify visits and assessments that should be performed if patient prematurely and permanently discontinue study medication (end-of-treatment and follow-up visits, PRO assessments, efficacy and safety assessments at visits Month 18 and Month 24).

- **To describe secondary analysis that will explore a potential acute hemodynamic effect.**

  In section: 11.4.2.1.1

  Rationale: to describe secondary analysis that will explore a potential acute hemodynamic effect using TKV data assessed from 1 month to 18 months.

- **To correct information of the section.**

  In Section: 12.2

  Rationale: to remove requirement that the written informed consent form can be signed and dated by the patient's legally acceptable representative.

- **To clarify information related to highly effective contraceptive method of birth control.**

  In section: Appendix B.

  Rationale: to specify that highly effective contraceptive method of birth control may be defined according to the local medical practice and regulations.

- **To clarify that Isolation of Urinary Exosomes analysis is part of ADPKD biomarkers assessment (required tests of the protocol).**

  In section: Appendix L.

  Rationale: to specify that isolation of Urinary Exosomes analysis is part of ADPKD biomarkers assessment and is covered by informed consent of EFC15392 study.

Protocol Amendment 01 Version number: 1 (electronic 1.0) Date: 19 April 2018

Changes made to the protocol are outlined as follows.

- **To clarify possible course of action with regard to the study drug dose in ongoing patients in Stage 1 after DMC review of safety data and dose selection for Stage 2.**

  In section: 6.1

  Rationale: described possible course of action with regard to the study drug dose in ongoing patients in Stage 1 that could be recommended by DMC to Sponsor after dose selection for Stage 2.

- **To clarify inclusion criteria.**

  In section: clinical trial summary, 7.1.

  Rationale: clarification has been made on inclusion criteria I01 and I02 to better define the targeted population and criterion I07 to describe written ICF collection before any study procedure.

- **To clarify exclusion criteria.**

  In section: 7.2.1, 7.2.3.

  Rationale: criterion E09 was modified to better detail uncontrolled medical conditions, criterion E10 was modified to address country-specific exclusion criteria, criterion E16 was revised to indicate the limits of total and direct bilirubin that are allowed for inclusion of patients with Gilbert`s syndrome.

- **To detail timing of evaluation of the secondary and exploratory endpoints.**

  In section(s): clinical trial summary, 9.2.2, 9.2.3.3, 9.3.3.

  Rationale: Details on the time point of evaluation of secondary and exploratory endpoints were included.

- **To add a stopping rule for individual treatment discontinuation.**

  Section 10.3.3

  Rationale: to include a stopping rule for individual treatment discontinuation in case of accelerated disease progression based on eGFR reduction.

- **To include blood pressure control recommendations.**

  In Section: 10.6.

  Rationale: Safety management was modified to include blood pressure control recommendations if patient requires modification of antihypertensive therapy during study participation.

- **To clarify that mGFR substudy is optional for eligible patients.**

  In section Appendix A, Section 4.

  Rationale: To clarify that mGFR substudy is optional for eligible patients.

Appendix O 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 7.2.4, Section 8.1.2, Section 9.4, Section 10, Section 10.3.1, Section 12.2) 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, randomization 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 labs).

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 Direct-to-Patient (DTP) supply of venglustat from the site where allowed by local regulations and agreed upon by the participant. Direct-to-Patient 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:

- Phone 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 patient safety) to be captured via phone 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 patients can measure temperature and BP at home). Visit ePROs (questionnaires) should be completed by the patient in the eDiary as usual. eDiary data can still be checked online by the investigator/site team prior to calling the patient to ensure any follow-up questions or findings can be discussed.

- If it is feasible and there is no additional risk for a patient from the hazard that 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 Chronic Kidney Disease Epidemiology Collaboration equation;
  - complete blood count.
- Patients with a recent eGFR **>45 mL/min/1.73 m^2**, may continue IMP up to 6 months, without having an on-site visit.

  Patients with a recent eGFR **≤45 and >30 mL/min/1.73 m^2**, may continue IMP up to 3 months, without having an on-site visit. Patient 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.

  Patients 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 patient will have to stop the treatment permanently.

- When phone 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 patients 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 patient from the hazard that led to declaration of national emergency.

New screenings 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 rescreened patient was screen-failed during a regional or national emergency for reasons not related to eligibility, rescreening shall be permitted when the situation normalizes.

If eligibility assessment cannot be performed due to department/service shutdowns (MRI, ophthalmology, etc) during the screening period, the patient 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 3:

- Blood chemistry (if >2 weeks after Visit 2)
- CBC (if >4 weeks after Visit 1)
- BCVA and lens cataract grading according to WHO simplified cataract grading system (if >3 months from Visit 2 eye exam)
- ECG (if >3 months from Visit 2 ECG test)
- BDII (if >2 weeks after Visit 2)
- MRI (decision on case by case basis: if >1-3 month before Visit 3)

If eligibility was confirmed but patient cannot attend site to perform Visit 3 because of a regional or national emergency declared by a governmental agency, a remote Visit 3 (randomization) can be performed where allowed by local regulations under condition that the Direct-to-Patient (DTP) supply of venglustat from the site is allowed by local regulations and agreed upon by the participant, and a home health vendor service is in place to visit patient in 1 month (for Visit 4) to collect laboratory samples and assess adverse event after 1 month on the double-blind treatment.

For a remote Visit 3, a home health vendor should visit the patient at least one day before the remote Visit 3 to collect blood pressure measurements, assess run-in medication compliance, adverse events, concomitant medications and perform urine pregnancy test (for WOCBP).

On the day of the remote Visit 3, the Investigator will evaluate assessments performed and provided by home health vendor, ePROs completed by the patient in the eDiary, and will randomize patient if eligibility is reconfirmed. If patient is randomized, IMP will be sent to patient via DTP process. Site will need to follow up via phone with the patient once IMP is delivered.

Contingencies implemented due to emergency will be documented.

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efc15392-16-1-1-amended-protocol07