STATISTICAL ANALYSIS PLAN

Protocol 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)**
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Short title:	**Staged PKD**
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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

VERSION HISTORY

This statistical analysis plan (SAP) for study EFC15392 is based on the protocol amendment 5 dated 17-July-2020. There are no major changes to the statistical analysis features in this SAP.

The first participant was randomized in the Stage 1 population on 11-Feb-2019. This SAP is approved before the futility analysis which is planned when all participants from Stage 1 have completed the first 9 months of treatment and approximately 30% have completed 18 months of treatment with Total Kidney Volume (TKV) available (or have prematurely discontinued).

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	19-Jan-2021	The Population without trial impact (disruption) due to COVID-19 has been defined and additional analysis performed according to this population	In order to assess the impact of the COVID19 on the study
2	22-Jun-2021	Labels of treatment group updated from GZ/SAR402671 to venglustat	Clarification
		Added definition of baseline specific to Patient symptom diaries parameters and urine osmolality (see Section 4.1 and Section 4.8.3)	Clarification
		Update of the definition the treatment emergent period for patients who participate to the long-term extension LTS15823 (see Section 4.1)	Clarification
		Update of the tertiary endpoint related to TLV to be analyzed in participants with height adjusted total liver volume [htTLV] >1 L/m instead of > 2L/m (see Section 1.2 and Section 4.5.1)	Selection of participant with htTLV >2 L/m was to strict. According to HALT publication (1) it's acceptable to consider moderate PLD as htLV >1 L/m.
		Update of tertiary endpoint related to hospitalization to analyze rate and time of all-cause hospitalization (see Section 1.2, Section 4.5.1 and Section 4.8.5)	Clarification of endpoint
		PK populations and PK data analysis time windows have been updated (see Section 3 and Section 5.4)	Correction of time points as per protocol

SAP Version	Approval Date	Changes	Rationale
		The two-step analysis is not applicable anymore and replaced by a single analysis of all data available on combined Stage 1 & Stage 2 analysis (see Section 1.1 and Section 4.9.3)	Following decision to discontinue EFC15392 and LTS15823 studies based on EFC15392 futility analysis
		Efficacy analyses on Stage 1 ITT population and combined Stage 1 and Stage2 population will be conducted on all data available up to database lock (see Section 4.1, Section 4.3.1). No multiple imputation will be done, only analysis on observed data will be performed (see Section 1.2.1, Section 4.3.1.1, Section 4.3.1.2, and Section 4.3.2.2).	
		As no post-baseline MRI data will be available in Stage 2 at the time of the study discontinuation, the analysis of TKV and TLV in Combined Stage 1 and Stage 2 will not be done (see Section 1.2.1, Section 4.4.2.2 & Section 4.5.2).	
		Secondary analysis of eGFR on all randomized participants will be replaced by descriptive summary across visit on the secondary Stage2 ITT population (see Section 3 and Section 4.3.2.4)	
		For all tertiary endpoints, due to the high number of missing data at month18 and month24, MMRM will be replaced by only descriptive summary by visits (see Section 4.5.2, Section 4.8.2, Section 4.8.3 and Section 4.8.4). For the secondary endpoints (BPI-Item3 & BFI Item3), in case the MMRM does not converge due to high number of missing data, then only descriptive summary by visits will be provided (see Section 4.4.1.2 and Section 4.4.2.2)	
		As no GM3 sample tested at the time of the study discontinuation, the analysis of GM3 will not be done (see Section 4.8.2)	
		Safety populations and all safety analyses on Stage 1 populations are removed. All safety analyses will be performed on the extended combined Stage 1 and Stage 2 safety population, including all participants with an eGFR between 30 and 89.9 mL/min/1.73 m^2 at screening (see Section 3 and Section 4.7).	
		mGFR analysis has been removed as no data available (see Section 4.5.1).	

1 INTRODUCTION

1.1 STUDY DESIGN

This is an international, multicenter, randomized, double-blind, placebo-controlled, two-stage study in adult participants at risk of rapidly progressive Autosomal Dominant Polycystic Kidney Disease (ADPKD) aged 18 to 50 years in Stages 1 and 2. In addition, Stage 2 also includes participants aged 18 to 55 years with a screening estimated Glomerular Filtration Rate (eGFR) between 30 and 44.9 mL/min/1.73 m^2.

The study is divided into 2 stages:

Stage 1: an up to 30-days screening period including a 2-week placebo run-in (to identify participants 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 participants, aged 18 to 50 years with an eGFR in (45 to 89.9) are randomized with a 1:1:1 ratio to placebo, 8 mg venglustat, or 15 mg venglustat.

Participants are stratified based on their predicted ADPKD progression rate (1C versus 1D versus 1E) according to Mayo Imaging Classification and geographical region (North America, Europe, China, Republic of Korea, Rest of the World).

After the interim unblinded aggregate safety review by the DMC of the first 150 randomized participants from Stage 1 having completed at least 1 month of treatment (or have prematurely discontinued), the DMC determined that the 15 mg dose was the highest dose to be safe and well tolerated in Stage 1, and recommended the venglustat 15 mg dose for Stage 2.

Stage 2: starts with an up to 30-day screening period including a 2-week 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, eligible participants aged 18 to 55 years with an eGFR of 30 to 89.9 are randomized with a 1:1 ratio to placebo and 15 mg venglustat. Participants are stratified based on their predicted progression rate (1C versus 1D versus 1E) according to Mayo Imaging Classification and geographical region (North America, Europe, China, Republic of Korea, Rest of the World).

Participants 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).

As per protocol a first step analysis was planned when all participants from Stage 1 have been randomized and have completed the Month 18 visit (or have discontinued the study) for the submission to the accelerated approval. Then a second step analysis was planned to be conducted after study completion of Stage 1 and Stage 2 participants.

Considering the decision after futility analysis to discontinue the study, the two-step analysis is no more applicable. Consequently, one single analysis will be conducted on all data available on participants from combined Stage 1 and Stage 2.

1.2 OBJECTIVE AND ENDPOINTS

The objectives and endpoints as defined in the protocol are summarized in Table 2.

Table 2 - Objectives and endpoints

Objectives		Endpoints
Stage 1		
Primary		
	• To determine the effect of venglustat on the rate of TKV growth in patients at risk of rapidly progressive ADPKD	• Annualized rate of change in TKV based on magnetic resonance imaging (MRI) from baseline to 18 months
Secondary		
• Efficacy objectives	• To determine the effect of venglustat on the rate of renal function (eGFR) decline	• Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 18 months
	• To determine the effect of venglustat on pain and fatigue, based on patient reported diary	• Change in pain from baseline to 18 months, based on BPI Item 3 assessed from the daily symptom diary
		• Change in fatigue from baseline to 18 months, based on BFI Item 3 assessed from the daily symptom diary
	• To evaluate the PK of venglustat in ADPKD patients	• Plasma venglustat concentrations
• Safety/tolerability objectives	• To characterize the safety profile of venglustat	• Treatment emergent adverse events (TEAEs)/adverse events (AEs)/serious adverse events (SAEs), laboratory parameters, vital signs, electrocardiogram and findings from physical examination
	• To evaluate the effect of venglustat on mood using BDI-II	• Change in score of BDI-II during the treatment emergent period
	• To evaluate the effect of venglustat on the lens by ophthalmological examination	• Change in the lens clarity by ophthalmological examination during the treatment emergent period
Tertiary/exploratory		
	• To explore the impact of venglustat on total liver volume (TLV) (in participants with height adjusted total liver volume htTLV >1 L/m)	• Annualized rate of change in TLV based on MRI (in participants with htTLV >1 L/m) from baseline to 18 months

Objectives	Endpoints
• To explore the effect of venglustat on kidney concentrating ability by assessing urine osmolality (in participants not on diuretic) • To explore the effect of venglustat on nocturia • 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 (Brief Pain Inventory [BPI]), fatigue (Brief Fatigue Inventory [BFI]), and general health status (EuroQoL 5-dimension 5-level [EQ 5D-5L]) to 18 months • 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 GCS in plasma and urine	• Change in urine osmolality from baseline to 18 months • Change in nocturia from baseline to 18 months, based on patient reported diary • Change in SBP/DBP during the treatment emergent period • Change in biomarkers associated with ADPKD (eg, FGF23 and ADMA) from baseline to 18 months • Change in pain (BPI) from baseline to 18 months • Change in fatigue (BFI) from baseline to 18 months • Change in health status (EQ 5D 5L) from baseline to 18 months • Type, frequency, and dosage of analgesic/over the counter (OTC) pain medication administration from baseline to 18 months • Rate of all-cause hospitalization • Change in Glucosylceramide (GL-1) and GM3 from baseline to 18 months
Stage 2	
Primary	
• 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	• Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months

	Objectives	Endpoints
Secondary		
• Efficacy 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	• Annualized rate of change in TKV based on MRI from baseline to 18 months • Change in pain from baseline to 24 months, based on BPI Item 3 assessed from the daily symptom diary • Change in fatigue from baseline to 24 months, based on BFI Item 3 assessed from the daily symptom diary
• Safety/tolerability objectives	• To evaluate the PK of venglustat in ADPKD patients • 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	• Plasma venglustat concentrations • TEAEs/AEs/SAEs, laboratory parameters, vital signs, electrocardiogram and findings from physical examination • Change in score of BDI- during the treatment emergent period • Change in the lens clarity by ophthalmological examination during the treatment emergent period
Tertiary/exploratory		
	• To explore the impact of venglustat on TLV (in participants htTLV >1 L/m)	• Annualized rate of change in TLV based on MRI (in participants with htTLV >1 L/m) from baseline to 18 months
	• To explore the effect of venglustat on kidney concentrating ability by assessing urine osmolality (in participants not on diuretic) • To explore the effect of venglustat on nocturia • To explore the effect of venglustat on systolic blood pressure (SBP) and diastolic blood pressure (DBP) • To explore the effect of venglustat on measured GFR (mGFR) (substudy) • 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 (Brief Pain Inventory [BPI]), fatigue (Brief Fatigue Inventory [BFI]), and	• Change in urine osmolality from baseline to 24 months • Change in nocturia from baseline to 24 months, based on patient reported diary • Change in SBP/DBP during the treatment emergent period • Annualized rate of change in mGFR from baseline to 24 months • Change in biomarkers associated with ADPKD (eg, FGF23 and ADMA) from baseline to 24 months • Change in pain (BPI) from baseline to 18 months • Change in fatigue (BFI) from baseline to 18 months • Change in health status (EQ 5D 5L) from baseline to 18 months • Type, frequency, and dosage of analgesic/over the counter (OTC) pain medication administration from baseline to 24 months • Rate of all-cause hospitalization

Objectives	Endpoints
general health status (EuroQoL 5-dimension 5-level [EQ 5D-5L]) to 24 months • 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 GCS in plasma and urine • To explore the effect of venglustat on eGFR (CKD-EPI equation) from baseline to 24 months in participants with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2	• Change in Glucosylceramide (GL-1) and GM3 from baseline to 24 months • Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months in participants with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2

1.2.1 Estimands

Primary estimand defined for main endpoints are summarized in below Table 3. More details are provided in Section 4.

Table 3 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Stage 1				
Primary objective: To determine the effect of venglustat on the rate of TKV growth in patients at risk of rapidly progressive ADPKD				
Primary endpoint (treatment policy)	Annualized rate of change in TKV based on MRI from baseline to 18 months	Stage 1 Intent-to-Treat (ITT)	regardless of adherence to study intervention	Difference in mean slope of log10-transformed TKV estimated from baseline to 18 months using a linear mixed effect model. Overall effect of venglustat assessed using a Multiple Comparison Procedure). No imputation of missing data
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**			
Secondary endpoint (treatment policy)	Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 18 months	Stage 1 ITT	regardless of adherence to study intervention	Difference in mean slope of eGFR estimated from baseline to 18 months using a linear mixed effect model. Overall effect of venglustat assessed using a Multiple Comparison Procedure). No imputation of missing data
Secondary endpoint (treatment policy)	Change in pain (BPI Item 3) from baseline to 18 months	Stage 1 ITT	regardless of adherence to study intervention	Overall effect of venglustat will be assessed using a Multiple Comparison Procedure using baseline adjusted least-squares means estimates at Month 18 from Mixed model with repeated measures (MMRM). No imputation of missing data
Secondary endpoint (treatment policy)	Change in fatigue (BFI Item 3) from baseline to 18 months	Stage 1 ITT	regardless of adherence to study intervention	Analysis of fatigue will be identical to the one of pain
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				
Primary endpoint (treatment policy)	Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months	Combined Stage 1 and Stage 2 ITT	regardless of adherence to study intervention	Analysis of eGFR in Stage 2 will be identical to the one of Stage 1

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
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**				
Secondary endpoint (treatment policy)	Annualized rate of change in TKV based on MRI from baseline to 18 months	Combined Stage 1 and Stage 2 ITT	regardless of adherence to study intervention	Analysis not done as no post-baseline MRI data available on Stage 2 at the time of study discontinuation
Secondary endpoint (treatment policy)	Change in pain (BPI Item 3) from baseline to 24 months	Combined Stage 1 and Stage 2 ITT	regardless of adherence to study intervention	Analysis of pain in Stage 2 will be identical to the one of Stage 1
Secondary endpoint (treatment policy)	Change in fatigue (BFI Item 3) from baseline to 24 months	Combined Stage 1 and Stage 2 ITT	regardless of adherence to study intervention	Analysis of fatigue in Stage 2 will be identical to the one of Stage 1

2 SAMPLE SIZE DETERMINATION

In Stage 1, approximately 240 participants will be randomized (with randomization ratio 1:1:1) to placebo (n=80) or venglustat 8 mg (n=80) or venglustat 15 mg (n=80mg).

In Stage 2, approximately 320 participants 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 participants 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 participants 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 participants 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 (Section 5.6.1). SAS program is provided in (Section 5.5). The following model parameters were estimated based on available datasets from a similar participant population (participants 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 log10(TKV) of 0.02591, 0.02832 and 0.03141 in participants 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 log10 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 m^2 per year in participants from Mayo class 1C, 1D and 1E respectively, resulting in average slope of -3.66 mL/min/1.73 m^2 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. Calculations were made using simulations (Section 5.5 and Section 5.6.1).

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 4 - Populations for analyses

Population	Description
Screened	All participants who signed the Informed Consent Form (ICF).
Randomized	All participants from screened population who have been allocated to a randomized intervention by Interactive Response Technology (IRT) regardless of whether the intervention was received or not.
Exposed	All screened participants who took at least 1 dose of study intervention.
Population without trial impact (disruption) due to COVID-19	All randomized participants without any critical or major deviation related to COVID19 and who did not permanently discontinue treatment due to COVID19 and who did not permanently discontinue study due to COVID19
Stage 1 Intent-to-treat (ITT)	All participants randomized in Stage 1. Participants will be analyzed according to the intervention allocated by randomization (venglustat 15 mg, venglustat 8 mg or placebo).
Stage 1 Pharmacokinetic (PK)	All participants randomized in Stage 1 who took at least 1 dose of study intervention and who have at least one post-baseline PK assessment. Participants will be analyzed according to the intervention they actually received.
Stage 1 Pharmacodynamic (PD)	All participants randomized in Stage 1 who took at least 1 dose of study intervention and who have at least one post-baseline PD assessment. Participants will be analyzed according to the intervention they actually received.
Combined Stage 1 and Stage 2 ITT	All participants 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. Participants will be analyzed according to the intervention allocated by randomization (venglustat 15 mg, venglustat 8 mg or placebo).
Secondary Stage 2 ITT	All participants with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening who are randomized in Stage 2. Participants will be analyzed according to the intervention allocated by randomization (venglustat 15 mg or placebo).
Extended Combined Stage 1 and Stage 2 Safety	All participants with an eGFR between 30 and 89.9 mL/min/1.73 m^2 at screening who are randomized in Stage 1 or Stage 2 and who took at least 1 dose of study intervention. Participants will be analyzed according to the intervention they actually received.
Stage 2 Pharmacokinetic (PK)	All participants with an eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening who are randomized in Stage 2, who took at least 1 dose of study intervention and who have at least one post-baseline PK assessment. Participants will be analyzed according to the intervention they actually received.
Combined Stage 1 and Stage 2 Pharmacodynamic (PD)	All participants 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, who take at least 1 dose of study intervention and who have at least one post-baseline PD assessment. Participants will be analyzed according to the intervention they actually received.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

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

For any participant 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 reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the one to which the participant was treated with the longest duration.

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, [Q1, Q3] minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before or equal to the first dose of double-blind investigational medicinal product (IMP). For participants randomized but not exposed, the baseline value is defined as the last available value before or equal to the date and time of randomization.

Baseline eGFR is defined for each participant as the average of eGFR values assessed prior or equal to first IMP, or randomization for participants randomized and not exposed.

Baseline of patient daily diaries scores is defined for each participant as the average of the assessments during the 7 days prior the 1st IMP or prior randomization for participants randomized and not exposed.

Baseline of urine osmolality is defined as the average of the 3 separate assessments within the 3 days prior or equal to the baseline visit (Visit 3).

Primary efficacy analyses will be conducted on Stage 1 ITT population and on combined Stage 1 and Stage 2 ITT populations (see Section 3), including all data available at the time of database lock from baseline to Month 24:

- Participants 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. A supplemental descriptive efficacy analysis on these participants will be performed separately (see Section 3 and Section 4.3.2.4).

Safety analyses will be conducted in the extended combined Stage 1 and Stage 2 population (see Section 3) including all data available from baseline to the end of the 24-month double-blind treatment period. Unless otherwise specified, analyses will be performed by intervention group (and overall for baseline and demographics characteristics).

Observation period

The observation period will be divided into 4 segments:

- The **pre-treatment period** is defined as the period up to first IMP administration.
- The **treatment-emergent** (TE) **period** is defined as the period from the first IMP administration up to the last IMP administration in EFC15392 study +30 days or up to the first visit in LTS15823 study, whichever comes earlier. The treatment-emergent period includes the following 2 periods:

  - The **on-treatment period** is defined as the period from the first IMP administration to the last administration of the IMP +1 day.
  - The **residual treatment** period is defined as the period from the end of the on-treatment period to the end of the treatment-emergent period.
- The **post-treatment period** is defined as the period from the end of the treatment-emergent period.

The on-study observation period is defined as the time from the first administration of the IMP until the end of the study (defined as the last scheduled visit for those who completed the study and the end-of-study date collected on electronic case report form (e-CRF) page "Completion of End of Study" for those who did not complete the study. If death is the end-of-study reason, date of death will be used).

4.2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 4 will be summarized. The reasons for exclusion from the population without trial impact (disruption) due to COVID19 will be also summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Randomized participants.
- Randomized but not exposed participants.
- Randomized and exposed participants.
- Participants who completed the study treatment period as per protocol.
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation.
- Participants who completed the study period as per protocol.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation.

Reasons for permanent study intervention and study discontinuation "adverse event" and "other reasons" will be split as related versus not related to Covid-19, if applicable.

The number (%) of exposed and not randomized participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, randomized, with permanent intervention discontinuation and with early study discontinuation will be provided by country and site.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population as well as displayed separately as related versus not related to Covid-19.

Disposition by visit

Participant disposition by visit will be provided according to trial impact (disruption) due to COVID19, as reported in CRF.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

4.3.1 Stage 1

4.3.1.1 Definition of endpoint(s)

In Stage 1, the primary efficacy endpoint is the annualized rate of change in TKV based on MRI from baseline to 18 months. All the efficacy assessments collected during the study will be used, including those obtained after IMP discontinuation.

The primary estimand will be the difference in mean slope of log10-transformed TKV estimated from baseline to 18 months in all randomized participants, regardless of whether or not participants completed the treatment period. This estimand corresponds to a "treatment policy strategy". This estimand will be considered primary for supporting regulatory decision making.

A second estimand will be the difference in the mean slope of log10-transformed TKV estimated during the on-treatment period (from baseline to end of treatment). This estimand corresponds to "while on-treatment strategy" and will be evaluated for the primary efficacy endpoint only. This estimand will be considered for describing the effect of treatment as long as participants adhere to their randomized treatment.

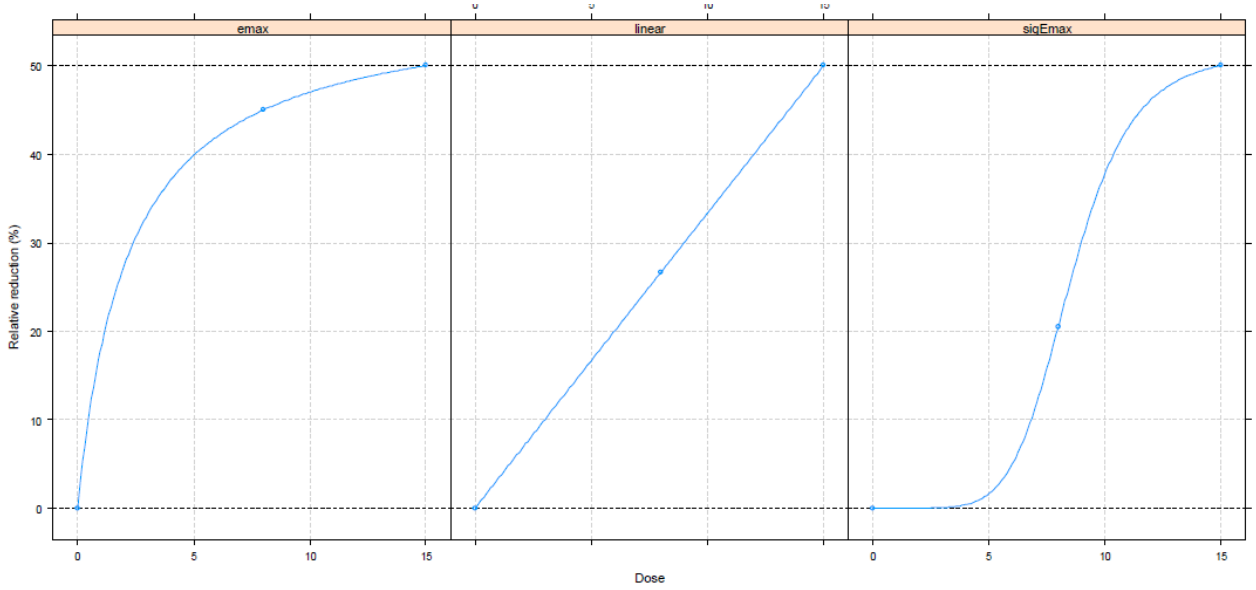
4.3.1.2 Main analytical approach

A linear mixed effect model will be fitted to the log10-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 log10-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 participants 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 (CI).

Overall effect of venglustat will be assessed using a Multiple Comparison Procedure. 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 1.

Figure 1 - Prespecified candidate of dose-response models



Optimal contrasts for each candidate model were derived using the R add-on package DoseFinding (2, 3) and are presented in Table 5. Contrasts will apply to treatment * time interaction term in the linear mixed effect model. P-value from the Multiple Comparison Procedure will be calculated as described in Section 5.6.3.

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

Dose	E_{max} model	Linear model	Sigmoid E_{max} model
Placebo	-0.8131	-0.7223	-0.6615
GZ/SAR402671 8 mg	0.3424	0.0314	-0.0838
GZ/SAR402671 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:

$$\text{Relative reduction } (\%) = \left(1 - \frac{\text{Annualized rate of change in TKV in GZ/SAR4026 71 arm}}{\text{Annualized rate of change in TKV in placebo arm}}\right) \times 100$$

Relative reduction for each dose of venglustat will be presented with 95% confidence intervals obtained using Fieller method (see Section 5.6.2) only if significant change is observed in the

placebo arm at the 0.05 level. In addition, p-values for the comparison of each dose of venglustat versus placebo will be presented for descriptive purpose.

Handling of missing data

The primary analysis will include all observed TKV data in randomized participants, regardless of whether or not participants completed the treatment period (treatment policy strategy). participants who prematurely and permanently discontinue study intervention will be requested to obtain an MRI scan at 18 months and their data collected after permanent intervention discontinuation will be included in the primary 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 intervention discontinuation.

4.3.1.3 Sensitivity analysis

4.3.1.4 No sensitivity analysis will be performed due to the discontinuation of the study after the futility analysis Supplementary analyses

While on-treatment estimand

A supplementary analysis will estimate the difference in mean slope of log10-transformed TKV during the on-treatment period. 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 participants will also be excluded from the analysis.

Other analysis

Another analysis will explore a potential acute hemodynamic effect. In this supplementary analysis only TKV assessed at least 30 days after the first IMP will be included in the linear mixed effect model. TKV at baseline will be excluded from this analysis.

4.3.1.5 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the primary endpoint across the following subgroups (categories with fewer than 5 participants may be combined with other categories):

- Age group (<40, and ≥40 years)
- Gender (Male, Female)
- Actual ADPKD progression rate (1C versus 1D versus 1E) at baseline
- Region (North America, Europe, China, Japan, Republic of Korea, Rest of the World)
- eGFR (CKD-EPI equation) at screening (45 to <60, 60 to <75, 75 to <90)
- Prespecified medical history of Hypertension (Yes/No)

The linear mixed effect model described as primary analysis will be repeated for each of the subgroups as appropriate. Subgroup factor-by-time interaction, treatment-by-subgroup factor interaction and treatment-by-subgroup-by-time interaction will be added in the primary model. For subgroup analyses by Mayo Imaging Classification, the linear mixed effect model will not include the fix effects of Mayo Imaging Classification nor Mayo Imaging Classification * time interactions. Forest plots of venglustat 8 mg and venglustat 15 mg relative reduction versus placebo and 95% CI will be presented.

4.3.1.6 Description of missing data

In order to explore missing data patterns for TKV in the primary efficacy analysis, number and percentage of participants in each of the following categories will be presented by study intervention group and displayed separately for participants on treatment at the time of Month 18 visit versus participants with permanent intervention discontinuation prior to Month 18:

- Pattern 1: Participants without post-baseline TKV assessment.
- Pattern 2: Participants with at least one post-baseline TKV assessment but not at Month 18.
- Pattern 3: Participants with TKV assessment at Month 18.

4.3.2 Combined Stage 1 and Stage 2

4.3.2.1 Definition of endpoint(s)

In combined Stage 1 and Stage 2, the primary efficacy endpoint is the annualized rate of change in eGFR (CKD-EPI equation).

The primary estimand will be the difference in mean slope of eGFR estimated from baseline to 24 months in all randomized population, regardless of whether or not participants completed the treatment period. This estimand corresponds to a “treatment policy strategy”.

4.3.2.2 Main analytical approach

The analysis of eGFR will be similar to those of TKV, with the exception that no log transformation will be used for eGFR (see Section 4.3.1.2).

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 participants, regardless of whether or not participants completed the treatment period (treatment policy strategy). Participants who prematurely and permanently discontinue study medication will be requested to obtain eGFR at 24 months.

No imputation of missing data will be performed.

4.3.2.3 Sensitivity analysis

No sensitivity analysis will be performed due to the discontinuation of the study after the futility analysis.

4.3.2.4 Supplementary analyses

While on-treatment estimand

A supplementary analysis will estimate the effect of venglustat while participants are still on treatment. eGFR assessed more than 30 days after the last IMP administration will be excluded from the analysis. eGFR assessed in randomized but not treated participants will also be excluded from the analysis.

Secondary analysis of eGFR

Descriptive summary of eGFR by analysis visit will be provided on the secondary Stage 2 ITT population (ie, all participants from Stage 2 with eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening) (see Section 3).

Time to Event analysis

Time to confirmed reduction in eGFR (local or central assessment using CKD-EPI formula) will be summarized in terms of cumulative incidence probabilities of occurrence with 95% CI as well as the number of participants at risk, number of participants censored and number of events at key time points (Month 1, Month 3, Month 6, Month 9, Month 12, Month 18, Month 21, Month 24) using the Kaplan-Meier estimates. In addition, Kaplan-Meier curves will be provided for each treatment arm.

- Time to confirmed 30% (resp. 40%) reduction in eGFR is defined as: the time from the date of randomization to the date of first eGFR assessment in case of 2 consecutive eGFR assessment with an observed reduction in eGFR from baseline of at least 30%.
  - If reduction in eGFR from baseline is less than 30% (resp. 40%) or if reduction is not observed at 2 consecutive visits before end of study, the participant will be censored at the date of the last participant's eGFR assessment for the combined Stage 1 and Stage 2 analysis.

4.3.2.5 Subgroup analyses

Subgroups analysis and description of missing data will be summarized using methods similar to those of TKV, except that eGFR (CKD-EPI equation) at screening will be (45 to <60, 60 to <75, 75 to <90) (see Section 4.3.1.5).

4.4 SECONDARY ENDPOINT(S) ANALYSIS

4.4.1 Stage 1 key/confirmatory secondary endpoint(s)

4.4.1.1 Definition of endpoint(s)

In Stage 1, the following endpoints are defined as key secondary endpoints:

- Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 18 months.
- Change in pain from baseline to 18 months. Pain score will be based on BPI Item 3, assessed from the daily symptom diary.
- Change in fatigue from baseline to 18 months. Fatigue score will be based on BFI Item 3, assessed from the daily symptom diary.

4.4.1.2 Main analytical approach

The analysis of eGFR in Stage 1 will be identical to those of Stage 2 (see Section 4.3.2.2).

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 non-missing data (4, 5).

Change in pain and change in fatigue from baseline to 18 months will be analyzed on the ITT population, regardless of whether or not participants completed the treatment period, 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 study intervention groups with their corresponding standard errors (SEs) 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 participants in each stratum in the Stage 1 ITT population (ie, “population weight”). Population weights are considered more appropriate than equal coefficients due to expected unbalances in the study population between levels of the randomization stratification factors.

Overall effect of venglustat will be assessed using a Multiple Comparison Procedure similar to those of the primary endpoint (see Section 4.3.1.2). In addition, p values for the comparison of each dose of venglustat versus placebo will be presented for descriptive purpose.

There will be no imputation of missing data.

In the case of the model does not converge due to high number of missing data, only descriptive summaries by visits will be provided.

4.4.2 Combined Stage 1 and Stage 2 key/confirmatory secondary endpoint(s)

4.4.2.1 Definition of endpoint(s)

In combined Stage 1 and Stage 2, the following endpoints are defined as key secondary endpoints:

- Annualized rate of change in TKV from baseline to 18 months
- Change in pain from baseline to 24 months, based on BPI Item 3 assessed from the daily symptom diary
- Change in fatigue pain from baseline to 24 months, based on BFI Item 3 assessed from the daily symptom diary

4.4.2.2 Main analytical approach

As no post-baseline MRI data will be available in Stage 2 at the time of the study discontinuation the analysis of TKV in Combined Stage 1 and Stage 2 will not be done.

Change in pain and change in fatigue from baseline to 24 months will be analyzed using an MMRM similar to the one used in Stage 1, except the time point will include Month 3, Month 12, Month 18 and Month 24 (see Section 4.4.1.2).

In the case of the model does not converge due to high number of missing data, only descriptive summaries by visits will be provided.

4.4.3 Supportive secondary endpoint(s)

Other safety secondary endpoints will be defined in Section 4.7.3.

- Change in BDI-II score during the treatment emergent period (Section 4.7.3.5)
- Change in the lens clarity by ophthalmological examination during the treatment emergent period (Section 4.7.3.4)

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

In Stage 1 and Stage 2, the following endpoints are defined as exploratory efficacy endpoints:

- Annualized rate of change in TLV based on MRI from baseline to 18 months on participants with htTLV >1 L/m
- Change in:
  - Urine osmolality from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2 (in participants not on diuretic at baseline)
  - Nocturia from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2, based on the daily symptom diary (see Section 4.8.3)
  - Systolic BP during the treatment emergent period (see Section 4.7.3.1)
  - Diastolic BP during the treatment emergent period (see Section 4.7.3.1)
  - Biomarkers associated with ADPKD (eg, FGF23 and ADMA) from baseline to 18 months from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2 (see Section 4.8.4)
  - Pain (BPI), fatigue (BFI) and health status (EQ-5D-5L) from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2 (see Section 4.8.3)
  - Glucosylceramide (GL1) and GM3 from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2 (see Section 4.8.2)
- Type, frequency, and dosage of analgesic/over the counter (OTC) pain medication administration from baseline to 24 months (see Section 4.8.3)
- Rate of all-cause hospitalization (see Section 4.8.5)

4.5.2 Main analytical approach

As no post-baseline MRI data will be available in Stage 2 at the time of the study discontinuation the analysis of TLV in Combined Stage 1 and Stage 2 ITT population will not be done.

For other quantitative exploratory endpoints only descriptive summaries by visits will be provided.

The urine osmolality will be analyzed using the average of the 3 separate measurements performed between visit date - 3 and visit date + 1 at each planned visit performed within analysis time windows (see Table 12):

- first spot at visit day-2 am
- second spot the day of visit am
- third spot from the 24-hour urine sample, if any, else sample at the time of visit

All participants on oral diuretic medications at the time of the 1st IMP administration (ie, start date of medication prior to the 1st administration of IMP and end of medication after the 1st administration of IMP or missing) will be excluded from the urine osmolality analysis.

Analyses of pain medications and hospitalization will be defined in Section 4.8.3 and Section 4.8.5.

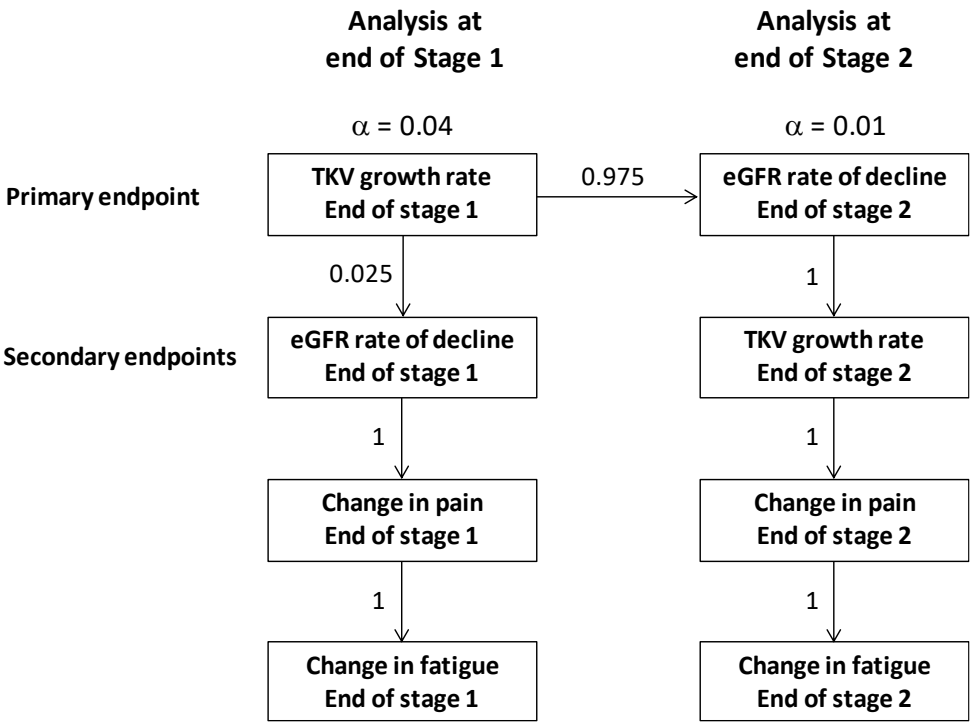
4.6 MULTIPLICITY ISSUES

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 4.3.1.2.

The statistical procedure is illustrated using a graphical approach (6) and is shown in Figure 2. 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 supplementary 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 2 - Graphical illustration of the procedure for handling multiplicity



4.7 SAFETY ANALYSES

All safety analyses will be performed on the Extended combined Stage 1 and Stage 2 safety population as defined in Section 3, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized will be provided separately if any.

4.7.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and compliance and summarized on the Extended combined Stage 1 and Stage 2 safety population.

In addition, summaries will be provided in the population with trial impact (disruption) due to Covid-19.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date + 1 day, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

Duration of IMP exposure will be summarized quantitatively and categorically:

- ≥1 day
- ≥1 Month
- ≥3 months
- ≥6 months
- ≥12 months
- ≥15 months
- ≥18 months
- ≥21 months
- ≥24 months

Additionally, the cumulative duration of treatment exposure (expressed in participant-years) will be provided.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the number of days of IMP as required by the protocol. No imputation will be made for participants with missing or incomplete data.

Percentage of treatment compliance for a participant will be defined as the number of days of IMP administered divided by the total number of days that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%.

Cases of overdose are reported in the adverse event (AE) e-CRF pages as Adverse Event of Special Interest (AESI) if symptomatic or AE if asymptomatic. The reported cases of overdose will be described in the AE analysis (see Section 4.7.2).

4.7.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period

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

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity will be left as missing.

The AE tables will be sorted as indicated in Table 6.

Table 6 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
SMQ/CMQ and PT	By decreasing frequency of SMQs/CMQs and PTs[a]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the venglustat 15 mg dose group
b The table of all TEAEs presented by SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE
- Any treatment emergent SAE
- TEAE leading to death
- Any TEAE leading to permanent intervention discontinuation
- Any treatment emergent AESI

The AE summaries of Table 7 will be generated with number (%) of participants experiencing at least one event. The all TEAE summary by Primary SOC and PT (and other safety summaries (eg, SAEs, deaths), if deemed needed after TEAE evaluation) will be performed by trial impact (disruption) due to Covid-19.

Table 7 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
Common TEAE (>5% in any group)	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
Treatment emergent AESI	Primary SOC and PT
TEAE leading to permanent intervention discontinuation	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
Treatment emergent Covid-19 related AE	Primary SOC and PT

Type of AE	MedDRA levels
Pretreatment AE	Overview[a]
Pretreatment AESI	Primary SOC and PT
Post-treatment AE	Overview[a]

a Will include the following AE categories: any AEs, any serious AEs, any AESIs any AEs leading to death, any AEs leading to permanent intervention discontinuation

Analysis of deaths

In addition to the analyses of deaths included in Table 7 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by reason for death
- Deaths in non-randomized participants or randomized but not exposed participants

Analysis of adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 8. Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 6.

Table 8 - Selections for AESIs

AESIs and other AEs of interest	Selection
Pregnancy of a female subject or female partner of a male subject	e-CRF specific pregnancy page
Symptomatic overdose (serious or non-serious) with IMP	e-CRF specific symptomatic overdose page
Increase in alanine transaminase (ALT)	e-CRF specific AESI tick box on the AE page
New or worsening lenticular opacities and cataracts	e-CRF specific AESI tick box on the AE page
AE related to Covid-19 illness	SMQ COVID19

4.7.3 Additional safety assessments

4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, erythrocyte count, platelet count, prothrombin time (PT), prothrombin international normalized ratio (INR), activated partial thromboplastin time (aPTT).

  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Clinical chemistry:
  - Metabolism: glucose, protein, albumin.
  - Electrolytes: sodium, potassium, chloride, bicarbonate, calcium.
  - Renal function: creatinine, blood urea nitrogen, serum cystatin C.
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transferase, total and direct bilirubin.
  - Pregnancy test: Serum β-human chorionic gonadotropin (all female participants).
- Urinalysis:
  - Urinalysis for quantitative analysis: pH, specific gravity, proteins, and glucose.
- Vital signs: heart rate, systolic and diastolic blood pressure, weight.
  - For all seated BP measurements, SBP and DBP will be analyzed using the average of the 3 to 5 separate measurements at each visit.
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Bazett/Fridericia).

Data below the lower limit of quantitation/detection limit (LLOQ) will be replaced by half of the LLOQ, data above the upper limit of quantification will be replaced by ULOQ value.

Quantitative analyses

For all laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each visit, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period.

All laboratory parameters (except urinalysis parameters) and vital signs parameters (except weight and height) will be summarized using the analysis windows as defined in Table 12. Urinalysis, ECG and weight will be summarized by planned visit using central measurements only.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

For parameters defined as efficacy endpoints, PCSA summaries will not be provided.

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

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

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

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

- Normal/missing
- Abnormal

Additional analyses for drug-induced liver injury

The following additional analyses will be performed for drug-induced liver injury:

- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
- For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 ULN) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value ≤ ULN in case of missing baseline) before last IMP dose, Returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status, No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 ULN).

The incidence of liver related AEs will be summarized by study intervention group. The selection of PT will be based on SMQ Hepatic disorder.

4.7.3.2 Physical examination

Each physical examination will include the following physical observations/measurements: head, heart, lung, abdomen, musculo/skeletal, skin, neurological and mental status.

Physical examination findings will be assessed as normal or abnormal.

Number and percentage of participants with complete abnormal physical examination will be summarized at each planned visit during the treatment emergent period.

4.7.3.3 Neurological examination

Each neurological examination will include, but are not limited to:

- cranial nerve examination: olfactory, optic, oculomotor, trochlear, trigeminal, abducens, facial, vestibulocochlear, glossopharyngeal, vagus, accessory, hypoglossal)

- extrapyramidal features: postural tremor, rest tremor, intention tremor, cogwheel rigidity, lead pipe rigidity, bradykinesia, postural deficit, dystonia, other
- gait examination: antalgic, staggering, steppage, waddle, difficulty initiating, glue footed, toe walking, other
- coordination examination: finger to nose test, rapid alternating movements, heel to shin, tandem gait
- motor examination (tone): spasticity, rigidity, paratonia, other, decreased muscle tone
- peripheral nervous system (sensory disturbances)
- reflexes examination
- strength examination: heel walking, sit to stand test, toe walking, other motor abnormality

These examination findings will be assessed as normal or abnormal.

Number and percentage of participants with abnormal neurological examination will be summarized by location (cranial nerve, Extrapyramidal features, motor, Peripheral nervous system strength, reflex, sensory, coordination, gait) at each planned visit during the treatment emergent period.

4.7.3.4 Ophthalmological examination

The full ophthalmological examination includes best corrected visual acuity (BCVA), slip-lamp examination, and examination of the cornea, lens, and retina. The examination should include pupil dilation and evaluation of the lens according to the lens opacities classification system III (LOCSIII), before implementation of protocol amendment 5. For opacities present at baseline/previous visit, changes in LOCSIII score of ≥0.5 (respectively ≥1) for nuclear opalescence, ≥0.8 (respectively ≥1) for cortical opacification, or ≥0.5 (respectively ≥1) for posterior subcapsular opacification compared with baseline or previous assessment will be considered as a worsening. After protocol amendment 5, the LOCSIII examination is replaced by the WHO simplified cataract grading system. For opacities present at baseline/previous visit, increases in WHO grade ≥1.0 for nuclear opacification, cortical opacification, or posterior subcapsular opacification compared with baseline or previous assessment will be considered as a worsening.

Secondary safety endpoints include change in the lens clarity by ophthalmological examination during the treatment emergent period.

Number and percentages of participants with abnormal ophthalmological examination on any eye at any time (whether present at screening or not) as well as number and percentages of participants with any new onset of abnormal ophthalmological examination on any eye during the treatment emergent period as per investigator (site ophthalmologist) assessment will be summarized along with a description of lens opacity according to LOCSIII or the WHO classification.

The decrease in BCVA will also be presented on any eye at any time (whether present at screening or not). This decrease will be presented according to 1, 2 or 3 lines (defined as 0.1, 0.2 or 0.3 increases in LogMAR) (see [7]).

4.7.3.5 Depression (BDI-II) examination

Depression will be monitored during the study by using the BDI-II.

Secondary safety endpoints include change in score of BDI-II during the treatment emergent period.

Descriptive statistics for values and changes from baseline in BDI-II total score will be presented for each time point during the on-treatment period (see Section 4.1). All measurements will be assigned to analysis windows defined in Table 12.

The worst (highest) BDI-II total score during the treatment emergent period will be categorized and summarized using the number and percentage of participants in each study intervention group within each of the following categories:

- 0-13 (minimal depression)
- 14-19 (mild depression)
- 20-28 (moderate depression)
- 29-63 (severe depression)

The worst (highest) score for suicidal thoughts (Item 9 of BDI-II) during the treatment emergent period will be summarized within each of the following categories:

- I don't have any thoughts of killing myself
- I have thoughts of killing myself, but I would not carry them out
- I would like to kill myself
- I would kill myself if I had the chance

In addition, the number of participants with BDI-II worsening from baseline during the treatment emergent period will be summarized.

4.8 OTHER ANALYSES

4.8.1 PK analyses

Plasma venglustat trough concentrations (pre dose) along with other single time point plasma concentration data will be summarized on the PK populations by dose and each analysis window (see Table 13 and Table 14) using the following descriptive statistics: mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics excepted for the geometric mean and associated coefficient of variation for which they will be considered as missing.

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.

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

4.8.2 Pharmacodynamic analyses

Exploratory endpoints include change in:

- GL1 from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2
- GM3 from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2

As no sample tested for GM3 at the time of the study discontinuation, the analysis of GM3 will not be done.

GL1 variable will be summarized on the pharmacodynamics populations using descriptive statistics at each time point, including assessment of observed values, change and percent change from baseline.

4.8.3 Patient reported outcomes analyses

Figure 3 shows the concepts of measurement and their related PRO questionnaires used in the trial.

Figure 3 - Patient reported outcome (PRO) concepts and questionnaires

Concept	PRO questionnaire
Overall pain	BPI-SF
Overall fatigue	BFI-SF
Global impression of severity	PGIS
Global impression of change	PGIC
Health status	EQ-5D-5L
Daily symptoms of ADPKD (worst pain, worst fatigue, nocturia)	Daily diary

ADPKD = Autosomal dominant polycystic kidney disease; BFI-SF = Brief Fatigue Inventory-short form; 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.

Overall pain

Overall pain will be measured using the BPI short-form (BPI-SF). Most BPI-SF items provide an 11-point numeric rating scale (NRS). Scores are by items and by dimensions; the global score ranges from 0 to 10. Lower scores indicate lower pain.

Exploratory endpoints include change in:

- Overall pain total score from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2
- Pain severity score from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2
- Pain interference score from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2
- Treatment relief score from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2

Overall fatigue

The Brief Fatigue Inventory-Short Form (BFI SF) will be used to measure overall fatigue. Scores are by dimension and the global score ranging from 0 to 10. Lower scores indicate lower fatigue.

Exploratory endpoints include change in:

- Overall fatigue total score from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2
- Fatigue severity score from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2
- Fatigue impact score from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2

Health status

The EuroQoL 5-dimension 5-level (EQ-5D-5L) is used to assess the 5 following dimensions of health outcome: Mobility, Self-care, Usual activities, Pain/Discomfort, Anxiety/Depression, ranged from "1": no problems to "5": extreme problems. The EuroQoL-5D index utility score is calculated using the crosswalk method based on the UK value set (8).

Exploratory endpoints include change in:

- EQ-5D-5L utility score change from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2
- Each of the EuroQol five dimensions (EQ-5D-5L) score from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2

Both total scores and subscale scores of PROs will be calculated according to their scoring guidelines, including handling the missing items.

Daily symptoms of ADPKD

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. 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) (analyzed as secondary endpoint see Section 4.4).
- 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) (analyzed as secondary endpoint see Section 4.4)
- Medication log entry item; "Have you taken any medication for your pain in the past 24 hours? Yes/No".

Daily diaries scores will be averaged over 7 consecutive assessments prior to the 1st IMP (or prior randomization for participants randomized and not exposed), Month 3 and Month 12 planned visit and over the 14 consecutive days prior to the planned Month 18 and Month 24 visits. 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 and Month 24) are required to calculate the average score on non-missing data (4, 5).

Exploratory endpoints include change in nocturia from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2, based on patient reported diary.

Main analytical approach

Change from baseline to Month 18 in Stage 1 and Month 24 in combined Stage 1 and Stage 2 in pain and fatigue Item 3 are described in Section 4.4.1.1.

Each other efficacy endpoints will be summarized using descriptive statistics at each time point, including assessment of observed values, change and percent change from baseline.

In addition, any analgesic/over the counter (OTC) medication administered for pain from baseline in combined Stage 1 and Stage 2 will be summarized by study intervention group. Medication type, frequency, and dosage will be also listed.

Patient global impression of severity

The PGIS is a single item scale in which patients indicate an overall assessment of their APKD symptoms (none, mild, moderate, and severe). PGIS 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 change from baseline.

Patient Global Impression of Change

The 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”). PGIC will be summarized and compared between venglustat 15 mg, venglustat 8 mg and placebo using descriptive statistics at each time point.

4.8.4 Biomarker analyses

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.

Exploratory endpoints include change in:

- FGF23 and ADMA from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2
- ADMA from baseline to 18 months in Stage 1 and 24 months in combined Stage 1 and Stage 2

Each biomarker will be summarized using descriptive statistics at each time point, including assessment of observed values, change and percent change from baseline.

4.8.5 Hospitalization analyses

Number and percentage of participants with all cause hospitalization, up to Month 18 visit for Stage 1 and up to Month 24 for combined Stage 1 and Stage 2 will be summarized.

Time to first all-cause hospitalization is defined as the time from randomization to the date of hospitalization. Participants who are not hospitalized before the last contact date will be censored at the last contact date. Time to hospitalization will be analyzed using Kaplan-Meier method.

4.9 INTERIM ANALYSES

4.9.1 Dose selection safety review

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

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

Based on this safety review, the DMC selected the venglustat 15mg dose for Stage 2. The venglustat 15 mg dose was the highest dose determined to be safe and well tolerated.

4.9.2 Interim futility analysis

An interim analysis for futility was performed when all participants 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 was performed by the external independent statistician and was reviewed under the supervision of the DMC. The interim analysis primarily focused on the primary endpoint in Stage 1 (annualized rate of change in TKV) and stopping rules were based on this primary endpoint. Data monitoring committee also reviewed 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.

As per protocol, 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 is determined from the Multiple Comparison Procedure described in Section 4.3.1.2. 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 than15%. Probability to declare futility under different scenarios is presented in Section 5.6.1.

Of note, the futility rule is non-binding and 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 reviews 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.

If the DMC recommends continuing the study, then the Sponsor is informed of the recommendation and have no access to any unblinded results.

If the DMC recommends stopping the study for futility, then unblinded results are made available to a limited number of Sponsor's senior management team. This limited team makes the final decision to stop or continue the study. To prevent internal exposure to unblinded interim data and informal or formal discussions that can present a substantial risk to the integrity of the trial and the Sponsor's ability to manage the trial without bias, only a small designated sub team of the Sponsor is unblinded, as described in DMC charter. This Sponsor's sub team is not involved in the direct conduct of the remainder of the study and any conduct of external committees related to the study to protect the overall integrity of the study.

In order to protect the global type one error in case the decision is taken to overrule the futility rule, non-binding futility rules are used for determination of alpha.

Based on the futility analysis reviewed by DMC on the 14 May 2021, the DMC recommended to stop the analysis for futility. The Sponsor's senior management team followed this recommendation and decided to discontinue the study.

4.9.3 Two-steps analysis

Not applicable.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

ADMA:	Asymmetric dimethylarginine
ADPKD:	Autosomal dominant polycystic kidney disease
AE:	Adverse event
AESI:	Adverse event of special interest
ALT:	Alanine transaminase
BCVA:	Best corrected visual acuity
BFI:	Brief fatigue inventory
BPI:	Brief pain inventory
CKD-EPI:	Chronic kidney disease epidemiologic collaboration
CRF:	electronic case report form
DBP:	Diastolic blood pressure
ECG:	Electrocardiogram
eGFR:	estimated glomerular filtration rate
EQ 5D-5L:	EuroQol 5 dimensions 5-level
FGF23:	Fibroblast growth factor 23
GCS:	Glucosylceramide synthase
GL-1:	Glucosylceramide
GM3:	Monosialodihexosylganglioside
HGLT:	High level group term
HLT:	High level term
htTLV:	height adjusted total liver volume
ICF:	Inform consent form
IRT:	Interactive response technology
ITT:	Intent-to-treat
LLOQ:	Lower limit of quantification
LLT:	Lower level term
LOCSIII:	Lens opacities classification system III
MedDRA:	Mecical dictionary for regulatory activities
mGFR:	measured glomerular filtration rate
MMRM:	Mixed model with repeated measures
MRI:	Magnetic resonance imaging
NRS:	Numeric rating scale
OTC:	Over the counter
PCSA:	Potentially clinically significant abnormality
PD:	Pharmacodynamic
PGIC:	Patient global impression of change
PGIS:	Patient global impression of severity
PK:	Pharmacokinetic
PRO:	Patient reported outcome
PT:	Preferred term

SAE:	Serious adverse event
SBP:	Systolic blood pressure
SD:	Standard deviation
SE:	Standard error
SOC:	System organ class
TE:	Treatment emergent
TEAE:	Treatment emergent adverse event
TKV:	Total kidney volume
TLV:	Total liver volume
ULOQ:	Upper limit of quantification
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Table 9 - Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
01	19 April 2018	Clarification on the timing of evaluation of the secondary and exploratory endpoints	To clarify
		Clarification of possible course of action with regard of study dose in ongoing participants in Stage 1 after DMC review of safety data and dose selection for Stage 2	To clarify
		Clarification on mGFR stusudy	To clarify that mGFR substudy is optional for eligible participants
02	25 May 2018	Addition of stratification of participants by region	To achieve balance between the treatment arms across the different regions
		Removal of exploratory objective of the study on mGFR sub-study	
		Addition of exploratory objectives of the study on effect of GZ/SAR402671 on type, frequency and dosage of analgesic/over the counter (OTC) pain medication administration	To explore the effect of GZ/SAR402671 on type, frequency and dosage of analgesic/over the counter pain medication administration
		Update of items of the Daily symptoms of autosomal dominant polycystic kidney disease diary to regroup pain and nocturia items of the diary and to add an additional item that will direct to the medication entry log	
		Addition of secondary analysis on TKV assessed from 1 month to 18 months, excluding baseline	To describe secondary analysis that will explore a potential acute hemodynamic effect using TKV data assessed from 1 month to 18 months
03	01 October 2018	Description of objective of mGFR sub-study	To explore the effect of GZ/SAR402671 on measured GFR (mGFR) substudy
		Added exploratory endpoint of Annualized rate of change in mGFR from baseline to 24 months in participants within Stage 2 substudy	

Amendment Number	Approval Date	Changes	Rationale
04	14 Aug 2019	Increase of the sample size for the Inclusion in Stage 2 of the study of 80 participants with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2 Addition of exploratory endpoint of Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months in participants with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2 added	To explore the effect of venglustat on eGFR (CKD-EPI equation) from baseline to 24 months in participants with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2
		Addition of statistical consideration related to probability of detecting a treatment effect in an additional 80 participants with screening eGFR between 30 and 44.9 mL/min/1.73 m^2	
		Addition of clarification to the definition of the combined Stage 1 and Stage 2 Safety population will be defined as all randomized participants with eGFR between 45 and 89.9 mL/min/1.73 m^2 at screening and participants from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening will be analyzed separately	
		Described secondary analysis including participants from Stage 2 with eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening	
		Clarification of inclusion criteria: between the ages of 18 to and 50 years (both inclusive) at screening for participants in Stage 1 between 18 and 50 years (inclusive) for participants 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 participants in Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m^2 during the screening period	To clarify and add participants with screening eGFR between 30 and 44.9 mL/min/1.73 m^2
		Systolic BP >160 mmHg* at run in and baseline visits. *mean value of three or five systolic BP measurements	To clarify calculation of SBP

Amendment Number	Approval Date	Changes	Rationale
		Clarification of the timing of the secondary analysis of TKV. TKV assessed more than 30 days instead of 4 weeks after the last IMP administration will be excluded from the analysis	To clarify
		Clarification of the residual treatment period defined as the time from the day after the last IMP administration, plus 30 days (instead of 4 weeks)	To clarify
		Clarification that the baseline value is defined generally as the last available value before first IMP administration	To clarify
		Clarification that 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
05	17 Aug 2020	Updated the hierarchy of the secondary and exploratory endpoints: 1. pain and fatigue are moved from exploratory to secondary endpoints 2. nocturia and urine osmolality (Stage 2) are moved from secondary to exploratory 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.
		PRO population deleted	PRO analysis will be performed on ITT population
		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.
		Change in definition of on-treatment period and treatment-emergent period	Clarification
		Presentation of statistical tables by SOC and PT	Clarification
		Statistical analysis of liver test data	Clarification
		Statistical analysis of PRO data using MMRM	Clarification
		Primary analysis of Stage 1 will include data available at the cut-off date, including data reported up to Month 24, if any	Clarification

Amendment Number	Approval Date	Changes	Rationale
06	16 Dec 2020	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
		Added inclusion criterion related to the screening eGFR value in patients eligible for the mGFR substudy	Clarification
07	19 Apr 2021	Exploratory objectives and corresponding endpoints were updated to consider all-cause hospitalization	Clarification
		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
		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	Clarification
		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
		Numbers of patients and samples for pharmacodynamics and exploratory biomarkers were updated.	Correction
		The definition of residual treatment period was updated.	Clarification
		Changes in previous amendment 06 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).

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

The following demographics and baseline characteristics, medical and surgical history and disease characteristics will be summarized using descriptive statistics in the randomized population.

Demographic and baseline characteristics

- Gender (Male, Female)
- Age in years (quantitative and categorical variable: <40, and ≥40 years),
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other)
- Ethnicity (Hispanic, non-Hispanic)
- Weight in kilograms (quantitative and categorical variable: <50, 50 to <100, ≥100)
- Body mass index (BMI) in kg/m² (quantitative and categorical variable: <30, ≥30)

Randomization strata

The randomization strata of predicted ADPKD progression rate (1C versus 1D versus 1E) according to Mayo Imaging Classification and region (North America, Europe, China, Japan, Republic of Korea, Rest of the World) as recording in IRT as well as actual strata (see Section 5.4).

Disease characteristics

eGFR at screening and at baseline (quantitative variable and qualitative variable: <30,30 to <45, 45 to <60, 60 to <75, 75 to <90, >=90) (see Section 5.4).

ADPKD gene mutation

The listing of participants with a genetic testing ever performed will be presented including the affected gene, the DNA sequence change and the AA change.

Medical or surgical history

Medical (or surgical) history includes previous relevant medical and surgery history collected at baseline. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Medical/surgical history will be summarized in each treatment arm by primary SOC and PT. Events will be sorted by SOC internationally agreed order and decreasing frequency of PT based on the incidence in the overall treatment arm.

Alcohol habits at baseline

Alcohol habits include:

- Frequency of alcoholic drinks in the last 12 months (Never/Occasional/At least monthly/At least weekly/At least daily)
- Number of standard drinks (1 or 2/Greater than 2, where standard drink means 1 pint/bottle of beer, 1 glass of wine, 1 shot of hard liquor…) per day when drinking alcohol

Baseline safety and efficacy parameters (apart from those listed above) will be presented along with the safety and efficacy summaries.

Prior or concomitant medications

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

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP during the on-treatment period.
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized for the randomized and exposed population, by anatomic and therapeutic level. The summaries for prior medications will be sorted by decreasing frequency of anatomic category (ATC) based on the overall incidence across study intervention group. The summaries for concomitant medications will be sorted by decreasing frequency of ATC based on the incidence the venglustat 15 mg group. In case of equal frequency, alphabetical order will be used.

Participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication.

In addition, any concomitant pain medication will be summarized.

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

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

Total kidney volume and total liver volume using MRI

All TKVs are evaluated by 2 independent reviewers and adjudicated in case of inconsistency (percentage difference ≥6%).

At each visit, the TKV selected by the adjudication, if any, will be used for analyses. Else the mean of the TKV provided by the 2 independent reviewers will be considered.

TLVs were evaluated by 2 independent reviewers at the start of the study for few participants, then upon team agreement evaluated by only one reviewer. At each visit, the mean of the TLV provided by the 2 independent reviewers, if any, will be considered for analysis.

Mayo imaging classification strata based on height-adjusted TKV (HtTKV in mL/m) relative to age

Actual Mayo imaging classification strata is based on participant's height adjusted TKV at screening (using TKV assessed by the screening radiologist) and age using the TKV growth rate per year r defined as (9):

$$r = 10^{**}((\log_{10}(\text{htTKV}) - \log_{10}(150)) / \text{age}) - 1$$

Then the Mayo imaging classification will be defined as follows:

Table 10 - Mayo imaging classification

r	Mayo Imaging classification
<1.5%	1A
1.5% to <3.0%	1B
3.0% to <4.5%	1C
4.5% to < 6.0%	1D
≥6.0%	1E

eGFR at screening

The screening eGFR is defined as the eGFR value that was selected to enroll the participant in the study:

- If eGFR at Visit 1 was between 45 and 89.9 mL/min/1.73 m² (or between 30 and 89.9 mL/min/1.73 m² for Stage 2), then the value at Visit 1 is considered as the screening value
- Else, if an additional eGFR measurement was done between Visit 1 and Visit 2, then this additional value is considered as the screening value
- Else, the eGFR at Visit 2 is considered as the screening value

Table 11 - eGFR values example

Subject	V1	Additional (between V1 and V2)	V2
1	**87**	ND	91
2	92	ND	**85**
3	95	**86**	93
4	92	**95**	88

eGFR at baseline

Baseline eGFR is defined for each participant as the average of eGFR values assessed prior or equal to 1st IMP or prior or equal to randomization for randomized and not exposed participants.

Analysis windows for time points

For efficacy and patient reported outcome endpoints, D1 will be defined as the day of randomization. For safety endpoints, D1 will be defined as the day of first IMP intake.

For endpoints not collected at each visit (including TKV, TLV, weight, height, ECG, complete physical examination, neurological examination and daily diaries), analysis by time points will be summarized using the protocol planned visits.

For endpoints collected at almost each visit, the following analysis windows will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy data (eGFR, urine osmolality), laboratory safety data (except urinalysis parameters), vital signs, (except weight and height), ophthalmological examination, patient reported outcome variables as well as PK variables. Only central assessments will be taken into account. For each parameter, only analysis time windows corresponding to a protocol planned visit for that parameter are applicable.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the value collected at the scheduled visit will be used, if any. Otherwise the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will

be used. For all endpoints except PK, if multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit.

Table 12 - Analyses window definition

Time point	Targeted study day	Analysis window in study days
Month 1	D30	D2 to D60
Month 3	D90	D61 to D135
Month 6	D180	D136 to D225
Month 9	D270	D226 to D315
Month 12	D360	D316 to D405
Month 15	D450	D406 to D495
Month 18	D540	D496 to D585
Month 21	D630	D586 to D675
Month 24	D720	D676 to D765

Table 13 - Analyses window definition for PK analyses - Stage 1

Time point	Target study day	Analysis window
Day 1/Post-dose	Day 1/3 hours Post-dose	2h00 to 4h00 after Day 1 dose
Month 1/Pre-dose	D30/Pre-dose	Before Month 1/Day 30 dose
Month 1/Post dose	D30/3 hours post dose	2h00 to 4h00 after Month 1/Day 30
Months 6/Pre-dose	D180/Pre-dose	Before Months 6/Day 180 dose
Months 18/Pre-dose	D540/Pre-dose	Before Months 1/Day 540 dose

Table 14 - Analyses window definition for PK analyses - Stage 2

Time point	Target study day	Analysis window
Month 1/Pre-dose	D30/Pre-dose	Before Month 1/Day 30 dose
Month 1/Post dose	D30/3 hours post dose	2h00 to 4h00 after Month 1/Day 30
Months 24/Pre-dose	D720/Pre-dose	Before Months 24/Day 720 dose

Unscheduled visits

Unscheduled visit measurements will be used for computation of baseline, the last on-treatment value and worst on-treatment value. For parameters summarized according to analysis time windows, unscheduled visit measurements may also be used to provide a measurement for a timepoint.

For efficacy analyses based on annualized rate of change, all assessments at planned visits and unscheduled visits will be taken into account.

For laboratory data, vital signs and ECG analysis unscheduled visit measurements will be used to provide the analysis according to the PCSA and the shift summaries for safety.

5.5 APPENDIX 6 SAMPLE SIZE SIMULATION SAS CODE

The sample SAS code for scenario 1 of Table 15 is provided below.

For any other scenario the RR on TKV and eGFR for 8 mg (Dose 1) and 15 mg (Dose 2) must be updated within the program using the following variables.

```
* Relative reduction in TKV and eGFR for 8 mg and 15 mg;
%let RRtkv_d1 = 50;
%let RRtkv_d2 = 50;
%let RRgfr_d1 = 30;
%let RRgfr_d2 = 30;
```

For scenario 7 and scenario 8 of Table 16, the number of patients should be updated to 160 patients in placebo and 8 mg and 0 patient in 15 mg as follows:

```
* Number of patients in stage 2 in placebo, 8 mg and 15 mg;
%let NpatS2_d0 = 160;
%let NpatS2_d1 = 160;
%let NpatS2_d2 = 0;
```

Sample SAS code for scenario 1:

```
* Number of simulations;
%let Nsim = 10000;

* Number of patients in stage 1 in placebo, 8 mg and 15 mg;
%let NpatS1_d0 = 80;
%let NpatS1_d1 = 80;
%let NpatS1_d2 = 80;

* Number of patients in stage 2 in placebo, 8 mg and 15 mg;
%let NpatS2_d0 = 160;
%let NpatS2_d1 = 160;
%let NpatS2_d2 = 0;

* Relative reduction in TKV and eGFR for 8 mg and 15 mg;
%let RRtkv_d1 = 50;
%let RRtkv_d2 = 50;
%let RRgfr_d1 = 30;
%let RRgfr_d2 = 30;

* Percentage of patients with data at Month 9 and Month 18 at futility
analysis (stage 1);
%let pM9f  = 100;
```

```
%let pM18f = 30;

* Percentage of patients with data at Month 21 and Month 24 at end of Stage 1;
%let pM21s1  = 50;
%let pM24s1  = 30;

* Mean slopes of log(TKV) in Placebo;
%let mStkv_d0 = 0.02764;

* SD of log(TKV): SD of slope and SD of residuals;
%let sdStkv = 0.01477;
%let sdRtkv = 0.02566;

* Mean slopes of eGFR in Placebo;
%let mSgfr_d0 = -3.66;

* SD of eGFR: SD of slope and SD of residuals;
%let sdSgfr = 1.98;
%let sdRgfr = 6.34;

* Correlation between slopes log(TKV) and GFR;
%let corr = -0.35;

* Mean and SD of intercept of log(TKV) - No impact on power, but needed for
simulations;
%let mItkv = 3.1693;
%let sdItkv = 0.13284;

* Mean and SD of intercept of eGFR - No impact on power, but needed for
simulations;
%let mIgfr = 75.5963;
%let sdIgfr = 10.3347;

* List of time-points of TKV and eGFR;
%let listtime   = 0,0.0833,0.25,0.50,0.75,1.00,1.25,1.50,1.75,2;
%let timetkv_S1 = 0,0.0833,0.75,1.5;
%let timetkv_S2 = 0,1.5;
%let timegfr_S1 = 0,0.0833,0.25,0.50,0.75,1.00,1.25,1.50,1.75,2;
%let timegfr_S2 = 0,0.0833,0.25,0.50,0.75,1.00,1.25,1.50,1.75,2;

* Seed for random numbers;
%let seed = 402671;

* Drop out rate (at time tdrop) ;
%let rdrop = 0.1;
%let tdrop = 2;


/*******************************/
/* STEP 1 : Simulation of data */
/*******************************/

data dataSim(keep=sim stage subject dose time logtkv gfr F S1);
  length sim stage subject dose time logtkv gfr F S1 8;

  retain seed &seed;
```

```
  do sim=1 to &Nsim;

    do subject=1 to
&NpatS1_d0+&NpatS1_d1+&NpatS1_d2+&NpatS2_d0+&NpatS2_d1+&NpatS2_d2;

      * Assign subjects to stage 1 or 2 ;
      if subject <= &NpatS1_d0+&NpatS1_d1+&NpatS1_d2 then stage = 1; else
stage = 2;

      * Assign subjects to dose 0, 1 or 2 in stage 1 ;
      if subject <= &NpatS1_d0 then dose = 0;
      else if subject <= &NpatS1_d0+&NpatS1_d1 then dose = 1;
      else if subject <= &NpatS1_d0+&NpatS1_d1+&NpatS1_d2 then dose = 2;

      * Assign subjects to dose 0, 1 or 2 in stage 2 ;
      else if subject <= &NpatS1_d0+&NpatS1_d1+&NpatS1_d2+&NpatS2_d0 then dose
= 0;
      else if subject <=
&NpatS1_d0+&NpatS1_d1+&NpatS1_d2+&NpatS2_d0+&NpatS2_d1 then dose = 1;
      else if subject <=
&NpatS1_d0+&NpatS1_d1+&NpatS1_d2+&NpatS2_d0+&NpatS2_d1+&NpatS2_d2 then dose =
2;

      * Determine if subject has Month 9 data at futility analysis in stage 1;
      pM9f = .;
      if 0 < subject <= &NpatS1_d0*&pM9f/100 then pM9f = 1;
      if &NpatS1_d0 < subject <= &NpatS1_d0+&NpatS1_d1*&pM9f/100 then pM9f =
1;
      if &NpatS1_d0+&NpatS1_d1 < subject <=
&NpatS1_d0+&NpatS1_d1+&NpatS1_d2*&pM9f/100 then pM9f = 1;

      * Determine if subject has Month 18 data at futility analysis in stage
1;
      pM18f = .;
      if 0 < subject <= &NpatS1_d0*&pM18f/100 then pM18f = 1;
      if &NpatS1_d0 < subject <= &NpatS1_d0+&NpatS1_d1*&pM18f/100 then pM18f =
1;
      if &NpatS1_d0+&NpatS1_d1 < subject <=
&NpatS1_d0+&NpatS1_d1+&NpatS1_d2*&pM18f/100 then pM18f = 1;

      * Determine if subject has Month 21 data at analysis of end of stage 1;
      pM21s1 = .;
      if 0 < subject <= &NpatS1_d0*&pM21s1/100 then pM21s1 = 1;
      if &NpatS1_d0 < subject <= &NpatS1_d0+&NpatS1_d1*&pM21s1/100 then pM21s1
= 1;
      if &NpatS1_d0+&NpatS1_d1 < subject <=
&NpatS1_d0+&NpatS1_d1+&NpatS1_d2*&pM21s1/100 then pM21s1 = 1;

      * Determine if subject has Month 24 data at analysis of end of stage 1;
      pM24s1 = .;
      if 0 < subject <= &NpatS1_d0*&pM24s1/100 then pM24s1 = 1;
      if &NpatS1_d0 < subject <= &NpatS1_d0+&NpatS1_d1*&pM24s1/100 then pM24s1
= 1;
      if &NpatS1_d0+&NpatS1_d1 < subject <=
&NpatS1_d0+&NpatS1_d1+&NpatS1_d2*&pM24s1/100 then pM24s1 = 1;
```

```
      * Determine mean slope of log(TKV) and GFR (depending on dose) ;
      if dose = 0 then do;
        mStkv = &mstkv_d0;
        mSgfr = &msgfr_d0;
      end;
      if dose = 1 then do;
        mStkv = log10((10**&mstkv_d0-1)*(1-&RRtkv_d1/100)+1);
        mSgfr = &msgfr_d0*(1-&RRgfr_d1/100);
      end;
      if dose = 2 then do;
        mStkv = log10((10**&mstkv_d0-1)*(1-&RRtkv_d2/100)+1);
        mSgfr = &msgfr_d0*(1-&RRgfr_d2/100);
      end;

      * Generate a random intercept of log(TKV) for the current patient ;
      call rannor(seed,x);
      inttkv = &mItkv + x*&sdItkv;

      * Generate a random intercept of GFR for the current patient ;
      call rannor(seed,x);
      intgfr = &mIgfr + x*&sdIgfr;

      * Generate a random slope of log(TKV) for the current patients ;
      call rannor(seed,x);
      slopetkv = mStkv + x*&sdStkv;

      * Generate a random slope of GFR for the current patients ;
      * Based on the conditional distribution, given slope of log(TKV) ;
      call rannor(seed,x);
      slopegfr = mSgfr + &corr*&sdSgfr/&sdStkv*(slopetkv-msTKV) +
x*&sdSgfr*sqrt(1-(&corr)**2);

      * Simulate time to dropout (assuming exponential time to drop-out and
rate at time &tdrop is &rdrop) ;
      call ranuni(seed,x);
      tdrop = log(x)*&tdrop/log(1-&rdrop);

        * Create observations at each time-point ;
      do time=&listtime;

        * Create an obsbservation for log(TKV) ;
        if (stage = 1 and time in (&timetkv_S1)) or (stage = 2 and time in
(&timetkv_S2)) then do;

          * Generate a residual error for the current observation ;
          call rannor(seed,x);
          etkv = &sdRtkv*x;

          * Generate an measurement at the given time-point ;
          logtkv = inttkv + slopetkv*time + etkv;
        end;
        else logtkv = .;

        * Create an obsbservation for GFR ;
```

```
        if (stage = 1 and time in (&timegfr_S1)) or (stage = 2 and time in
(&timegfr_S2)) then do;

          * Generate a residual error for the current observation ;
          call rannor(seed,x);
          egfr = &sdRgfr*x;

          * Generate an measurement at the given time-point ;
          gfr = intgfr + slopegfr*time + egfr;
        end;
        else gfr = .;

        * Determine if data available at futility analysis in stage 1;
        F = .;
        if stage = 1 and time <= 0.75 and pM9f  = 1 then F = 1;
        if stage = 1 and time <= 1.5  and pM18f = 1 then F = 1;

        * Determine if data available at stage 1 analysis;
        S1 = .;
        if stage = 1 and time <= 1.5 then S1 = 1;
        if stage = 1 and time <= 1.75 and pM21s1 = 1 then S1 = 1;
        if stage = 1 and time <= 2    and pM24s1 = 1 then S1 = 1;

        * Keep only observations before patient drops out;
        if time<tdrop then output;

      end;
    end;
  end;
run;


/*************************************/
/* STEP 2: Analysis of simulated data */
/*************************************/

/* Linear mixed models for different endpoints at different stages*/
/* Note: for each contrast, one-sided p-value is requested (lower tail for
TKV, upper tail for GFR) */

options nonotes;
ods listing close;


* TKV - Futility analysis ;
proc mixed data=dataSim noclprint;
  where stage = 1 and F = 1 and not(missing(logtkv));
  by sim;
  class subject dose;
  model logtkv = dose time time*dose;
  estimate "Slope0"  int 0 dose 0 0 0 time 1 time*dose  1 0 0;
  estimate "Slope1"  int 0 dose 0 0 0 time 1 time*dose  0 1 0;
  estimate "Slope2"  int 0 dose 0 0 0 time 1 time*dose  0 0 1;
  estimate "Emax"    int 0 dose 0 0 0 time 0 time*dose -0.8131  0.3424 0.4707
/ lower;
```

```
  estimate "Linear"  int 0 dose 0 0 0 time 0 time*dose -0.7223  0.0314 0.6909
/ lower;
  estimate "SigEmax" int 0 dose 0 0 0 time 0 time*dose -0.6615 -0.0838 0.7453
/ lower;
  random int time / type=un subject=subject;
  ods output estimates=esttkv_F;
  ods output covparms=covtkv_F;
run;


* TKV - End of stage 1;
proc mixed data=dataSim noclprint;
  where S1 = 1 and not(missing(logtkv));
  by sim;
  class subject dose;
  model logtkv = dose time time*dose / ddfm=satterthwaite;
  estimate "Slope0"  int 0 dose 0 0 0 time 1 time*dose  1 0 0;
  estimate "Slope1"  int 0 dose 0 0 0 time 1 time*dose  0 1 0;
  estimate "Slope2"  int 0 dose 0 0 0 time 1 time*dose  0 0 1;
  estimate "Emax"    int 0 dose 0 0 0 time 0 time*dose -0.8131  0.3424 0.4707
/ lower;
  estimate "Linear"  int 0 dose 0 0 0 time 0 time*dose -0.7223  0.0314 0.6909
/ lower;
  estimate "SigEmax" int 0 dose 0 0 0 time 0 time*dose -0.6615 -0.0838 0.7453
/ lower;
  random int time / type=un subject=subject;
  ods output estimates=esttkv_S1;
  ods output covparms=covtkv_S1;
run;


* TKV - End of stage 2;
proc mixed data=dataSim noclprint;
  where not(missing(logtkv));
  by sim;
  class subject dose;
  model logtkv = dose time time*dose / ddfm=satterthwaite;
  estimate "Slope0"  int 0 dose 0 0 0 time 1 time*dose  1 0 0;
  estimate "Slope1"  int 0 dose 0 0 0 time 1 time*dose  0 1 0;
  estimate "Slope2"  int 0 dose 0 0 0 time 1 time*dose  0 0 1;
  estimate "Emax"    int 0 dose 0 0 0 time 0 time*dose -0.8131  0.3424 0.4707
/ lower;
  estimate "Linear"  int 0 dose 0 0 0 time 0 time*dose -0.7223  0.0314 0.6909
/ lower;
  estimate "SigEmax" int 0 dose 0 0 0 time 0 time*dose -0.6615 -0.0838 0.7453
/ lower;
  random int time / type=un subject=subject;
  ods output estimates=esttkv_S2;
  ods output covparms=covtkv_S2;
run;


* GFR - End of stage 1;
proc mixed data=dataSim noclprint;
  where S1 = 1 and not(missing(gfr));
  by sim;
```

```
  class subject dose;
  model gfr = dose time time*dose / ddfm=satterthwaite;
  estimate "Slope0"  int 0 dose 0 0 0 time 1 time*dose  1 0 0;
  estimate "Slope1"  int 0 dose 0 0 0 time 1 time*dose  0 1 0;
  estimate "Slope2"  int 0 dose 0 0 0 time 1 time*dose  0 0 1;
  estimate "Emax"    int 0 dose 0 0 0 time 0 time*dose -0.8131  0.3424 0.4707
/ upper;
  estimate "Linear"  int 0 dose 0 0 0 time 0 time*dose -0.7223  0.0314 0.6909
/ upper;
  estimate "SigEmax" int 0 dose 0 0 0 time 0 time*dose -0.6615 -0.0838 0.7453
/ upper;
  random int time / type=un subject=subject;
  ods output estimates=estgfr_S1;
  ods output covparms=covgfr_S1;
run;


* GFR - End of stage 2;
proc mixed data=dataSim noclprint;
  where not(missing(gfr));
  by sim;
  class subject dose;
  model gfr = dose time time*dose / ddfm=satterthwaite;
  estimate "Slope0"  int 0 dose 0 0 0 time 1 time*dose  1 0 0;
  estimate "Slope1"  int 0 dose 0 0 0 time 1 time*dose  0 1 0;
  estimate "Slope2"  int 0 dose 0 0 0 time 1 time*dose  0 0 1;
  estimate "Emax"    int 0 dose 0 0 0 time 0 time*dose -0.8131  0.3424 0.4707
/ upper;
  estimate "Linear"  int 0 dose 0 0 0 time 0 time*dose -0.7223  0.0314 0.6909
/ upper;
  estimate "SigEmax" int 0 dose 0 0 0 time 0 time*dose -0.6615 -0.0838 0.7453
/ upper;
  random int time / type=un subject=subject;
  ods output estimates=estgfr_S2;
  ods output covparms=covgfr_S2;
run;

ods listing;
options notes;

/*************************************************************************/
/* STEP 3: Calculate distribution of Z statistic from multiple comparison */
/* procedure under null hypothesis */
/*************************************************************************/

* Generate 10000000 samples from Z statistic under null hypothesis;
data simz(keep=z:);
  retain seed 123;

  do i=1 to 10000000;

    * Generate independent normal for 3 doses ;
    call rannor(seed,y1);
    call rannor(seed,y2);
    call rannor(seed,y3);
```

```
    * Calculate all contrasts ;
    c1 = -0.8131*Y1+0.3424*Y2+0.4707*Y3;
    c2 = -0.7223*Y1+0.0314*Y2+0.6909*Y3;
    c3 = -0.6615*Y1-0.0838*Y2+0.7453*Y3;

    * Z-statistic : maximum of all contrasts ;
    z = round(max(of c1--c3),0.0001);

    output;
  end;
run;


* Calculate cumulative distribution of Z statistic;
ods listing close;
proc freq data=simz;
  table z;
  ods output OneWayFreqs=distz;
run;
ods listing;


* Create all possible values of Z from -5 to +10 (by 0.0001 increment);
data pz(keep=z);
  do x=-5 to 10 by 0.0001;
    z = round(x,0.0001);
    output;
  end;
run;
data pz(keep=z pvalue);
  merge pz distz;
  by z;
  retain lastcum 0;
  if cumpercent = . then cumpercent = lastcum;
  lastcum = cumpercent;
  pvalue = 1-cumpercent/100;
run;


* Create a format associating each possible value of Z with its associated p-
value ;
data PZFMT(keep=fmtname start label);
  length FMTNAME $8 START 8 LABEL $20;
  set pz;
  fmtname = "PZFMT";
  start   = z;
  label   = put(pvalue,10.8);
run;
proc format cntlin=PZFMT;
run;




/*****************************************/
```

```
/* STEP 4: Combine results of all analyses */
/*****************************************/

* Combine all estimates;
data allest;
  length endpoint $3 stage $2 sim 8 label $20;
  set esttkv_f (in=tkvf)
      esttkv_s1(in=tkvs1)
      esttkv_s2(in=tkvs2)
      estgfr_s1(in=gfrs1)
      estgfr_s2(in=gfrs2)
      ;
  if tkvf or tkvs1 or tkvs2 then endpoint = "TKV";
  if gfrs1 or gfrs2 then endpoint = "GFR";
  if tkvf then stage = "F";
  if tkvs1 or gfrs1 then stage = "S1";
  if tkvs2 or gfrs2 then stage = "S2";

  length id $30;
  id = compress(lowcase(label)) || "_" || compress(lowcase(endpoint)) || "_"
|| compress(lowcase(stage));

  if tails = "Lower" then tvalue = -tvalue;
  drop tails;
run;

* Combine all variances;
data allcov;
  length endpoint $3 stage $2 sim 8 label $20;
  set covtkv_f (in=tkvf)
      covtkv_s1(in=tkvs1)
      covtkv_s2(in=tkvs2)
      covgfr_s1(in=gfrs1)
      covgfr_s2(in=gfrs2)
      ;
  if tkvf or tkvs1 or tkvs2 then endpoint = "TKV";
  if gfrs1 or gfrs2 then endpoint = "GFR";
  if tkvf then stage = "F";
  if tkvs1 or gfrs1 then stage = "S1";
  if tkvs2 or gfrs2 then stage = "S2";

  if covparm = "UN(2,2)"  then do; estimate = sqrt(estimate); label =
"SDslope"; end;
  if covparm = "Residual" then do; estimate = sqrt(estimate); label = "SDres";
end;

  length id $30;
  id = compress(lowcase(label)) || "_" || compress(lowcase(endpoint)) || "_"
|| compress(lowcase(stage));

  if covparm in ("UN(2,2)","Residual") then output;

  drop covparm subject;
run;
```

```
* Combine all results ;
data allMixed;
  set allest allcov;
run;
proc sort data=allMixed;
  by sim stage;
run;


* Transpose results (one record per simulation) ;
proc transpose data=allmixed out=estimate(drop=_name_);
  where label in ("Slope0","Slope1","Slope2","SDslope","SDres");
  by sim;
  var estimate;
  id id;
run;
proc transpose data=allmixed out=zvalue(drop=_name_ _label_) prefix=z_;
  where label notin ("Slope0","Slope1","Slope2","SDslope","SDres");
  by sim;
  var tvalue;
  id id;
run;


* Combine all results and calculate p-values from Multiple Comparison
Procedure ;
data simResults;
  merge estimate zvalue;
  by sim;

  * TKV slope in %/year ;
  slope0_tkv_f  = 10**slope0_tkv_f-1;
  slope1_tkv_f  = 10**slope1_tkv_f-1;
  slope2_tkv_f  = 10**slope2_tkv_f-1;
  slope0_tkv_s1 = 10**slope0_tkv_s1-1;
  slope1_tkv_s1 = 10**slope1_tkv_s1-1;
  slope2_tkv_s1 = 10**slope2_tkv_s1-1;
  slope0_tkv_s2 = 10**slope0_tkv_s2-1;
  slope1_tkv_s2 = 10**slope1_tkv_s2-1;
  slope2_tkv_s2 = 10**slope2_tkv_s2-1;

  * RR on TKV;
  RR1_tkv_f  = 1-slope1_tkv_f/slope0_tkv_f;
  RR2_tkv_f  = 1-slope2_tkv_f/slope0_tkv_f;
  RR1_tkv_s1 = 1-slope1_tkv_s1/slope0_tkv_s1;
  RR2_tkv_s1 = 1-slope2_tkv_s1/slope0_tkv_s1;
  RR1_tkv_s2 = 1-slope1_tkv_s2/slope0_tkv_s2;
  RR2_tkv_s2 = 1-slope2_tkv_s2/slope0_tkv_s2;

  * RR on GFR;
  RR1_gfr_s1 = 1-slope1_gfr_s1/slope0_gfr_s1;
  RR2_gfr_s1 = 1-slope2_gfr_s1/slope0_gfr_s1;
  RR1_gfr_s2 = 1-slope1_gfr_s2/slope0_gfr_s2;
  RR2_gfr_s2 = 1-slope2_gfr_s2/slope0_gfr_s2;
```

```
  * Z-value of Multiple Comparison Procedure (maximum of z-value of Emax,
Linear and SigEmax);
  z_mcp_tkv_f  = max(z_emax_tkv_f ,z_linear_tkv_f ,z_sigemax_tkv_f );
  z_mcp_tkv_s1 = max(z_emax_tkv_s1,z_linear_tkv_s1,z_sigemax_tkv_s1);
  z_mcp_tkv_s2 = max(z_emax_tkv_s2,z_linear_tkv_s2,z_sigemax_tkv_s2);
  z_mcp_gfr_s1 = max(z_emax_gfr_s1,z_linear_gfr_s1,z_sigemax_gfr_s1);
  z_mcp_gfr_s2 = max(z_emax_gfr_s2,z_linear_gfr_s2,z_sigemax_gfr_s2);

  * One-sided p-value of Multiple Comparison Procedure;
  p_mcp_tkv_f  = input(put(round(z_mcp_tkv_f ,0.0001),pzfmt.),best.);
  p_mcp_tkv_s1 = input(put(round(z_mcp_tkv_s1,0.0001),pzfmt.),best.);
  p_mcp_tkv_s2 = input(put(round(z_mcp_tkv_s2,0.0001),pzfmt.),best.);
  p_mcp_gfr_s1 = input(put(round(z_mcp_gfr_s1,0.0001),pzfmt.),best.);
  p_mcp_gfr_s2 = input(put(round(z_mcp_gfr_s2,0.0001),pzfmt.),best.);

  format slope0_tkv: slope1_tkv: slope2_tkv: percent8.2 slope0_gfr:
slope1_gfr: slope2_gfr: 6.2 sd: 7.4 p_: 6.4 RR: percentn8.1 z: 6.3;
run;


/*************************************************************************/
/*STEP 5:Apply strategy for multiplicity and determine outcome of the study */
/*************************************************************************/

data outcome;
  set simresults;

  * Futility if one-sided p-value of TKV at interim analysis > 0.30;
  if p_mcp_tkv_f > 0.30 then do;
    TKVs1     = 0;
    GFRs1     = 0;
    GFRs12    = 0;
    TKVGFRs12 = 0;
    Futility  = 1;
  end;

  else do;

    * Significant effect on TKV at stage 1 if two-sided p-value < 0.04;
    if 2*p_mcp_tkv_s1 < 0.04 then do;

      * Significant effect on GFR at stage 1 if two-sided p-value < 0.001;
      if 2*p_mcp_gfr_s1 < 0.001 then do;
        TKVs1     = 1;
        GFRs1     = 1;
        GFRs12    = 1;
        TKVGFRs12 = 1;
        Futility  = 0;
      end;

      * Significant effect on GFR at stage 2 if two-sided p-value < 0.049;
      else if 2*p_mcp_gfr_s2 < 0.049 then do;
        TKVs1     = 1;
        GFRs1     = 0;
        GFRs12    = 1;
        TKVGFRs12 = 1;
```

```
        Futility  = 0;
      end;

      * Otherwise: no effect on GFR;
      else do;
        TKVs1     = 1;
        GFRs1     = 0;
        GFRs12    = 0;
        TKVGFRs12 = 0;
        Futility  = 0;
      end;
    end;

    * If no significant effect on TKV at stage 1;
    else do;

      * Significant effect on both TKV and GFR at stage 2 if two-sided p-value
< 0.01 ;
      if 2*p_mcp_gfr_s2 < 0.01 and 2*p_mcp_tkv_s2 < 0.01 then do;
        TKVs1     = 0;
        GFRs1     = 0;
        GFRs12    = 1;
        TKVGFRs12 = 1;
        Futility  = 0;
      end;

      * Significant effect on GFR at stage 2 if two-sided p-value < 0.01;
      else if 2*p_mcp_gfr_s2 < 0.01 then do;
        TKVs1     = 0;
        GFRs1     = 0;
        GFRs12    = 1;
        TKVGFRs12 = 0;
        Futility  = 0;
      end;

      * Otherwise, no effect on TKV and GFR;
      else do;
        TKVs1     = 0;
        GFRs1     = 0;
        GFRs12    = 0;
        TKVGFRs12 = 0;
        Futility  = 0;
      end;
    end;

  end;

run;


* Calculate probability of each outcome;
proc means data=outcome noprint nway;
  var TKVs1 GFRs1 GFRs12 TKVGFRs12 Futility;
  output out=prob(keep=TKVs1 GFRs1 GFRs12 TKVGFRs12 Futility) mean=TKVs1 GFRs1
GFRs12 TKVGFRs12 Futility;
run;
```

```
* Print probabilities;
options nocenter;

title1 "Operating characteristics of the study design ";
title2 "Scenario: 15 mg: &RRtkv_d2.% on TKV, &RRgfr_d2% on eGFR";
title3 "          8 mg:  &RRtkv_d1.% on TKV, &RRgfr_d1% on eGFR";

proc print data=prob noobs l;
  var TKVs1 GFRs1 GFRs12 TKVGFRs12 Futility;
  format TKVs1 GFRs1 GFRs12 TKVGFRs12 Futility percent8.1;
  label TKVs1     = "Probability to detect an effect on TKV at the end of
Stage 1"
        GFRs1     = "Probability to detect an effect on eGFR at the end of
Stage 1"
        GFRs12    = "Probability to detect an effect on eGFR at end of Stage 1
and/or end of Stage 2"
        TKVGFRs12 = "Overall probability to detect an effect on TKV and eGFR"
        Futility  = "Probability to declare futility at interim analysis"
  ;
run;
```

5.6 APPENDIX 7 STATISTICAL TECHNICAL DETAILS

5.6.1 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 participants per arm in Stage 1 (randomized 1:1:1 to placebo, venglustat 8 mg or venglustat 15 mg) and of 160 participants 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 15. Additional scenarios assuming that the 8 mg dose was selected in Stage 2 were considered and are presented in Table 16. Sample SAS code of simulations is provided in Section 5.5.

For each scenario, 10 000 trials were simulated. Each simulated trial was analyzed according to the procedure described in Section 4.3.1.2:

- An interim analysis was performed when all participants from Stage 1 had TKV at baseline, 1 month and 9 months and 30% of participants 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 participants 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 participants 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 Section 4.6), 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 participants 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 15 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 15 - 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 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 16. 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 16 - 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	92.6%	6.4%	80.1%	2.3%
8 mg: 50% on TKV, 30% on eGFR				
Scenario 8				
15 mg: 70% on TKV, 50% on eGFR	99.3%	26.4%	98.3%	0.3%
8 mg: 50% on TKV, 30% on eGFR				

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

5.6.2 Confidence interval for relative reduction

5.6.2.1 Annualized rate of change in TKV

The relative reduction in annualized rate of change in TKV for venglustat 15 mg dose versus placebo is defined as:

$$RR_{15} = \left(1 - \frac{\widehat{\theta_{15}}}{\widehat{\theta_0}}\right) \times 100$$

where:

$$\widehat{\theta_i} = \text{Annualized rate of change in TKV in arm i} = 10^{\widehat{\beta_i}} - 1$$

and $\widehat{\beta_i}$ is the slope of $\log_{10}$-transformed TKV in arm i (i=0 for the placebo arm and i=15 for the venglustat 15 mg dose arm), estimated from the linear mixed-effect model.

Using the properties of the log-normal distribution in base 10, it can be shown that $\widehat{\theta_i}$ has mean and variance equal to m_i and s_i^2:

$$m_i = \exp\left(\widehat{\beta_i} \ln 10 + \frac{Var(\widehat{\beta_i})(\ln 10)^2}{2}\right) - 1$$

$$s_i^2 = \exp\left[2\widehat{\beta_i} \ln 10 + Var(\widehat{\beta_i})(\ln 10)^2\right]\left(\exp\left[Var(\widehat{\beta_i})(\ln 10)^2\right] - 1\right)$$

Using the Fieller method, the $100 \times (1-\alpha)\%$ confidence interval of the ratio $\frac{\widehat{\theta_{15}}}{\widehat{\theta_0}}$ has lower and upper limit equal to L_{15} and U_{15} :

$$L_{15} = \frac{m_0 m_{15} - \sqrt{(m_0 m_{15})^2 - \left(m_0^2 - {z_{\alpha/2}}^2 s_0^2\right)\left(m_{15}^2 - {z_{\alpha/2}}^2 s_{15}^2\right)}}{m_0^2 - {z_{\alpha/2}}^2 s_0^2}$$

$$U_{15} = \frac{m_0 m_{15} + \sqrt{(m_0 m_{15})^2 - \left(m_0^2 - {z_{\alpha/2}}^2 s_0^2\right)\left(m_{15}^2 - {z_{\alpha/2}}^2 s_{15}^2\right)}}{m_0^2 - {z_{\alpha/2}}^2 s_0^2}$$

where $z_{\alpha/2}$ is the quantile of the normal distribution.

Therefore, the 95% confidence interval for the relative reduction in annualized rate of change in TKV for venglustat 15mg dose versus placebo will be calculated as:

$$(1 - U_{15}) \times 100 \ ; \ (1 - L_{15}) \times 100$$

The same method will be used for the relative reduction of venglustat 8 mg dose versus placebo.

5.6.2.2 Annualized rate of change in eGFR

The same method will be used for the relative reduction in annualized rate of change in eGFR, with the exception that in absence of $\log_{10}$-transformation, RR_{15}, m_i and s_i^2 are defined as:

$$RR_{15} = \left(1 - \frac{\widehat{\beta_{15}}}{\widehat{\beta_0}}\right) \times 100$$

$$m_i = \widehat{\beta_i}$$

$$s_i^2 = Var\left(\widehat{\beta_i}\right)$$

where $\widehat{\beta_i}$ is the slope of eGFR in arm i, estimated from the linear mixed-effect model.

5.6.3 P-values from multiple comparison procedure

As described in Section 4.3.1.2 , the overall effect of venglustat will be assessed using 3 pre-specified contrasts Z_1, Z_2 and Z_3. (corresponding to the contrasts associated with the candidate models Emax, linear and Sigmoid Emax). The test statistic Z is the maximum of Z_1, Z_2 and Z_3.

Assuming the observed statistic is Z_{obs}, the one-sided p-value from the Multiple Comparison Procedure can be defined as the probability that Z is greater than Z_{obs}, under the null hypothesis. In the asymptotic case, random samples of Z under the null hypothesis can be generated using the SAS code below.

The two-sided p-value will be defined as twice the one-sided p-value, and truncated to 1 in case the one-sided p-value is greater than 0.5.

```
* Observed Z statistic;
%let Zobs = 2.25;

data pvalue;
  * Initialization of seed ;
  retain seed 15392;

  * Initialize the number of samples with Z > Zobs;
  Ngreater = 0;

  * Generate 1000000 samples from the distribution of the Z statistic
under the null hypothesis ;
  do i=1 to 1000000;

    * Generate independent normal for the 3 arms ;
    call rannor(seed,u0);
    call rannor(seed,u1);
    call rannor(seed,u2);

    * Calculate the 3 contrasts ;
    Z1 = -0.8131*u0 + 0.3424*u1 + 0.4707*u2;
    Z2 = -0.7223*u0 + 0.0314*u1 + 0.6909*u2;
    Z3 = -0.6615*u0 - 0.0838*u1 + 0.7453*u2;

    * Z-statistic : maximum of all contrasts ;
    Z = Max(Z1,Z2,Z3);

    * Increment the number of samples with Z > Zobs;
    Ngreater = Ngreater + (Z > &Zobs);

  end;

  * One-sided pvalue ;
  pvalue_onesided = Ngreater/1000000;

  * Two-sided p-value ;
  pvalue_twosided = min(2*pvalue_onesided,1);
run;
```

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