NCT04705051

STATISTICAL ANALYSIS PLAN

Protocol title:	**Multicenter, open-label, extension study to characterize the long-term efficacy and safety of early versus delayed treatment with venglustat (GZ/SAR402671) in patients at risk of rapidly progressive autosomal dominant polycystic kidney disease (ADPKD)**
Protocol number:	**LTS15823**
Compound number (INN/Trademark):	**venglustat/GZ402671**
Study phase:	**Phase 3**
Short title:	**Long-term treatment of autosomal dominant polycystic kidney disease (ADPKD) with venglustat STAGED-PKD-EXT**
Statistician:	[redacted]
Statistical project leader:	
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VERSION HISTORY

This statistical analysis plan (SAP) for study LTS15823 is based on the protocol amendment 1 dated 16-Mar-2021. This section summarizes the major changes to the statistical analysis features in the SAP.

This SAP is approved before the Stage 1 database lock of the parent study EFC15392 and before LTS15823 database lock.

The first participant was enrolled on 09-Feb-2021.

Table 1 - Major changes in statistical analysis plan

SAP Version	Approval Date	Changes	Rationale
1	22-Jun-2021	All analyses of primary, secondary and tertiary efficacy endpoints are removed (Section 1.2, Section 4.3, Section 4.4, Section 4.5). Safety analyses is restricted to the summaries of treatment emergent adverse events in the long-term safety population only. Any other analyses are not done (Section 4.7.2, Section 4.7.3, Section 4.8) Analysis populations are limited to screened, enrolled and safety population (see Section 3). All analyses will be presented on a single overall all participants group (see Section 4.1)	Following decision to discontinue EFC15392 and LTS15823 studies based on EFC15392 futility analysis

1 INTRODUCTION

1.1 STUDY DESIGN

This is international, multicenter, open-label extension study to characterize the long-term efficacy and safety of early versus delayed treatment with venglustat (GZ/SAR402671) in patients at risk of rapidly progressive autosomal dominant polycystic kidney disease (ADPKD). All participants will be treated with venglustat 15 mg once daily for up to 24 months.

After completion of 24 month of treatment in the parent study EFC15392, participants may be enrolled immediately in the LTS15823. Participants who cannot be included in the extension study at the time of Visit 12 of the EFC15392 study will have a separate Screening visit (Visit 0) performed and must be enrolled in the LTS15823 study within 2 months of the last dose of IMP (Visit 12 [Month 24]) administered in the EFC15392 study. This 2-month window can be further extended up to 6 months following review and approval by the Sponsor.

After a screening phase, when applicable, of up to 2 weeks, participants will be centrally enrolled via Interactive Response Technology (IRT) and treated with open label venglustat 15 mg for 2 years. A maximum of 640 participants who completed the EFC15392 study will be enrolled in LTS15823.

Based on the EFC15392 futility analysis and the sponsor decision to discontinue the EFC15392 and LTS15823 studies, the LTS15823 study analysis will be conducted after the early study termination.

1.2 OBJECTIVE AND ENDPOINTS

The Table 2 provides the objectives and endpoints as planned in protocol. Considering the decision to discontinue the study after enrollment of only 24 patients, statistical analyses of the study are revised and only demographic, baseline characteristics and adverse events will be summarized overall.

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To determine the effect of early versus delayed treatment with venglustat on the total kidney volume (TKV) in participants at risk of rapidly progressive ADPKD.	• Percent change in TKV based on magnetic resonance imaging (MRI) from the EFC15392 study baseline to 24 months of open-label extension study, in early-treated and delayed-treated participants.
Secondary	
• To determine the effect of early versus delayed treatment with venglustat on the renal function (estimated glomerular filtration rate [eGFR]).	• Change in eGFR (Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) from the EFC15392 study baseline to 24 months of open-label extension study, in early-treated and delayed-treated participants.

Objectives	Endpoints
• To characterize the safety profile of venglustat.	• Safety in terms of treatment-emergent adverse events (TEAEs), adverse events (AEs), serious adverse events (SAEs), laboratory parameters, vital signs, electrocardiogram and findings from physical examination will be assessed through the study and will be reported in the electronic case report form (eCRF).
• To evaluate the effect of venglustat on the lens by ophthalmological examination.	• Change from EFC15392 study baseline in the lens clarity by ophthalmological examination during the open-label extension treatment-emergent period.
• To evaluate the effect of venglustat on mood using Beck Depression Inventory-II (BDI-II).	• Change from EFC15392 study baseline in BDI-II score during the open-label extension treatment-emergent period.
Tertiary	
• To explore the impact of venglustat on total liver volume (TLV) (in participants with height adjusted TLV [htTLV] >2 L/m).	• Change in TLV based on MRI (in participants with htTLV >2 L/m) from EFC15392 study baseline to 24 months of the open-label extension study.
• To explore the effect of venglustat on systolic blood pressure (SBP) and diastolic blood pressure (DBP).	• Change from EFC15392 study baseline during the open-label extension treatment-emergent period in: - SBP, - DBP.
• To explore the effect of venglustat on type, frequency and dosage of analgesic/over the counter (OTC) pain medication administration.	• Change from EFC15392 study baseline in type, frequency, and dosage of analgesic/OTC pain medication administration during the open-label extension study.
• To explore the effect of venglustat on time to confirmed 30% and 40% reduction in eGFR.	• Time to confirmed 30% reduction in eGFR since randomization in the EFC15392 study, in early-treated compared to late-treated participants during the combined EFC15392 and LTS15823 period. • Time to confirmed 40% reduction in eGFR since randomization in the EFC15392 study, in early-treated compared to late-treated participants during the combined EFC15392 and LTS15823 period.
• To explore the effect of venglustat on biomarkers associated with ADPKD (eg, Fibroblast Growth Factor 23 [FGF23], asymmetric dimethylarginine [ADMA]) (not applicable for Chinese participants).	• Change in the levels of biomarkers associated with ADPKD (eg, FGF23, ADMA) from EFC15392 study baseline to 24 months of open-label extension study (not applicable for Chinese participants).
• To explore the pharmacodynamic (PD) effects of venglustat by measuring downstream metabolites of glucosylceramide synthase (GCS) in plasma (not applicable for Chinese participants).	• Change in the levels of downstream metabolites of GCS in plasma from EFC15392 study baseline to 24 months of open-label extension study (not applicable for Chinese participants).
• To explore the effect of venglustat on pain (brief pain inventory short form [BPI-SF]), fatigue (Brief Fatigue Inventory [BFI]), and the EuroQoL 5-dimension 5 level (EQ-5D-5L) score.	• Change from EFC15392 study baseline to 24 months of open-label extension study in: - BPI-SF, - BFI, - EQ-5D-5L.

1.2.1 Estimands

Not applicable.

2 SAMPLE SIZE DETERMINATION

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

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

Nevertheless, based on the following protocol assumptions:

- TKV growth rate in EFC15392:
  - in placebo group of 0.02764 on log10 scale (6.6%/year)
  - in venglustat group, expecting a 50% reduction of the TKV growth rate, ie, 0.01404/year on log10 scale (3.3%/year)
- TKV growth rate in LTS15823:
  - in Early venglustat group, of 0.01404 on log10 scale (3.3%/year)
  - in Delayed venglustat group: 0.01404 on log10 scale (3.3%/year)
- a standard deviation for the residual error of TKV (on the log10 scale) of 0.02566 and
- a standard deviation for the random effect of slope of 0.01477

And assuming 10% of dropout rate in EFC15392, 20% of participants having completed EFC15392 will not participate to LTS15823 (or will be enrolled with more than 3 months delay), then 25% additional will dropout during LTS15823 (due to venglustat becoming commercially available in some countries), the power to detect a difference in TKV at Month 24 between “Early venglustat” and “Delayed venglustat” is approximately 95%.

In the case the venglustat 8 mg will not show similar effect compared to venglustat 15 mg in Stage 1 of the EFC15392 study (RR8 <2/3 RR15), then participants from venglustat 8mg will be excluded from the efficacy analyses, in that case the LTS15823 has 92% power to detect a difference in TKV at Month 24 between “Early venglustat” and “Delayed venglustat”.

3 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Population	Description
Screened	All participants who sign the LTS15823 study ICF.
Enrolled	All participants from screened population who have been allocated to an LTS15823 intervention kit by interactive response technology (IRT) regardless of whether the intervention was received or not.
Long-term extension safety	All participants who take at least 1 dose of study intervention in the LTS15823 study.

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

4 STATISTICAL ANALYSES

4.1 GENERAL CONSIDERATIONS

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.

All analyses will be presented on a single all participants group.

Observation period of the open-label extension study

The observation period will be divided into 4 segments:

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

The on-study period is defined as the time from enrollment 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 3 will be summarized.

Screen failures are defined as participants who consent to participate in the LTS15823 study but are not subsequently enrolled. 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:

- Enrolled participants.
- Enrolled but not exposed participants.

- Enrolled and exposed participants.
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation.
- 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 enrolled participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, enrolled, 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) during the long-term extension open-label period will be summarized in the enrolled population, as well as displayed separately as related versus not related to Covid-19 if applicable.

4.3 PRIMARY ENDPOINT(S) ANALYSIS

Not done.

4.3.1 Definition of endpoint(s)

The primary endpoint of percent change in TKV based on MRI from the EFC15392 study baseline to 24 months of open-label extension study will not be analyzed.

4.3.2 Main analytical approach

Not applicable.

4.3.3 Sensitivity analysis

Not applicable.

4.3.4 Supplementary analyses

Not applicable.

4.3.5 Subgroup analyses

Not applicable.

4.4 SECONDARY ENDPOINT(S) ANALYSIS

4.4.1 Key/Confirmatory secondary endpoint(s)

The secondary endpoint of change in eGFR from the EFC15392 study baseline to 24 months of open-label extension study will not be analyzed.

Other secondary endpoints analyses are defined in Section 4.7.2 (AE, SAE).

4.4.1.1 Definition of endpoint(s)

4.4.1.2 Main analytical approach

Not applicable.

4.4.2 Supportive secondary endpoint(s)

Not applicable.

4.5 TERTIARY/EXPLORATORY ENDPOINT(S) ANALYSIS

4.5.1 Definition of endpoint(s)

Not applicable.

4.5.2 Main analytical approach

Not applicable.

4.6 MULTIPLICITY ISSUES

Not applicable.

4.7 SAFETY ANALYSES

All safety analyses will be essentially descriptive, and no testing is planned.

4.7.1 Extent of exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure and summarized within the long-term safety population.

Duration of IMP exposure

Duration of LTS15823 IMP exposure is defined as last LTS15823 IMP administration date – first LTS15823 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

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

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 currently 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 AE reporting will be on TEAEs.

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.

Multiple occurrences of the same event in the same participant will be counted only once in the tables within a treatment phase.

The AE tables will be sorted as indicated in Table 4.

Table 4 - 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 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]

a Sorting will be based on the overall incidence
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 5 will be generated with number (%) of participants experiencing at least one event.

Table 5 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT
	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
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 AESI	Primary SOC and PT
Treatment emergent COVID-19 related AE	Primary SOC and PT

Analysis of deaths

In addition to the analyses of deaths included in Table 4 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-enrolled participants or enrolled but not treated participants

Analysis of adverse events of special interest (AESIs) and other AEs of interest

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 6. Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 4.

Table 6 - Selections for AESIs and other AEs of interest

AESIsand 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

The analyses of additional safety assessments will not be done.

4.7.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

Not applicable.

4.7.3.2 Neurological examination

Not applicable.

4.7.3.3 Ophtalomological examination

Not applicable.

4.7.3.4 Depression (BDI_II) examination

Not applicable.

4.8 OTHER ANALYSES

The analysis of the other parameters will not be done.

4.8.1 Pharmacodynamic analyses

Not applicable.

4.8.2 Patient reported outcomes analyses

Not applicable.

4.8.3 Biomarker analyses

Not applicable.

4.9 INTERIM ANALYSES

No interim analysis is planned.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

AESIs: adverse events of special interest
ALT: Alanine transaminase
HGLT: high level group term
IMP: Investigational medicinal product
MedDRA: medicinal dictionary for regulatory activities
PT: preferred term
SAP: statistical analysis plan
SD: standard deviation
SOC: system organ class
TEAE: treatment-emergent adverse event

5.2 APPENDIX 2 CHANGES TO PROTOCOL-PLANNED ANALYSES

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

Table 7 - Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
1	16 Mar 2021	All participants will be treated for the duration of 24 months. The protocol instruction "or until venglustat is commercially available for patients, whichever comes first" is not applicable to the countries listed	To comply with the request raised during the EU VHP review phase, study participants in Belgium, Czech Republic, Denmark, Germany, Italy, Poland, Portugal, Romania, and Spain will receive venglustat (15 mg once daily) for the duration of 24 months

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

Demographics, baseline characteristics

The following demographics and baseline characteristics and disease characteristics at baseline will be summarized using descriptive statistics in the enrolled population.

Demographic and baseline characteristics

- Gender (Male, Female)
- Age in years (quantitative and categorical variable: <40, and ≥40 years) at the EFC15392 baseline as well as the LTS15823 baseline

- 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) at the EFC15392 as well as the LTS15823 baseline

Disease characteristics

eGFR at EFC15392 screening, EFC15392 baseline and LTS15823 baseline (quantitative variable and qualitative variable: <30,30 to <45, 45 to <60, 60 to <75, 75 to <90, >=90) (see Section 5.4).

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

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

eGFR at EFC15392 screening

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

- If eGFR at EFC15392 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 EFC15392 Visit 1 and EFC15392 Visit 2, then this additional value is considered as the screening value
- Else, the eGFR at EFC15392 Visit 2 is considered as the screening value

Table 8 - eGFR values example

Subject	EFC15392 V1	EFC15392 Additional (between V1 and V2)	EFC15392 V2
1	**87**	ND	91
2	92	ND	**85**
3	95	**86**	93
4	92	**95**	88

eGFR at EFC15392 baseline

EFC15392 Baseline eGFR is defined for each participant as the average of eGFR values assessed prior or equal to 1st IMP in the EFC15392 study or prior or equal to randomization for randomized and not exposed participants.

eGFR at LTS15823 baseline

LTS15823 Baseline eGFR is defined:

- as the eGFR assessment performed at the time of EFC15392 V12 for each participant enrolled at the time of the EFC15392 V12.
- else, as the average of eGFR values assessed between LTS15823 screening visit up to 1st IMP in the LTS15823 (including) or prior or equal to enrollment for enrolled and not exposed participants.

6 REFERENCES

Not applicable.

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