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Sponsor: Sanofi **Drug substance(s):** GZ402671 - venglustat	**Study Identifiers:** UTN: U1111-1202-0775, IND number: 130913, NCT number: NCT03523728, EudraCT Number: 2017-004084-12 **Study code:** EFC15392
Title of the study: Multicenter, randomized, double-blind, placebo-controlled two stage study to characterize the efficacy, safety, tolerability and pharmacokinetics of GZ/SAR402671 in patients at risk of rapidly progressive Autosomal Dominant Polycystic Kidney Disease (ADPKD)	
Study center(s): This study was conducted at 93 centers that enrolled participants in 23 countries.	
Study Period: Date first participant enrolled: 27 September 2018 Date last participant completed: 03 August 2021 Study Status: Terminated (Interim analysis for futility of the Stage 1 of the EFC15392 study met the protocol specified stopping rule based on the primary endpoint. EFC15392 study was stopped for futility based on prespecified criteria and recommendation from DMC)	
Phase of development: Phase 2/Phase 3	
Objectives **Stage 1 Primary objective:** To determine the effect of venglustat on the rate of TKV growth in participants at risk of rapidly progressive ADPKD **Stage 1 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 participant reported diary To evaluate the PK of venglustat in ADPKD participants 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

Stage 2 Primary objective:

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

Stage 2 Secondary objectives:

To determine the effect of venglustat on the rate of TKV growth

To determine the effect of venglustat on pain and fatigue, based on participant reported diary

To evaluate the PK of venglustat in ADPKD participants

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

Methodology

This was 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 with a screening estimated glomerular filtration rate (eGFR) between 45 and 89.9 mL/min/1.73 m^2 in Stage 1 and Stage 2 and participants aged 18 to 55 years with a screening eGFR between 30 and 44.9 mL/min/1.73 m^2 in Stage 2 only.

The study was divided into 2 stages:

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

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

At randomization, participants were stratified based on their predicted ADPKD progression rate (1C versus 1D versus 1E) according to Mayo Imaging Classification and by geographic region (North America, Europe, China, Japan, Republic of Korea, Rest of the World). A review of the unblinded aggregate safety data from Stage 1 by the DMC was planned, after at least 1 month of treatment of the first 150 randomized participants from Stage 1, to select the dose of venglustat to be used for Stage 2. In case the DMC recommended the 8 mg dose for Stage 2, then the DMC had the possibility to recommend switching participants on 15 mg treatment arm in Stage 1 to the 8 mg arm.

Stage 2: After the first 150 randomized participants from Stage 1 had completed at least 1 month of treatment (or had prematurely discontinued), the DMC reviewed in an unblinded fashion the aggregate safety data from Stage 1 and selected the venglustat

dose 15 mg for Stage 2 participants. The selected dose was the highest dose determined to be safe and well tolerated in Stage 1.

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

After run-in, participants were randomized with a 1:1 ratio to placebo and venglustat (dose determined from Stage 1).

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

Participants who completed 24 months of treatment in either Stage 1 or Stage 2 of EFC15392 study had the option to enroll into an open-label long-term extension study LTS15823.

Number of participants:

Planned:

Stage 1: Approximately 240 participants (80 participants per arm).

Stage 2: Approximately 400 participants (200 participants on venglustat and 200 participants on placebo).

Actual:

A total of 201 participants were enrolled in placebo group, 78 participants in 8 mg venglustat group, and 199 participants in 15 mg venglustat group.

Diagnosis and criteria for inclusion:

Inclusion criteria:

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

- between 18 and 50 years (inclusive) for 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*
- Diagnosis of ADPKD in participants with a family history, was based on unified Pei criteria. In the absence of a family history, the diagnosis was based on the presence of renal cysts bilaterally, totaling at least 20, in the absence of findings suggestive of other cystic renal diseases.

Mayo Imaging Classification of ADPKD Class 1C, 1D, or 1E**.

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

Estimated glomerular filtration rate between 45 and 89.9 mL/min/1.73 m^2 during the screening period* (Chronic Kidney Disease Epidemiology Collaboration [CKD EPI] equation) for Stage 1. Estimated glomerular filtration rate between 30

and 89.9 mL/min/1.73 m^2 during the screening period* (CKD-EPI equation) for Stage 2.

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

Study Products

Investigational medicinal product(s): Venglustat, matched placebo.

Formulation/Form & composition:

Venglustat was provided in capsule formulation containing 4 mg or 15 mg of venglustat (active moiety).

Matched placebo is provided as a capsule indistinguishable from venglustat.

Route(s) of administration: Oral.

Duration of treatment/participation:

Stage 1

Total study duration: 26 months (maximal).

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

Stage 2

Total study duration: 26 months (maximal).

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

Criteria for evaluation:

Stage1:

Primary endpoints:

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

Secondary endpoints:

Efficacy endpoints:

Annualized rate of change in eGFR (CKD-EPI equation) from baseline to 18 months

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

Plasma venglustat concentrations

Safety/tolerability objectives:

Treatment-emergent adverse events (TEAEs)/AEs/SAEs, laboratory parameters, vital signs, ECG and findings from physical examination

Change in score of BDI-II during the treatment-emergent period

Change in the lens clarity by ophthalmological examination during the treatment-emergent period

Stage 2

Primary endpoints:

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

Secondary endpoints:

Efficacy endpoints:

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:

Plasma venglustat concentrations

TEAEs/AEs/SAEs, laboratory parameters, vital signs, ECG and findings from physical examination

Change in score of BDI-II- during the treatment-emergent period

Change in the lens clarity by ophthalmological examination during the treatment-emergent period

Statistical methods:

Sample size determination:

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

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

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

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

In addition, sample size and power calculations assumed an overall significance level of 0.05 (2-sided), 10% dropout rate and included adjustments for handling of multiplicity of tests and futility analysis (as described in later sections).

A sample size of 80 participants (40 per arm) with an eGFR between 30 and 44.9 mL/min/1.73 m^2 at screening provided approximately 80% probability to detect a treatment effect in this subgroup at the 0.20 significance level (two-sided), based on a model evaluating the dependence of the treatment effect on baseline eGFR.

Analysis population:

Stage 1:

Stage 1 intent-to-treat (ITT) population included all participants who are randomized in Stage 1.

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

Stage 2:

The combined Stage 1 and Stage 2 ITT population included all participants with an eGFR between 45 and 89.9 mL/min/1.73 m2 at screening who are randomized in Stage 1 or Stage 2, analyzed according to the treatment group allocated by randomization (venglustat 15 mg, venglustat 8 mg, or placebo). Participants from Stage 2 with an eGFR between 30 and 44.9 mL/min/1.73 m2 at screening were not included in the primary efficacy and safety analyses population but the data from these participants were planned to be analyzed separately.

Summary Results

Demographic and other baseline characteristics:

A total of 201 participants were randomized in placebo group, 78 participants in 8 mg venglustat group and 199 participants in 15 mg venglustat group. Of these, 200 participants in placebo group and all participants in 8 mg and 15 mg venglustat group were exposed to IMP. Twelve (6.0%) participants in placebo group, 10 participants (12.8%) in 8 mg venglustat group, and 12 participants (6.0%) in 15 mg venglustat group completed the study treatment. Sixteen (8.0%) participants in placebo group, 12 participants (15.4%) in 8 mg venglustat group and 16 participants (8.0%) in 15 mg venglustat group completed the study. All participants were alive at the time of last contact in the study.

The mean (SD) age was 42.2 (6.5) years for all participants. More than half of the total population were males (282 participants [59.0%]). Majority of the study population were Whites (280 participants [58.6%]) followed by Asians (188 participants [39.3%]). The mean (SD) BMI was 26.1 (5.2) kg/m^2. All demographics were well balanced across the placebo, 8 mg venglustat, and 15 mg venglustat groups.

Efficacy results:

The primary endpoint in Stage 1 was annualized rate of change in TKV based on MRI from baseline to 18 months. The annualized rate of change in TKV was 6.35% per year (95% CI: 5.10 to 7.62) in placebo group, 7.71% per year (95% CI: 6.46 to 8.98) in 8 mg venglustat group and 6.38% per year (95% CI: 5.11 to 7.66) in 15 mg venglustat group. The two-sided p-value of 8 mg venglustat group versus placebo was 0.1367 and 15 mg venglustat group versus placebo was 0.9812.

The primary efficacy endpoint in combined Stage 1 and Stage 2 was annualized rate of change in eGFR (CKD-EPI equation) from baseline to 24 months. The annualized rate of change in eGFR estimate (SE) was -2.40 (0.46) mL/min/1.73m^2/year in placebo group, -4.82 (0.50) mL/min/1.73m^2/year in 8 mg venglustat group and -4.89 (0.46) mL/min/1.73m^2/year in 15 mg venglustat group. The two-sided p-value when placebo was compared with 8 mg venglustat group was 0.0005 and with 15 mg venglustat group was 0.0002.

Safety results:

There were 128 participants (64.0%) in placebo group, 65 participants (83.3%) in 8 mg venglustat group and 143 participants (71.9%) in 15 mg venglustat group with any TEAE reported during the study. There were 14 participants (7.0%) in placebo group, 15 participants (19.2%) in 8 mg venglustat group and 26 participants (13.1%) in 15 mg venglustat group who experienced treatment-emergent SAEs. There were no TEAEs leading to death in this study. Three participants (1.5%) in placebo group, 2 participants (2.6%) in 8 mg venglustat group and 6 participants (3.0%) in 15 mg venglustat group experienced TEAE leading to permanent study intervention discontinuation. Eleven participants (5.5%) in placebo group, 6 participants (7.7%) in 8 mg venglustat group and 14 participants (7.0%) in 15 mg venglustat group experienced TE AESI.

Pharmacokinetic results:

As determined from Stage 1 of the study, following venglustat 8 mg or 15 mg QD oral administration, steady state was achieved on or before 1 month (assessed from pre-dose concentrations, Ctrough), with an accumulation of approximately 3-fold (assessed from post-dose concentrations). In general, venglustat plasma exposure (C_{trough}) at steady state increased in a close to dose proportional manner with an increase in dose from 8 to 15 mg.

Venglustat PK in Stage 2 of the study was consistent with that observed in Stage 1. Following venglustat 15 mg QD dose, the mean (SD) pre-dose (C_{trough}) concentrations ranged from 103.9 (50.2) ng/mL- 120.3 (73.1) ng/mL in Stage 1 and 109.3 (60.7) ng/mL at 1 month in Stage 2.

Pharmacodynamic results:

Plasma glucosylceramide (GL-1) results for Stage 1 showed dose dependent decreases following treatment with venglustat compared to baseline: 76.9% and 75.4% with 8 mg dose and 83.0% and 84.1% with 15 mg dose at 6 and 12 months, respectively. Plasma GL-1 results from the placebo group did not show any difference at 6 and 12 months compared to baseline levels. Plasma GL-1 data for 24 months is limited.

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