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Sponsor:	**Study Identifiers:**
Sanofi **Drug substance(s):** Venglustat	UTN: U1111-1256-8805, NCT number: NCT04705051, EudraCT Number: 2020-004400-34 **Study code:** LTS15823

Title of the study:

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)

Study center(s):

This study was conducted at 11 centers that enrolled participants in Australia, Belgium, Germany, Spain, Japan, Republic of Korea, Netherlands, and the United States.

Study period:

Date first participant enrolled: 09 February 2021

Date last participant completed: 13 July 2021

Study Status: Terminated, The study was terminated prematurely by the Sponsor following a decision to terminate Study EFC15392 based on the results of the futility analysis of Study EFC15392. Neither Study EFC15392 nor Study LTS15823 were terminated for safety reasons.

Phase of development: Phase 3

Objectives:

Primary objectives: To determine the effect of early versus delayed treatment with venglustat on the total kidney volume in participants at risk of rapidly progressive autosomal dominant polycystic kidney disease (ADPKD).

Secondary objectives:

- To determine the effect of early versus delayed treatment with venglustat on the renal function (estimated glomerular filtration rate [eGFR]).

- To characterize the safety profile of venglustat.

- To evaluate the effect of venglustat on the lens by ophthalmological examination.

- To evaluate the effect of venglustat on mood using Beck Depression Inventory-II (BDI-II).

Methodology:

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

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

This was an international, multicenter, open-label extension roll-over study that included adult participants at risk of rapidly progressive ADPKD who had previously completed Stage 1 or Stage 2 of Study EFC15392. All participants were to be treated with venglustat 15 mg once daily for 24 months or until venglustat was commercially available, whichever came first. The study was terminated prematurely by the Sponsor following a decision to terminate Study EFC15392 based on the results of the futility analysis of Study EFC15392. Neither Study EFC15392 nor Study LTS15823 were terminated for safety reasons.

The study duration was to be a maximum of 25.5 months, consisting of a screening period (when applicable) of up to 2 weeks, a core treatment period of 24 months, and a follow-up period of 30 days after final dose of the investigational medicinal product (IMP) (venglustat).

Enrollment in this LTS15823 study was to coincide with Visit 12 (Month 24; end-of-treatment visit) of the EFC15392 study. Participants who were not able to be included in this extension study at the time of Visit 12 for administrative or logistical reasons, and provided they agreed to participate in the LTS15823 study, had a separate screening visit (Visit 0) performed and were to 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 may have been further extended up to 6 months with approval by the Sponsor.

Detailed description of the study methodology is provided in the clinical study protocol and its amendment.

Number of participants:

Planned: Approximately 640 participants.

Enrolled: 24 participants

Treated: 23 participants

Evaluated:

Safety: 23 participants

Diagnosis and criteria for inclusion:

Key Inclusion Criteria:
Male or female adults with ADPKD who completed the treatment period in Stage 1 or Stage 2 of Study EFC15392 and had an eGFR >30 mL/min/1.73 m2.

Study products

Investigational medicinal product(s): Venglustat

Formulation/Form & composition: capsule

Route(s) of administration: orally

Duration of treatment/participation:

Venglustat was to be administered once daily for 24 months.

Criteria for evaluation:

Primary endpoints:

Percent change in total kidney volume based on magnetic resonance imaging from the EFC15392 study baseline to 24 months of open-label extension study, in early-treated and delayed-treated participants.

Secondary endpoints:

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

- Safety in terms of treatment-emergent adverse events (TEAEs), adverse events (AE), serious adverse events, laboratory parameters, vital signs, electrocardiogram and findings from physical examination were assessed through the study and reported in the electronic case report form.

- Change from EFC15392 study baseline in the lens clarity by ophthalmological examination during the open label extension treatment-emergent period.

- Change from EFC15392 study baseline in BDI-II score during the open-label extension treatment emergent period.

Statistical methods:

A detailed description of the planned statistical methods is provided in the statistical analysis plan. The efficacy analysis specified in the protocol was not conducted as the study was terminated early. Therefore, this report includes a summary of the safety data generated only.

Safety variables were analyzed using descriptive statistics. All AEs were coded using the Medical Dictionary for Regulatory Activities (Version 24.0). The AEs were analyzed in the 3 categories: pre-treatment AEs, TEAEs, and post-treatment AEs. The AE reporting was on TEAEs. Summaries were provided for TEAEs, including TEAEs related to IMP, TEAEs by maximum severity, and coronavirus disease 2019 (COVID-19)-related TEAEs; serious TEAEs; TEAEs leading to treatment discontinuation; treatment-emergent adverse events of special interest (AESI); deaths; and adverse events leading to death. The AESIs included pregnancy of a female participant or female partner of a male participant, symptomatic overdose (serious or non-serious) with IMP, increase in alanine transaminase, and new or worsening lenticular opacities and cataracts.

Summary Results:

A total of 24 participants were enrolled in the study, of which 23 (95.8%) participants were treated. All the participants who were treated discontinued the study treatment permanently. The reason for study treatment discontinuation in all participants was due to the termination of the preceding Study EFC15392. Study EFC15392 was terminated by the sponsor based on the results of the futility analysis.

One participant ([4.2%]) reported critical or major deviations related to COVID-19. This participant had critical or major deviations of examination (BDI-II) not performed and planned sample (blood) not performed.

The critical or major deviations not related to COVID-19 impact were reported for 6 (25.0%) participants. The most commonly reported protocol deviations not related to COVID-19 impact were examination (BDI-II) not performed (4 [16.7%] participants) and study informed consent/ assent form not obtained before intervention(s) performed as specified in protocol (2 [8.3%] participants)

No other deviations occurred in >1 participant.

Demographic and other baseline characteristics:
Overall, the mean (standard deviation [SD]) age was 45.3 (4.7) years. All participants were either White or Asian (12 [50%] participants, each). A total of 15 (62.5%) enrolled participants were male and 9 (37.5%) participants were female. No participants were Hispanic or Latino and the mean (SD) body mass index was 26.4 (4.9) kg/m2. Overall, the mean (SD) eGFR (CKD-EPI) at LTS15823 baseline was 60.37 (12.80) mL/min/1.73 m2. The majority of participants (14 [58.3%] participants) had eGFR between 45 to 59.9 mL/min/1.73 m2 at baseline. Four (16.7%) participants had eGFR between 60 to 74.9 mL/min/1.73 m2, 4 (16.7%) participants had eGFR between 75 to 89.9 mL/min/1.73 m2 and 1 (4.2%) participant had eGFR ≥90 mL/min/1.73 m2.

Exposure:
The mean (SD) duration of exposure was 5.2 (4.5) weeks. All 23 participants had ≥1 day of IMP exposure; 11 (47.8%) participants had IMP exposure ≥4 weeks (1 month); and 2 (8.7%) participants had IMP exposure ≥13 weeks (3 months).

Efficacy results:
Efficacy was not assessed due to early termination of the study.

Safety results:
Two (8.7%) participants had TEAEs during the study. One of these participants had a serious TEAE of wound infection, and the other had a TEAE of thirst. The wound infection for which the participant was hospitalized was reported as not resolved and considered not related to IMP by the Investigator. No participant had a TEAE leading to death or permanent treatment discontinuation, a treatment-emergent AESI, or an IMP-related TEAE.

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