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Venglustat, a Novel Glucosylceramide Synthase Inhibitor, in Patients at Risk of Rapidly Progressing ADPKD: Primary Results of a Double-Blind, Placebo-Controlled, Phase 2/3 Randomized Clinical Trial

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Venglustat, a Novel Glucosylceramide Synthase Inhibitor, in Patients at Risk of Rapidly Progressing ADPKD: Primary Results of a Double-Blind, Placebo-Controlled, Phase 2/3 Randomized Clinical Trial

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Abstract

Rationale and Objective: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the formation of multiple kidney cysts that leads to growth in total kidney volume (TKV) and progression to kidney failure. Venglustat is a glucosylceramide synthase inhibitor that has been shown to inhibit cyst growth and reduce kidney failure in preclinical models of ADPKD.

Study Design: STAGED-PKD was a two-stage, multicenter, double-blind, randomized, placebo-controlled Phase 2/3 study in adults with ADPKD at risk of rapidly progressive disease, selected based on Mayo Kidney Volume Class 1C–1E and an estimated glomerular filtration rate (eGFR) of 30–89.9 mL/min/1.73 m^2.

Setting and Participants: Enrollment included 236 and 242 patients in Stages 1 and 2, respectively.

Intervention(s): In Stage 1, patients were randomized 1:1:1 to venglustat 8 mg or 15 mg, or placebo. In Stage 2, patients were randomized 1:1 to venglustat 15 mg (highest dose identified as safe and well tolerated in Stage 1) or placebo.

Outcomes: Primary endpoints were rate of change in TKV over 18 months in Stage 1 and eGFR slope over 24 months in Stage 2. Secondary endpoints were eGFR slope over 18 months (Stage 1), rate of change in TKV (Stage 2), and safety/tolerability, pain, and fatigue (Stages 1 and 2).

Results: A prespecified interim futility analysis showed that venglustat treatment had no effect on the annualized rate of change in TKV over 18 months (Stage 1) and had a faster rate of decline in eGFR slope over 24 months (Stage 2). Due to this lack of efficacy, the study was terminated early.

Limitations: The short follow-up after end-of-treatment and limited generalizability of findings.

Conclusions: In patients with rapidly progressing ADPKD, treatment with venglustat at either 8 mg or 15 mg showed no change in the rate of change in TKV and a faster rate of eGFR decline in the STAGED-PKD trial despite a dose-dependent decrease in plasma glucosylceramide (GL-1) levels.

Funding: This study was funded by Sanofi.

Trial Registration: Rregistered at ClinicalTrials.gov with study number NCT03523728.

Index words: Autosomal dominant polycystic kidney disease; venglustat; total kidney volume; glomerular filtration rate

Plain Language Summary

Patients with autosomal dominant polycystic kidney disease (ADPKD) develop cysts in the kidneys that lead to inflammation, scarring, and obstruction of urine flow with progression to kidney failure. Currently, there is only one drug that is approved for the treatment of ADPKD; however, it is associated with liver toxicity. Venglustat is an oral medication that has been shown to prevent the development of kidney cysts and preserve kidney function in preclinical studies of ADPKD. The STAGED-PKD trial evaluated the efficacy and safety of venglustat in patients with rapidly progressing ADPKD. In this patient population, venglustat provided no benefit and in fact resulted in a faster decline in kidney function. Based on these preliminary findings, the STAGED-PKD trial was stopped.

Introduction

Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic kidney disease, occurring in approximately 3 in 10,000 individuals.[1,2] ADPKD is characterized by development of fluid-filled cysts, kidney enlargement, hypertension, and eventual progression to kidney failure in most patients.[3,4] As kidney cysts expand, cytokines and chemokines are released, which cause inflammation and fibrosis. In addition, growing cysts can obstruct urine flow, damaging surrounding kidney tissue.[5,6] The only drug approved to slow kidney function decline and cyst development in adults with rapidly progressing ADPKD is the vasopressin receptor antagonist, tolvaptan.[7,8] However, liver toxicity and tolerability issues relating to aquaresis with tolvaptan[7-9] have meant that a substantial unmet need persists for new treatments for patients with ADPKD.

Accumulation of glycosphingolipids (GSLs), lipid molecules that serve as structural components of cellular membranes and modulate cell signaling, is observed in ADPKD.[10] Accumulation of GSLs is a result of increased activity of glucosylceramide synthase (GCS) and can promote kidney cyst growth in ADPKD;[11,12] however, the mechanism by which this occurs is still unclear. Venglustat is a once-daily (QD), orally administered investigational GCS inhibitor that inhibits the enzymatic conversion of ceramide to glucosylceramide (GL-1), the first step in GSL synthesis.[15] Patients with ADPKD have been shown to have elevated levels of GL-1 in the kidney.[14] In preclinical mouse models of ADPKD, venglustat treatment decreased levels of kidney GL-1 by ≥70% and reduced cyst growth, induced cyst cell differentiation, and preserved kidney function.[14] In three completed Phase 1 studies, repeated QD doses of venglustat (up to 20 mg) for 14 days in healthy individuals resulted in a time- and dose-dependent reduction in GL-1 levels by approximately 67–76%.[15] At the doses and dosing regimen tested, venglustat showed a

safety and tolerability profile without any serious or severe adverse events.[15] Based on these findings, GCS inhibition with venglustat was a viable therapeutic treatment to slow cyst growth and preserve kidney function in individuals with ADPKD.

In this paper, we report the findings from the **S**tudy **T**o **A**ssess **G**lucosylceramide synthase inhibitor **E**fficacy in A**DPKD** (STAGED-PKD) study, a Phase 2/3 study designed to assess the efficacy, safety, tolerability, and pharmacokinetics of venglustat in patients with rapidly progressing ADPKD.

Methods

Trial Design

STAGED-PKD was an international, multicenter, randomized, double-blind, placebo-controlled, two-stage study that was conducted by the Sponsor (Sanofi) and clinical investigators in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practice, all applicable laws, rules, and regulations (**Item S1**). The protocol and informed consent form was approved by the appropriate institutional review board and independent ethics committee. The trial design and protocol has been published previously.[16]

From February 2019 to June 2021, participants were enrolled in the study across 84 centers in 21 countries. Eligible participants were males and females aged 18–50 years with a high likelihood of rapid disease progression, as indicated by an estimated glomerular filtration rate (eGFR) 45–89.9 mL/min/1.73 m^2 (Stages 1 and 2) or aged 18–55 years and an eGFR 30–44.9 mL/min/1.73 m^2 (Stage 2 only) and a Mayo Imaging Classification of ADPKD Class 1C, 1D, or 1E (**Items S2, S3**).[17] Because of the observation of reversible lens degeneration in

juvenile toxicity and a 26-week study of venglustat administration in rats, the potential risk of cataract was monitored and evaluated in this study by means of periodic ophthalmologic examinations.

The trial consisted of two stages. Each stage consisted of a screening period of up to 30 days, including a 2-week, single-blind, placebo run-in period (to identify patients unlikely to follow the assigned treatment regimen) followed by randomization to treatment for 24 months. In Stage 1, participants were randomized 1:1:1 to placebo, venglustat 8 mg, or venglustat 15 mg. In Stage 2, participants were randomized 1:1 to placebo or either venglustat 8 mg or 15 mg (highest dose considered safe and well tolerated in Stage 1). The dose for Stage 2 was based on a review of unblinded aggregate safety data from Stage 1 after the first 150 randomized patients had completed ≥1 month of treatment (or prematurely discontinued). For each stage, end-of-treatment was defined as completion of 24 months of treatment. End-of-study was defined as completion of the last scheduled visit; the last scheduled visit was 30 days after the last treatment at Month 24 or, for patients who permanently discontinued treatment, it was the follow-up visit at Month 24 if they continued for all remaining visits or their premature follow-up visit at 30 days after their last treatment. At randomization, participants were stratified based on their predicted ADPKD progression rate (1C vs 1D vs 1E) according to Mayo Imaging Classification and by geographic region.[16]

Enrollment of approximately 240 patients (80 patients in each study group) in Stage 1 was planned between February 2019 and June 2020. In February 2020, the data monitoring committee (DMC) reviewed the aggregate safety data and selected venglustat 15 mg for Stage 2 (**Item S1**). Target enrollment of approximately 400 patients (200 patients each in venglustat 15 mg and placebo) in Stage 2 started in June 2020 immediately after Stage 1 enrollment ended.

This included 80 additional patients with an eGFR 30 to 44.9 mL/min/1.73 m^2 randomized to venglustat (n = 40) or placebo (n = 40).

Trial Assessments

Evaluations were performed at baseline (during screening and placebo run-in period) and during the 24-month treatment period. A full schedule of assessments for both stages has been published previously.[16] After the first month of treatment, patients were evaluated every 3 months until the end of the treatment period. In Stages 1 and 2, total kidney volume (TKV) was measured at baseline and Months 1, 9, and 18; eGFR was measured at baseline, Month 1, Month 3, and every 3 months thereafter. For patients who discontinued treatment permanently, an end-of-treatment assessment that was originally scheduled for the 24-month visit was performed within 7 days of discontinuing treatment, and a premature follow-up assessment was performed 30 days later. The effect of venglustat on the lens was closely monitored throughout the study (**Item S4**).

Outcome Measures

The primary endpoint in Stage 1 was the annualized rate of change in TKV based on magnetic resonance imaging (MRI) from baseline to 18 months. The main secondary endpoint in Stage 1 was the annualized rate of change in eGFR from baseline to 18 months.

In Stage 2, the primary endpoint was the annualized rate of change in eGFR from baseline to 24 months. The main secondary endpoint was the annualized rate of change in TKV based on MRI from baseline to 18 months. Additional details on the endpoints for Stages 1 and 2 are provided in Perrone et al.[16]

Dose Selection

In a repeated dose study of healthy volunteers, venglustat 8 mg and 15 mg QD resulted in reductions from baseline in plasma GL-1 of 70% and 75%, respectively.[13] This degree of plasma GL-1 reduction was similar to that observed in an animal model of ADPKD that demonstrated efficacy after oral treatment of GCS inhibitors.[14] Approximately 30% of venglustat is excreted unchanged in the urine; therefore, the potential for increased exposure to venglustat in patients with impaired kidney function was considered in choosing the study dose. A physiologically-based pharmacokinetic model predicted that a mean plasma steady-state exposure with venglustat 15 mg QD in a population with moderate kidney impairment (eGFR 30–60 mL/min/1.73 m^2) and aged 18–50 years would be within the range of steady-state exposures observed in a Phase 1 study of healthy volunteers[13,18] and a Phase 2 study of patients with Fabry disease.[19] Therefore, venglustat 8 mg and 15 mg QD were selected for assessment in STAGED-PKD, and no dose adjustment was deemed necessary in patients with eGFR ≥30 mL/min/1.73 m^2.

Statistical Methods

Sample size of Stage 1 (n = 80 patients per arm) was determined to provide approximately 89% power to detect a 50% reduction versus placebo on the TKV rate of change; sample size of Stage 2 (n = 160 patients per arm, in addition to the 80 patients from Stage 1) was determined to provide approximately 87% power to detect a 30% reduction versus placebo in the eGFR rate of change. Detailed assumptions and sample size calculations are published elsewhere.[16]

An interim analysis for futility was planned when all patients from Stage 1 had completed the first 9 months of treatment and approximately 30% had completed 18 months of treatment with TKV available (or premature discontinuation) (**Item S5**). The interim analysis focused on the primary endpoint in Stage 1 (annualized rate of change in TKV), and stopping rules were based on this primary endpoint. If insufficient effect of venglustat on the annualized rate of change in TKV was observed based on prespecified but nonbinding criteria, futility could be declared if the relative reduction versus placebo in TKV growth rate estimated at the interim analysis was less than 15% (the one-sided *P* value of the primary endpoint determined from the Multiple Comparison Procedure is >0.30).

The duration of treatment exposure was defined as the date of last treatment administration − date of first treatment administration + 1 day. The duration of treatment exposure is calculated as cumulative exposure expressed in participant years, and mean exposure (standard deviation [SD]) is expressed in weeks.

The annualized rate of change in TKV from baseline to 18 months in Stage 1 (intent-to-treat [ITT] population) is presented as TKV least-squares (LS) mean percentage change from baseline (+/- standard error [SE]) across planned visits. For this analysis, a linear mixed-effect model was fitted to the $\log_{10}$-transformed TKV, which included fixed effects of treatment (venglustat or placebo), Mayo Imaging Classification (as per randomization stratification factor: Class 1C versus 1D versus 1E), time (as continuous variable), treatment × time interaction, Mayo Imaging Classification × time interaction, and random intercept and slope. Within-group mean slope of $\log_{10}$-transformed TKV was obtained from the linear mixed-effect model. A back transformation was applied to obtain annualized rate of change in TKV (in percentage per year) within each treatment arm, along with their 95% confidence intervals (CI).

The statistical analysis plan included prespecified analyses for evaluating the overall effect of venglustat. The overall effect of venglustat 8 mg or 15 mg was assessed using a Multiple Comparison Procedure.[20] The prespecified primary analysis included adjustment for multiple doses using a Multiple Comparison Procedure. However, due to the early termination of the study for futility, only results by dose and nominal *P* values were presented.

The annualized rate of change in eGFR from baseline to 24 months was calculated in the combined Stage 1 and 2 ITT population and is presented as LS mean change from baseline (+/- SE) across analysis visits. The analysis of eGFR in Stage 2 was similar to that of TKV, except no log transformation was used. Baseline eGFR for each patient was the average of three eGFR values assessed prior to randomization. Primary analysis included all observed eGFR data in randomized patients, regardless of whether patients completed the treatment period.

Results

Patients

A total of 760 patients were screened, of whom 478 were randomly assigned to placebo (201, with one patient not receiving any study medication), venglustat 8 mg (78 patients), and venglustat 15 mg (199 patients) (**Figure 1**). Based on the results from the futility analysis, in May 2021 the DMC recommended stopping the study. The Sponsor followed this recommendation and discontinued the study in June 2021, resulting in a stop of Stage 2 enrollment. At that time 12 (6.0%) patients on placebo, 10 (12.8%) patients on venglustat 8 mg, and 12 (6.0%) patients on venglustat 15 mg completed the 24-month treatment period. Sixteen (8.0%) patients on placebo, 12 (15.4%) patients on venglustat 8 mg, and 16 (8.0%) patients on venglustat 15 mg completed the study. Figure 1 shows the reasons why patients discontinued

treatment. In the majority of patients across all groups, this was due to termination of the study (173 patients on placebo, 59 on venglustat 8 mg, and 166 on venglustat 15 mg). All patients were alive at the time of last contact in the study.

The primary efficacy analysis in Stage 1 included 236 patients (Stage 1 ITT) across placebo (78 patients), venglustat 8 mg (78 patients), and venglustat 15 mg (80 patients). The primary efficacy analysis in Stage 2 included 423 patients (combined Stage 1 and Stage 2) across placebo (175 patients), venglustat 8 mg (78 patients), and venglustat 15 mg (170 patients). The safety analysis included 477 patients (extended combined Stage 1 and Stage 2) across placebo (200 patients), venglustat 8 mg (78 patients), and venglustat 15 mg (199 patients). All demographic and baseline characteristics were balanced across groups (**Tables 1 and S1**). At baseline, the mean age for all patients was 42.2 years, and 59% were males. Most of the patients had hypertension (90.4%) and hepatic cysts (64.4%). Medical history incidences were in general similar across groups. The majority of patients included in the study had Mayo Class 1C (46.7%), followed by 1D (36.0%) and 1E (17.4%), which aligns with protocol assumptions.[16] Randomization factors were similar across groups.

Duration of Exposure

In Stages 1 and 2, duration of exposure was similar across groups; however, since the study was discontinued based on results from the interim analysis, the overall duration of exposure in Stage 2 (venglustat 15 mg and placebo) was lower than in Stage 1 (venglustat 8 mg, venglustat 15 mg, and placebo). The cumulative exposure to treatment (in participant years) was 176.5 in placebo, 119.8 in venglustat 8 mg, and 180.2 in venglustat 15 mg. Since venglustat 8 mg was only included in Stage 1 and the study was discontinued 28 months after the start of Stage 1 but only

12 months after the start of Stage 2, the mean [SD] duration of exposure in the venglustat 8 mg group (80.1 weeks [21.2]) was longer compared with venglustat 15 mg (47.2 weeks [32.0]) and placebo (46.5 weeks [31.9]), which were both included in Stages 1 and 2 (**Table S2**).

Efficacy

Plasma GL-1 Levels: Venglustat treatment showed a dose-dependent decrease in plasma GL-1 levels from baseline (**Table 2**). At Months 6 and 12, plasma GL-1 levels were reduced by 76.9% and 75.4% with the 8 mg dose, and 83.0% and 84.1% with the 15 mg dose, respectively. Plasma GL-1 levels in the placebo remained the same at 6 and 12 months compared with baseline levels; plasma GL-1 data for 24 months were limited and therefore not included.

Effect of Venglustat on Annualized Change in TKV: At baseline, the mean TKV levels were 1774.7 mL in the venglustat 8 mg group, 2036.8 mL for venglustat 15 mg, and 1886.1 mL for placebo. During the 18 months of the study, venglustat at 8 mg or 15 mg had no effect on the annualized rate of change in TKV compared with placebo (**Figure 2**). The annualized rate of change in TKV from baseline was 7.71% per year (95% CI: 6.46 to 8.98; $P = 0.1$ vs placebo) for venglustat 8 mg and 6.38% per year (95% CI: 5.11 to 7.66; $P = 0.9$ vs placebo) for venglustat 15 mg versus 6.35% per year (95% CI: 5.10 to 7.62) for placebo. Venglustat's lack of effect on the annualized rate of change in TKV resulted in futility being declared and discontinuation of the study.

Assessment of eGFR: The mean baseline levels of eGFR were similar across all groups: 66.3 mL/min/1.73m^2 for venglustat 8 mg, 65.4 mL/min/1.73m^2 for venglustat 15 mg, and 66.0 mL/min/1.73m^2 for placebo. In the combined Stage 1 and Stage 2 population, venglustat-treated patients had a faster decline in eGFR from baseline to 24 months (**Figure 3**). The annualized rate

of change in eGFR (mL/min/1.73m^2/year) during venglustat 8 mg and 15 mg treatments versus placebo was –4.82 (95% CI: –5.82 to –3.83; $P < 0.001$ vs placebo) and –4.89 (95% CI: –5.80 to –3.99; $P < 0.001$ vs placebo) versus –2.40 (95% CI: –3.30 to –1.49), respectively. Of note, the rate of change in eGFR observed in the overall population was generally consistent across the eGFR subgroups (45 to 59.9, 60 to 74.9, and 75 to 89.9) at enrollment.

Safety

Due to the shorter duration of exposure in the venglustat 15 mg and placebo groups (in the extended combined Stage 1 and Stage 2 population) compared with venglustat 8 mg (in Stage 1 only), direct comparison of incidence of adverse events (AEs) between the 8 mg and other groups is inappropriate. For this reason, all safety data for venglustat 8 mg are presented in supplementary materials (**Table S3**), and direct comparisons are only made between venglustat 15 mg and placebo (**Table 3**).

The overall incidence of all treatment-emergent adverse events (TEAEs) was slightly higher for venglustat 15 mg (71.9%) compared with placebo (64.0%) (**Table 3**). The most frequently reported TEAEs (in ≥5% of patients) in the venglustat 15 mg group were headache (9.5%), cough (7.5%), nausea (6.5%), upper respiratory tract infection (6.0%), hypertension (5.5%), constipation (5.5%), and fatigue (5.5). The most frequently reported TEAEs (in ≥5% of patients) for placebo were headache (6.5%), back pain (6.5%), and nasopharyngitis (6.0%). Treatment-emergent serious AEs were more prevalent in venglustat 15 mg (13.1%) compared with placebo (7.0%), particularly infections and infestations and renal and urinary disorders. Treatment-emergent AEs of special interest were reported in 7.0% and 5.5% of patients on venglustat 15 mg and placebo, respectively. There were no deaths due to TEAEs. Permanent

discontinuation of the study due to TEAEs occurred in 3.0% of patients on venglustat 15 mg and 1.5% on placebo. Treatment-emergent cataracts and lenticular opacities were observed in 5.5% of patients on venglustat 15 mg and 5.0% on placebo. Among these patients, development of new lenticular opacities or cataracts was observed in seven patients in each group. A transient acute increase in systolic and diastolic blood pressure was observed in the venglustat arm compared with the placebo arm. This difference (vs placebo) peaked at Month 1, and no notable difference compared with placebo was observed after 6 months (**Figure S1**). No patient went on renal replacement therapy during the study.

The overall incidence of TEAEs as well as the incidence of the most frequently reported TEAEs was, in general, similar in patients treated with venglustat 8 mg compared with venglustat 15 mg and placebo (**Table S3**).

Discussion

In patients with rapidly progressing ADPKD and eGFR of 45–89.9 mL/min/1.73m^2, our preplanned interim futility analysis showed that treatment with venglustat at either of the doses evaluated in the STAGED-PKD trial had no impact on the annualized rate of change in TKV from baseline to 18 months of treatment in the patients treated with either venglustat 8 mg or 15 mg compared with patients given placebo (**Figure 2**). Furthermore, at 24 months of treatment, the rate of change in eGFR was significantly worse in patients in the venglustat 8 mg or 15 mg groups than placebo (**Figure 3**).

In preclinical models of ADPKD, GCS inhibition via oral administration of venglustat significantly reduced GSL levels, reduced cyst growth, and preserved renal function,[14] forming the basis for the STAGED-PKD trial. However, these preclinical findings did not translate to a

clinically meaningful benefit on TKV in this study. The lack of clinical efficacy in the STAGED-PKD trial was observed despite a dose-dependent decrease in plasma GL-1 levels.

There was a faster decline in the rate of eGFR in patients treated with venglustat compared with placebo. This may be due to an acute effect of venglustat occurring in the first 6 months of treatment. Due to this, a secondary analysis was considered after removing the acute effects of venglustat on rate of change of eGFR. From Month 6 to Month 24, there was no change in the eGFR slope between venglustat- and placebo-treated patients (**Figure S2**). Interestingly, the rate of eGFR decline in the placebo-treated patients is unexpectedly low in this patient population; based on other interventional studies that were enriched for patients with rapidly progressing ADPKD,[21-25] we anticipated observing an eGFR slope of approximately –3.66 mL/min/1.73 m^2/year in the placebo group. In contrast to the eGFR data, the observed TKV rate of change of 6.35% per year in the placebo-treated patients was consistent with the anticipated rate of change (6.6% per year).[16] It should be noted that, due to large within-patient and between-patient variability in eGFR values, a large sample size (greater than for TKV) is required for accurate eGFR analysis.[26] In this study, the eGFR analysis was to include 240 patients per arm; however, due to early study termination, the eGFR analysis at Month 6 included about half the planned number of patients (n = 132; **Figure 3**). The worsening in the rate of change in eGFR in patients treated with venglustat despite a reduction in plasma GL-1 levels suggests that normalization of the GSL biosynthesis pathway[16] may not be sufficient to slow kidney disease in this specific patient population. Use of venglustat in other populations has not been associated with eGFR decline.[13]

The exact mechanism by which venglustat may have an acute effect on eGFR is not clear. Of note, this effect has not been observed in clinical studies in other indications, including Fabry

disease, ganglioside monosialic 2-gangliosidoses (GM2), Gaucher disease type 3, and glucocerebrosidase gene -associated (GBA) Parkinson's disease. We postulate ADPKD-specific, ceramide-mediated changes in vascular function as a possible explanation. As was shown in animal models, ceramide can act as a lipotoxic mediator and contribute to vascular dysfunction in kidneys.[27] Since venglustat may increase the levels of ceramide, administration of this GCS inhibitor in ADPKD patients with initially altered GSL balance in kidney tissues could possibly contribute to the ceramide-mediated physiologic adaptation in the kidneys. The acute effect of venglustat on eGFR may also be explained by vascular alterations due to possible ceramide-induced blood vessel vasoconstriction[28] and physiologic adaptations, such as transient changes in blood pressure that were observed in the first 6 months of venglustat treatment.

In ADPKD, progression of kidney disease has been associated with hypertension. In the HALT-PKD trial, patients on a rigorous regimen that lowered blood pressure to a target of 95/60 to 110/75 mm Hg had a 14.2% slower annual increase in TKV but no overall effect on change in eGFR compared with patients on a standard blood pressure regimen (target of 120/70 to 130/80 mm Hg).[29]

The overall incidence of TEAEs in this trial was slightly higher in the venglustat 15 mg arm compared with both the placebo arm in this trial as well as with previous findings in the Phase 1 trials of venglustat.[15] Reversible lens degeneration of unknown pathogenesis has previously been observed in juvenile rats after venglustat administration.[13] The histopathology of this finding was similar to age-related cortical cataract in humans, although the lipid content of the rodent lens contains four times less lipid than the human lens, meaning rats may be more susceptible to lens cataract and oxidative damage. In addition, mild lenticular opacities were observed in one patient from the Phase 2 study that included a Fabry disease population (where

lens opacities are part of the disease's natural history).[19] This was the reason to study specifically the incidence of cataract as AEs of special interest. In the STAGED-PKD trial, venglustat showed no additional risk of cataract.

The STAGED-PKD trial had an adaptive two-stage design that allowed for early efficacy evaluation and was enriched with patients who had rapidly progressive disease that allowed for increased trial design efficiency. Despite this, the study had its limitations, including the short follow-up after end-of-treatment and limited generalizability of findings.

In the interim analysis for futility using Stage 1 data, the STAGED-PKD study met the prespecified stopping rule for efficacy based on the primary endpoint. Due to venglustat's lack of effect on the annualized rate of change in TKV, the study was terminated. In conclusion, venglustat treatment at a dose of either 8 mg or 15 mg in patients with ADPKD at risk of progressive disease showed a dose-dependent decrease in plasma GL-1 levels; however, there was no reduction in the rate of change of TKV and a faster decline in eGFR.

Supplementary Material

Supplementary File (PDF)

Figure S1. Change from baseline in systolic and diastolic blood pressure (extended Stage 1 and Stage 2 population with eGFR 30–89.9 mL/min/1.73m^2)
Figure S2. Change in eGFR from Month 6 to Month 24 (combined Stage 1 and Stage 2 population with eGFR 45–89.9 mL/min/1.73m^2)
Item S1: Data monitoring committee (DMC)
Item S2: Assessment of estimated glomerular filtration rate (eGFR)
Item S3: Exclusion criteria
Item S4: Ophthalmologic examination
Item S5: Interim analysis
Table S1. Demographics and patient characteristics at baseline, separated by stage
Table S2. Duration of exposure
Table S3. Safety data in the extended Stage 1 and Stage 2 population, including venglustat 8 mg.

Supplementary Material Descriptive Text for Online Delivery
Supplementary File (PDF). Figures S1-S2; Items S1-S5; Tables S1-S3.

Article Information

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Table 1. Demographics and patient characteristics at baseline

	Placebo (N = 201)	Venglustat 8 mg (N = 78)	Venglustat 15 mg (N = 199)	All (N = 478)
Sex, n (%)				
Male	118 (58.7)	47 (60.3)	117 (58.8)	282 (59.0)
Female	83 (41.3)	31 (39.7)	82 (41.2)	196 (41.0)
Age (years), mean (SD)	42.0 (6.6)	41.7 (6.9)	42.7 (6.3)	42.2 (6.5)
Race, n (%)				
White	114 (56.7)	50 (64.1)	116 (58.3)	280 (58.6)
Asian	79 (39.3)	27 (34.6)	82 (41.2)	188 (39.3)
Others	6 (3)	1 (1.3)	1 (0.5)	8 (1.6)
Weight (kg), mean (SD)	77.3 (17.6)	81.8 (19.2)	79.2 (19.6)	78.8 (18.7)
eGFR at screening ($mL/min/1.73m^2$), mean (SD)	61.5 (15.0)	66.4 (12.5)	61.3 (14.8)	62.2 (14.6)
eGFR at screening ($mL/min/1.73m^2$), n (%)				
30 to 44.9 $mL/min/1.73m^2$	25 (12.4)	0	29 (14.6)	54 (11.3)
45 to 59.9 $mL/min/1.73m^2$	66 (32.8)	29 (37.2)	66 (33.2)	161 (33.7)
60 to 74.9 $mL/min/1.73m^2$	70 (34.8)	27 (34.6)	56 (28.1)	153 (32)
75 to 89.9 $mL/min/1.73m^2$	39 (19.4)	22 (28.2)	48 (24.1)	109 (22.8)
Total kidney volume (mL), mean (SD)	2059 (1031)	1775 (765)	2152 (1116)	2053 (1038)
Median	1772	1584	1833	1748
IQR	1325:2565	1225:2170	1290:2738	1300:2565
Height-adjusted total kidney volume (mL/m), mean (SD)	1189 (583)	1020 (439)	1240 (638)	1184 (591)
Median	1028	893	1052	1005
IQR	774:1467	730:1266	756:1565	756:1479
Blood pressure (mm Hg), mean (SD)				
Systolic	125.4 (11.1)	126.3 (11.1)	125.7 (12.4)	125.7 (11.7)
Diastolic	83.4 (8.5)	84 (9.1)	84.4 (9.8)	83.9 (9.2)
Mayo Class (stratification factor), n (%)				
1C	90 (44.8)	43 (55.1)	90 (45.2)	223 (46.7)
1D	73 (36.3)	26 (33.3)	73 (36.7)	172 (36.0)
1E	38 (18.9)	9 (11.5)	36 (18.1)	83 (17.4)
Prespecified medical history, n (%)				
Hypertension	181 (90.0)	73 (93.6)	178 (89.4)	432 (90.4)
Hepatic cyst	136 (67.7)	51 (65.4)	121 (60.8)	308 (64.4)
Back pain	47 (23.4)	31 (39.7)	40 (20.1)	118 (24.7)
Hematuria	44 (21.9)	19 (24.4)	38 (19.1)	101 (21.1)
Nephrolithiasis	45 (22.4)	13 (16.7)	38 (19.1)	96 (20.1)
Proteinuria	43 (21.4)	14 (17.9)	32 (16.1)	89 (18.6)
Urinary tract infection	30 (14.9)	14 (17.9)	23 (11.6)	67 (14.0)
Abdominal pain	20 (10.0)	10 (12.8)	26 (13.1)	56 (11.7)
Aneurysm cerebral	8 (4.0)	2 (2.6)	4 (2.0)	14 (2.9)
Prior medication, n (%)				
ARBs*	96 (47.8)	38 (48.7)	100 (50.3)	234 (49.0)
ACE inhibitors*	61 (30.3)	27 (34.6)	59 (29.6)	147 (30.8)
ARBs, ACE inhibitors, or both	155 (77.1)	64 (82.1)	156 (78.4)	375 (78.5)
Calcium channel blockers				
Beta-blocking agents	57 (28.4)	18 (23.1)	42 (21.1)	117 (24.5)

Diuretics	37 (18.4) 25 (12.4)	16 (20.5) 9 (11.5)	34 (17.1) 30 (15.1)	87 (18.2) 64 (13.4)
Region (stratification factor), n (%)				
North America	37 (18.4)	16 (20.5)	38 (19.1)	91 (19.0)
Europe	78 (38.8)	35 (44.9)	77 (38.7)	190 (39.7)
China	42 (20.9)	5 (6.4)	40 (20.1)	87 (18.2)
Japan	25 (12.4)	10 (12.8)	28 (14.1)	63 (13.2)
Republic of Korea	10 (5.0)	8 (10.3)	10 (5.0)	28 (5.9)
Rest of the world	9 (4.5)	4 (5.1)	6 (3.0)	19 (4.0)

*Plain or combinations. ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; eGFR, estimated glomerular filtration rate; IQR, interquartile range; SD, standard deviation.

Table 2. Plasma glucosylceramide (GL-1) levels in Stage 1 over 12 months of treatment

	GL-1 (mg/mL), mean (SD)*		
	Placebo (n = 56)	**Venglustat 8 mg (n = 58)**	**Venglustat 15 mg (n = 61)**
Baseline	5.8 (1.33)	5.6 (1.39)	5.5 (1.36)
Month 6	5.42 (1.33)	1.51 (0.82)	0.95 (0.33)
Month 12	5.7 (1.5)	1.5 (0.69)	0.88 (0.32)

*Includes only randomized and exposed patients who had plasma GL-1 levels assessed at baseline and/or post baseline during the on-treatment period. GL-1, glucosylceramide; SD, standard deviation.

Table 3. Safety data in the extended Stage 1 and Stage 2 population, excluding the venglustat 8 mg group

N (%)	Placebo (N = 200)*	Venglustat 15 mg (N = 199)
Any TEAE	128 (64.0)	143 (71.9)
Any treatment-emergent SAE	14 (7.0)	26 (13.1)
Any TEAE leading to death	0	0
TEAEs leading to discontinuation of study drug	3 (1.5)	6 (3.0)
Any treatment-emergent AESI	11 (5.5)	14 (7.0)
Most frequently reported TEAEs†		
Infections and infestations		
Upper respiratory tract infection	4 (2.0)	12 (6.0)
Urinary tract infection	10 (5.0)	9 (4.5)
COVID-19	10 (5.0)	8 (4.0)
Nasopharyngitis	12 (6.0)	6 (3.0)
Nervous system disorders		
Headache	13 (6.5)	19 (9.5)
Vascular disorders		
Hypertension	6 (3.0)	11 (5.5)
Respiratory, thoracic, and mediastinal disorders		
Cough	2 (1.0)	15 (7.5)
Gastrointestinal disorders		
Nausea	1 (0.5)	13 (6.5)
Constipation	0	11 (5.5)
Musculoskeletal and connective tissue disorders		
Back pain	13 (6.5)	10 (5.0)
Pain in extremity	1 (0.5)	0
General disorders and administration site conditions		
Fatigue	4 (2.0)	11 (5.5)
Blood pressure increased	0	3 (1.5)
Most frequently reported treatment-emergent SAEs‡		
Infections and infestations		
Urinary tract infection	1 (0.5)	2 (1.0)
COVID-19	2 (1.0)	0
Appendicitis	1 (0.5)	2 (1.0)
Diverticulitis	0	1 (0.5)
Pneumonia	0	1 (0.5)
Renal cyst infection	0	2 (1.0)
Infected cyst	0	1 (0.5)
Kidney infection	0	1 (0.5)
Nervous system disorders		
Carpal tunnel syndrome	0	1 (0.5)
Intracranial aneurysm	0	1 (0.5)
Loss of consciousness	0	1 (0.5)
Polyneuropathy	0	1 (0.5)
Syncope	0	1 (0.5)
Renal and urinary disorders		
Renal cyst hemorrhage	0	2 (1.0)
Calculus urinary	0	1 (0.5)
Renal hemorrhage	0	1 (0.5)
Chronic kidney disease	1 (0.5)	0
Treatment-emergent AESI§		
Eye disorders		

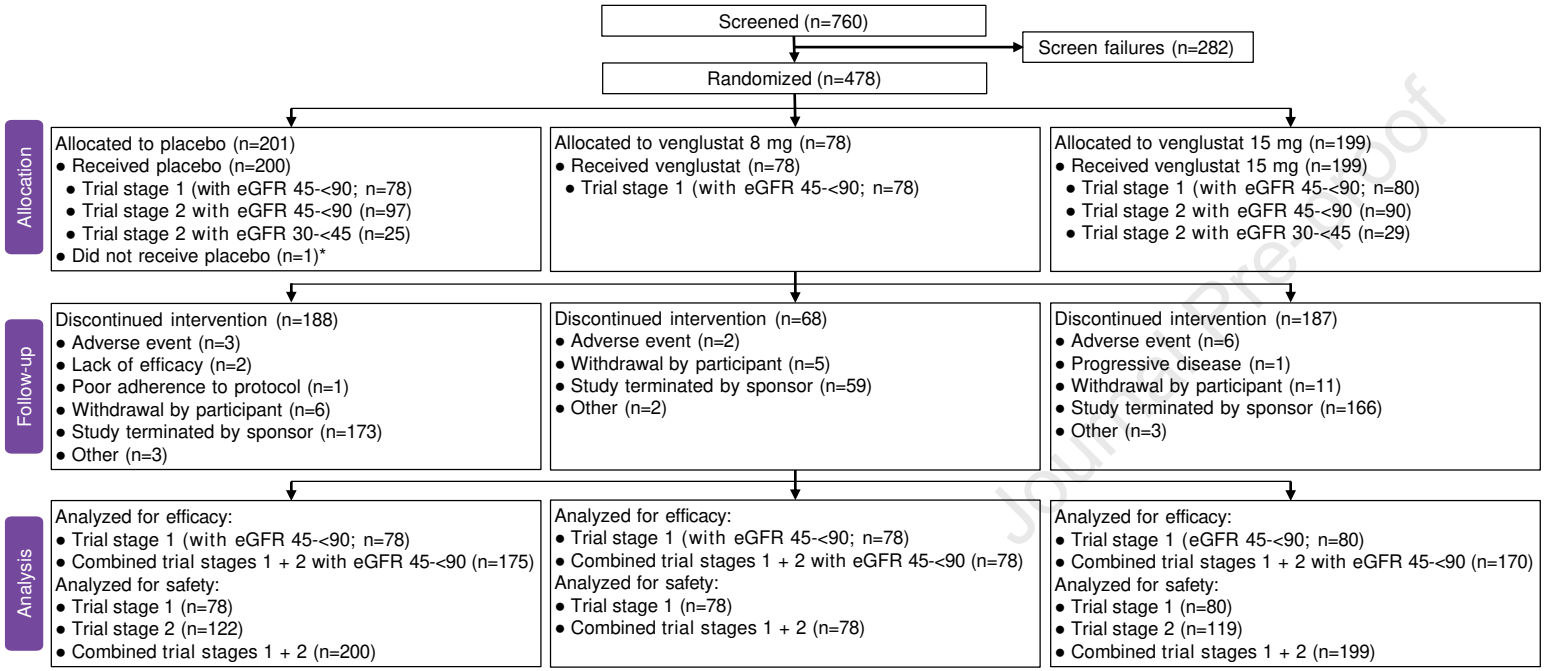
Cataract cortical	6 (3.0)	5 (2.5)
Cataract nuclear	6 (3.0)	5 (2.5)
Lenticular opacities	1 (0.5)	3 (1.5)
Cataract subcapsular	1 (0.5)	1 (0.5)
Pregnancy, puerperium, and perinatal conditions		
Pregnancy	0	1 (0.5)
Injury, poisoning, and procedural complications		
Accidental overdose	0	1 (0.5)
Social circumstances		
Pregnancy of partner	1 (0.5)	1 (0.5)

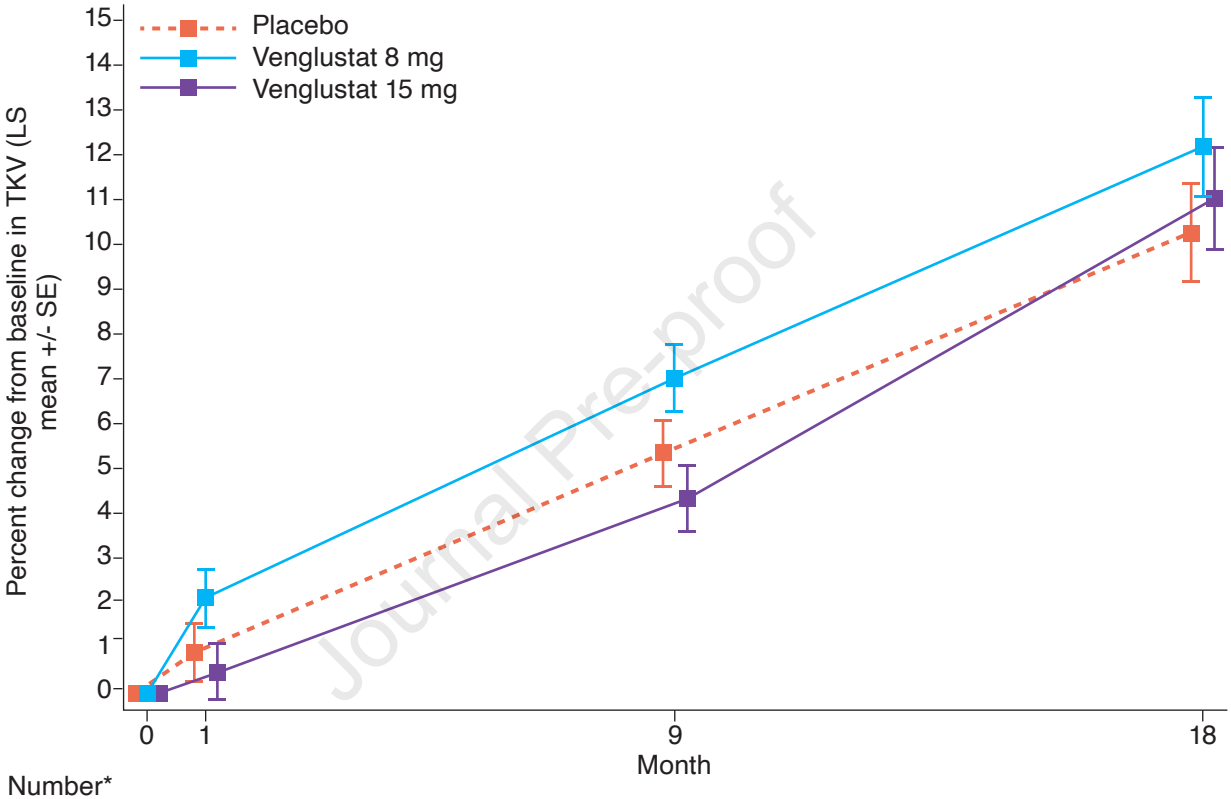
*Excludes one patient who was randomized to the placebo group but did not receive placebo; †Includes all AEs that occurred in >5% of the patients in the placebo or venglustat 15 mg groups by primary system organ class and preferred term; ‡Includes all SAEs that occurred in ≥2% of the patients in the placebo or venglustat 15 mg groups by primary system organ class; §Sorted by an internationally agreed order of system organ class and preferred term sorted by decreasing frequency according to all AE summary.
AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Figure 1. Patient enrollment and analysis population
*Patient did not receive any study treatment and was not included in any safety or efficacy analysis.
eGFR, estimated glomerular filtration rate.

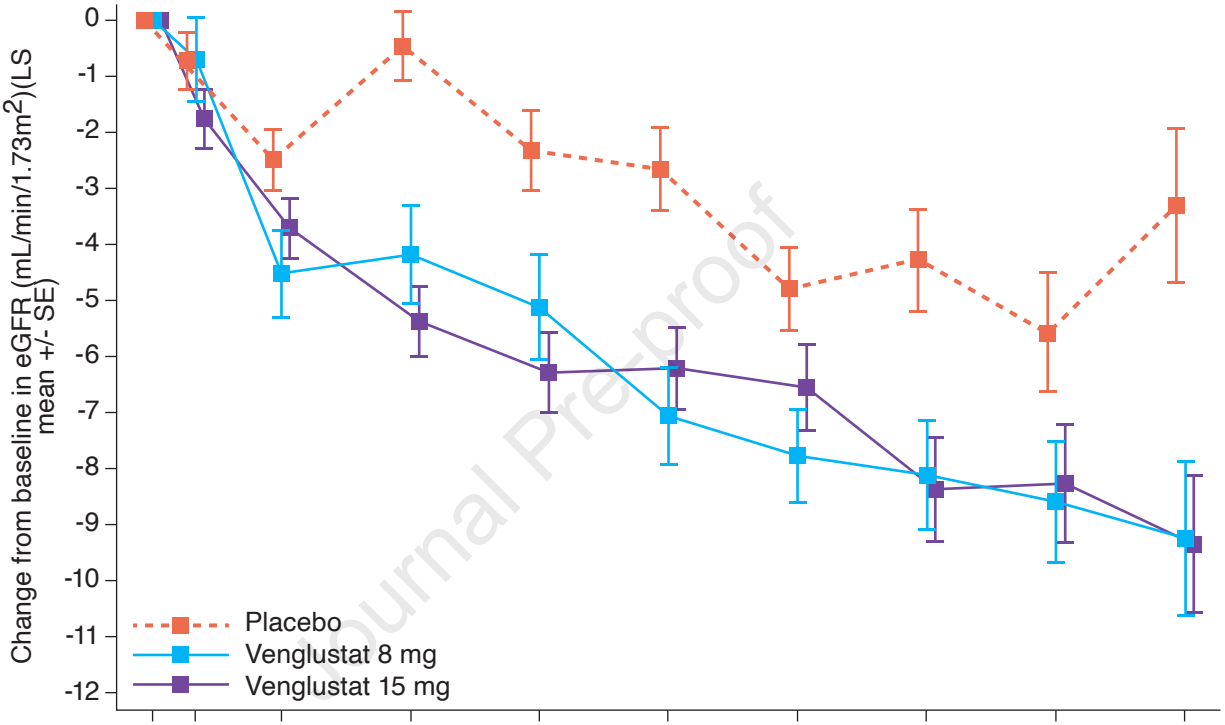
Figure 2. Effect of venglustat on rate of change in total kidney volume from baseline to Month 18 (Stage 1, ITT population)
*Includes patients with a baseline value and/or postbaseline value. At baseline, four patients on venglustat 8 mg and one patient on venglustat 15 mg had missing TKV. Due to technical issues with MRI image transfer to the central reader, baseline TKV values for these 5 patients were not included in the clinical database. However, these patients were enrolled based on local MRI readings.
No difference in the annualized rate of change in TKV in venglustat 15 mg ($P = 0.9$) and venglustat 8 mg ($P = 0.1$) groups vs placebo.
ITT, intention-to-treat; LS, least squares; SE, standard error; TKV, total kidney volume.

Figure 3. Effect of venglustat on change in eGFR from baseline to Month 24 (combined Stage 1 and Stage 2 population with eGFR 45–89.9 mL/min/1.73m^2)
*Includes patients with a baseline value or at least one postbaseline value.
Significant difference in the annualized rate of change in eGFR in venglustat 15 mg ($P < 0.001$) and venglustat 8 mg ($P < 0.001$) groups vs placebo.
eGFR, estimated glomerular filtration rate; LS, least squares; SE, standard error.





Number*				
Placebo	78	73	67	47
Venglustat 8 mg	74	71	69	48
Venglustat 15 mg	79	75	72	44



Number*									
Placebo	175	165	152	132	109	84	70	60	40	23
Venglustat 8 mg	78	76	75	70	67	70	68	59	46	24
Venglustat 15 mg	170	154	156	132	106	81	67	57	43	31