#LB-36

Efficacy and Safety Study of Venglustat in Patients with Symptomatic Fabry Disease: Updates on the PERIDOT Study, A 12-Month Phase 3 Randomized Clinical Trial

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INTRODUCTION

- Fabry disease (FD), is a rare lysosomal disorder, characterized by cellular accumulation of globotriaosylceramide (GL-3 or Gb3) and its derivative globotriaosylsphingosine (lyso-GL-3 or lyso-Gb3) which occurs in multiple tissues, primarily affecting kidneys, heart, and central nervous system, resulting in progressive target organ deterioration.[1] Neuropathic pain and abdominal pain in FD are common symptoms and significantly impact quality of life.[2,3]
- Treatment options for FD are limited to enzyme replacement therapy (ERT) or an oral pharmacological chaperone for patients with amenable mutations.
- Venglustat is an oral, brain-penetrant, glucosylceramide synthase inhibitor that prevents GL-3 accumulation by blocking the initial step in glycosphingolipid synthesis and has therapeutic potential in multiple lysosomal disorders including FD.
- Venglustat has been investigated in Phase 2 studies (NCT02228460/NCT02489344) evaluating its safety, pharmacodynamics, pharmacokinetics and exploratory efficacy in treatment-naïve adult patients with Fabry disease. Venglustat is currently being investigated in two Phase 3 studies: CARAT (NCT05280548) in patients with Fabry disease and LEAP2MONO (NCT05222906) in patients with Gaucher disease type 3 (GD3).
- Patient demographics and baseline characteristics of patients enrolled in the Phase 3 PERIDOT study are presented here.

OBJECTIVES

- The primary objective of the ongoing PERIDOT study is to evaluate the effect of venglustat on neuropathic and abdominal pain in symptomatic patients ≥16 years of age with FD who are treatment-naïve or untreated for at least 6 months.

METHODS

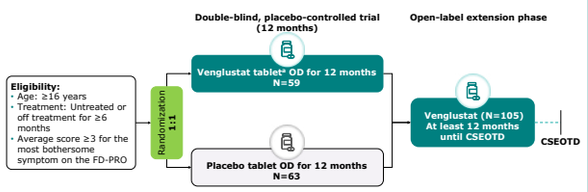
Study design

- Patients from multiple centers globally were enrolled in the PERIDOT study (NCT05206773) - a 12-month, phase 3, randomized, double-blind, placebo-controlled clinical trial (**Figure 1**).
- Eligible participants were randomized in a 1:1 ratio to receive venglustat or placebo orally once daily for 12 months. The randomization was stratified based on FD subtype (classic male, non-classic male, classic female, non-classic female) and on the most bothersome symptom selected by the participants at screening (**Figure 2**).
- Patient-reported outcomes (PROs) were collected via an electronic diary.

Figure 1: Participating sites countries of the PERIDOT study

Countries	
Argentina	Italy
Austria	Japan
Australia	Mexico
Brazil	Norway
Canada	Poland
China	Romania
Denmark	Switzerland
Finland	Turkey
France	United Kingdom
Germany	United States
Greece	

Figure 2: Study design of the Phase 3 PERIDOT trial evaluating venglustat in patients with Fabry disease



*Venglustat dosing regimen: 15 mg for adults, weight-based for ≥16 to <18 years.
CSEOTD, common study end of treatment date; FD-PRO, Fabry disease patient-reported outcomes; OD, once daily.

Study Population

Inclusion Criteria

- Male and female patients aged ≥16 years and body weight ≥30 kg with a previously confirmed diagnosis of FD and a documented history of Fabry-related clinical symptoms.
- Patients who were treatment-naïve or without prior treatment with any approved or investigational Fabry disease therapy for at least 6 months prior to screening.
- Symptom severity:
  Average score of ≥3 (0=no symptom, 10=worst imaginable) on the participant-defined most bothersome symptom as assessed by the Fabry Disease Patient-Reported Outcome (FD-PRO) at screening for:
  - Neuropathic pain in upper extremities,
  - Neuropathic pain in lower extremities, or
  - Abdominal pain

Key Exclusion Criteria

- Patients presenting with manifestations of FD that preclude placebo administration
- Patients with a history of
  - Transient ischemic attack, stroke, myocardial infarction, heart failure, evidence of left ventricular hypertrophy and/or cardiac fibrosis, major cardiovascular surgery, or kidney transplantation, clinically significant cardiac arrhythmia, and well-controlled atrial fibrillation
  - Seizures currently requiring treatment
  - Drug and/or alcohol abuse
  - Or active hepatobiliary disease
- Neuropathic pain in upper or lower extremities, or abdominal pain not related to Fabry disease.
- Estimated glomerular filtration rate <60 mL/min/1.73m².
- Urine protein to creatinine ratio ≥1 g/g at screening.
- Moderate to severe hepatic impairment.
- Initiation of chronic treatment for pain, or change in pain medication regimen, within 3 months prior to randomization.

Study Endpoints

Primary Endpoint

- The primary endpoint was the percent change from baseline at 6 and 12 months in participant-defined most bothersome symptom selected at screening among three Fabry Disease Patient-Reported Outcome (FD-PRO) items: neuropathic pain in upper extremities, neuropathic pain in lower extremities or abdominal pain

Key Secondary Endpoints

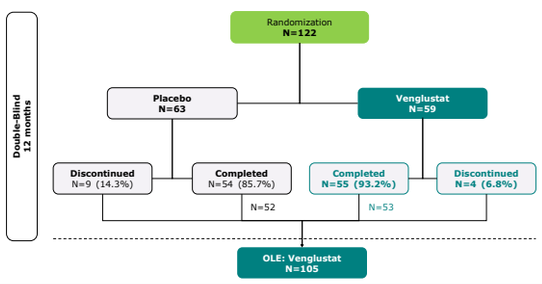
- Percent change in plasma lyso-GL-3 from baseline to 6 and 12 months
- Frequency of rescue pain medication use during the 12-month period
- Change in the percentage of days with at least one stool reflecting diarrhea (BSFS Type 6 or 7) from baseline to 12 months
- Change in the FD-PRO tiredness component from baseline to 12 months
- Proportion of responders for neuropathic or abdominal pain at 12 months, as assessed by FD-PRO

RESULTS

Patient demographics and baseline characteristics

- Overall, 122 patients were enrolled in the PERIDOT study, with 53 male and 69 female patients with FD.
- 63 patients were randomized in placebo arm and 59 patients were randomized in venglustat arm, and 105 patients were enrolled in the OLE treatment period receiving venglustat treatment (52 from placebo arm and 53 from venglustat arm).
- Participant disposition is shown in **Figure 3**.

Figure 3: Participant disposition



- Patient demographics and baseline characteristics are presented in **Table 1**.

Table 1: Patient demographics and baseline characteristics.

Demographics	Placebo (N =63)	Venglustat (N =59)
Age (years)		
Mean (SD)	31.9 (10.5)	32.7 (13.8)
Adolescents (12-17 yrs). n (%)	1 (1.6)	1 (1.7)
18-64 yrs. n (%)	62 (98.4)	57 (96.6)
65-84 yrs. n (%)	0	1 (1.7)
Sex, n (%)		
Male	27 (42.9)	26 (44.1)
Female	36 (57.1)	33 (55.9)
Race, n (%)		
White	35 (55.6)	44 (74.6)
Black or African American	1 (1.6)	0
Asian	12 (19.0)	7 (11.9)
American Indian or Alaska native	3 (4.8)	1 (1.7)
Multiple	0	1 (1.7)
Not Reported	6 (9.5)	5 (8.5)
Unknown	6 (9.5)	1 (1.7)
Fabry disease subtype per IVRS, n (%)		
Classic male	27 (42.9)	26 (44.1)
Non-classic male	0	0
Classic female	29 (46.0)	30 (59.8)
Non-classic female	7 (11.1)	3 (5.1)
Most bothersome symptoms per IVRS, n (%)		
Neuropathic pain in upper extremities	15 (23.8)	15 (25.4)
Neuropathic pain in lower extremities	35 (55.6)	31 (52.5)
Abdominal pain	13 (20.6)	13 (22.0)
Previous Fabry therapy, n (%)		
Treatment-naïve	51 (81.0)	46 (78.0)
Untreated for at least 6 months	12 (19.0)	13 (22.0)

IVRS, interactive voice response survey; SD, standard deviation.

CONCLUSION

- The PERIDOT study is fully enrolled and the OLE is ongoing.
- Demographics and disease characteristics are balanced in the placebo and venglustat arms.
- Discontinuations during the randomized period were lower in the venglustat arm than in the placebo arm.
- Analysis of the double-blinded period of this study is ongoing and results will inform the therapeutic potential of venglustat, a novel substrate reduction therapy in FD.

DISCLOSURES

RH: Consultant for Acadia, Amicus, Chiesi. Danali, GC biopharma, Hanmi, Octant bio, Sangamo, and Sanofi; **AM:** Consultant for Chiesi, Sanofi, Amgen; **PD, SL, SA, HG, QZ, and SS:** full-time employees of Sanofi and may hold/have held stock and/or stock options in the company; **JMP:** Declares no relevant conflicts of interest; **DPG:** consultant for Chiesi, Idorsia, Sanofi, and Takeda.

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