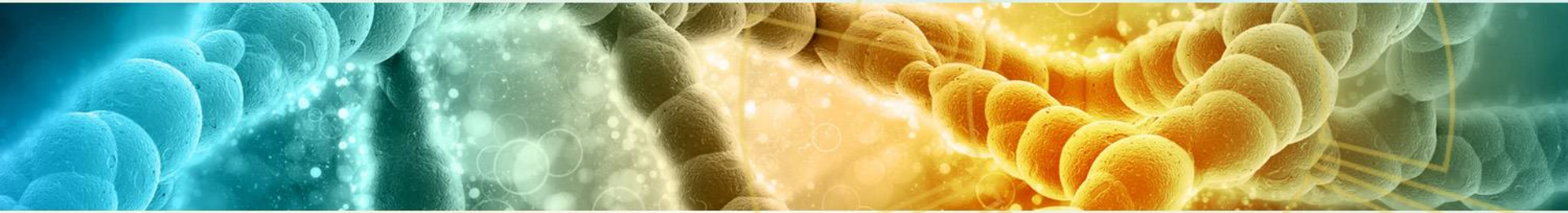

Projet du Centre de Référence constitutive des maladies lysosomales et de la maladie de Fabry

Prof. Dominique P. Germain, MD, PhD
Division of Medical Genetics
University of Versailles, France – Paris Saclay University
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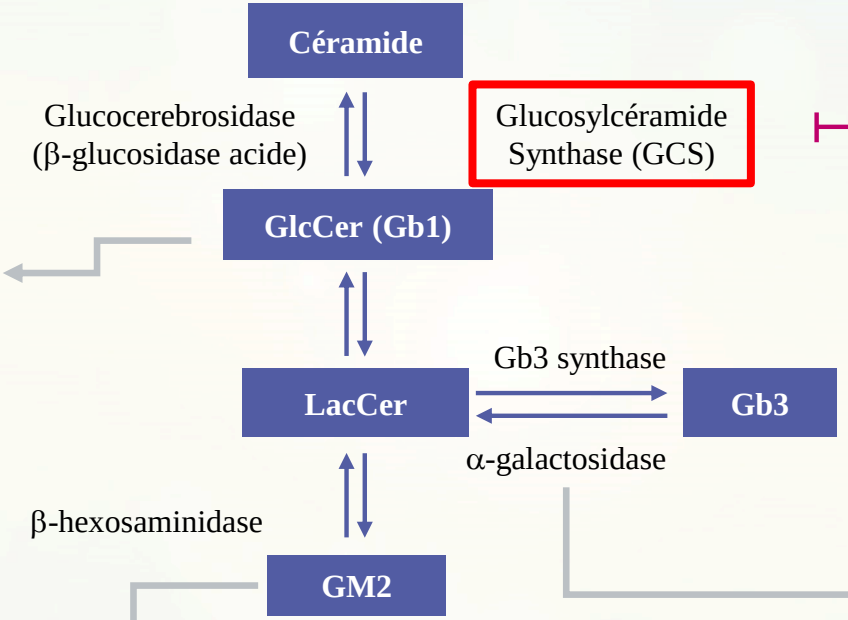
Inhibition de la glucosylcéramide synthase pour une thérapie par réduction des substrats glycosphingolipides



Maladie de Gaucher disease

- Variants pathogènes bi-allèliques de *GBA* mutation
- Accumulation de Gb1 dans la rate, le foie, la moelle osseuse, les poumons (et le cerveau)

Inhibition de synthèse par
Eliglustat
Lucerastat
Venglustat (CNS)

Maladie de Fabry

- Variants de l'α-galactosidase
- Accumulation de Gb3 et lyso-Gb3 dans les lysosomes

GM2 gangliosidosis

- b-hexosaminidase mutations and Accumulation lysosomale de GM2

MODIFY and MODIFY-OLE Phase 3 studies

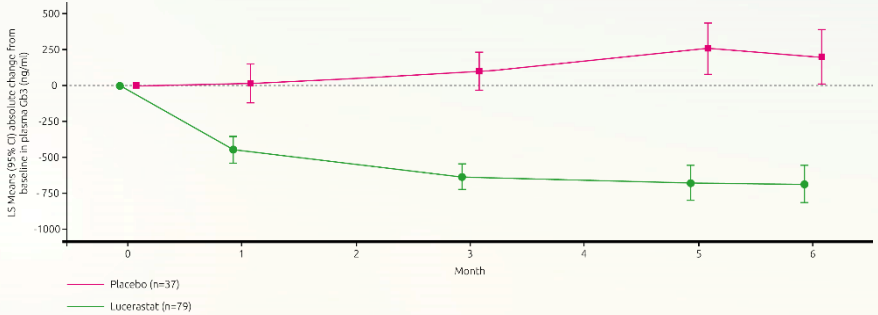
A multicenter, double-blind, randomized, placebo controlled, parallel-group phase 3 study to determine the efficacy and safety of lucerastat oral monotherapy in adult patients with Fabry disease

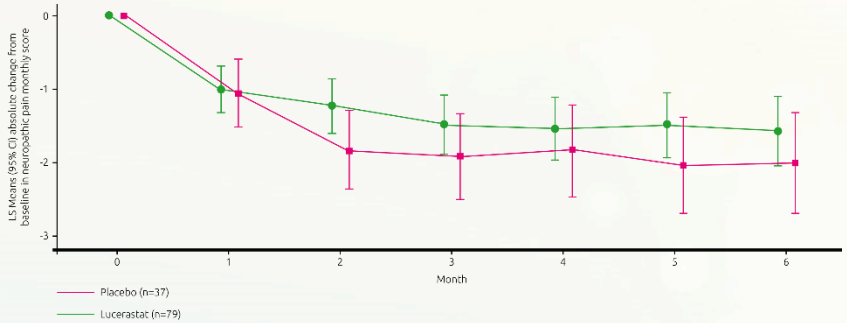
Screening **6-7 weeks**	**Treatment 6 months**	Open Extension

Randomization 2:1

Lucerastat (80 patients)

Placebo (38 patients)

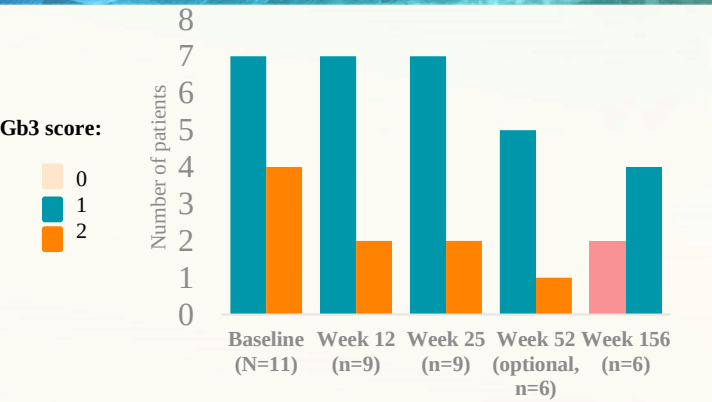




Project in 2025
MODIFY-OLE “Kidney sub-study”

Développement de la thérapie par reduction de substrat

Prof. Dominique P. Germain, MD PhD – Centre de Référence des maladies lysosomales



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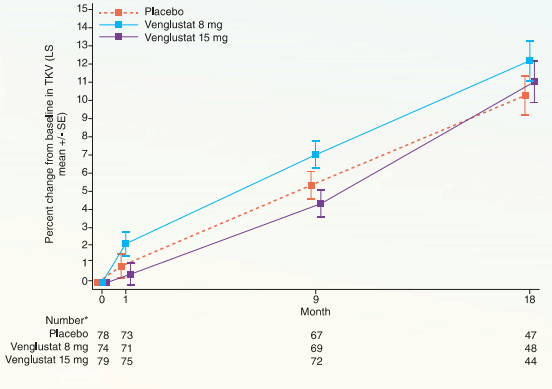
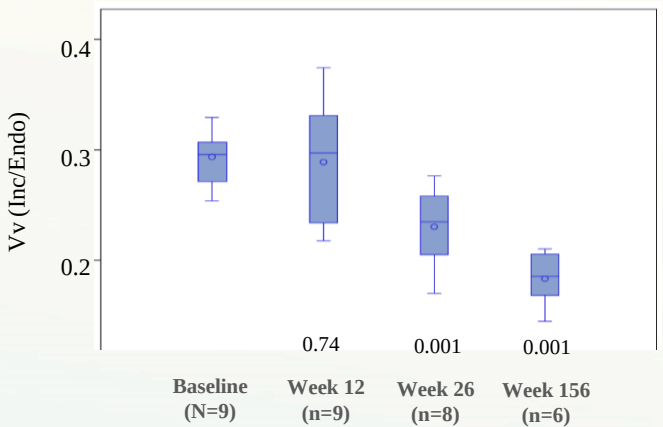
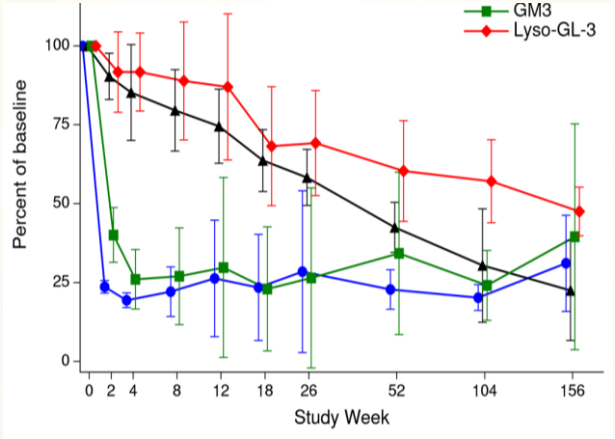
Venglustat, an orally administered glucosylceramide synthase inhibitor: Assessment over 3 years in adult males with classic Fabry disease in an open-label phase 2 study and its extension study

Patrick B. Deegan [a,*], Ozlem Goker-Alpan [b], Tarekegn Geberhiwot [c], Robert J. Hopkin [d], Elena Lukina [e], Anna Tylki-Szymanska [f], Atef Zaher [g], Charlotte Sensinger [h], Sebastiaan J.M. Gaemers [i], Vijay Modur [j], Beth L. Thurberg [k], Jyoti Sharma [h], Behzad Najafian [l], Michael Mauer [m], Pronabesh DasMahapatra [h], William R. Wilcox [n], Dominique P. Germain [o,p]







Safety and efficacy of venglustat in *GBA1*-associated Parkinson's disease: an international, multicentre, double-blind, randomised, placebo-controlled, phase 2 trial

Ni Gilad, Roy N Alcalay, Gary Cutter, Thomas Gasser, Tanya Gurevich, Günter U Höglinger, Kenneth Marek, Claudio Pisciotti, Anthony H V Schapira, Clemens R Scherzer, Tanya Simuni, Pascal Minini, S Pablo Sardi, M Judith Peterschmitt

Summary

Background Variants in the *GBA1* gene, which encodes lysosomal acid glucocerebrosidase, are among the most common genetic risk factors for Parkinson's disease and are associated with faster disease progression. The mechanisms involved are unresolved but might include accumulation of glucosylceramide. Venglustat is a brain-penetrant glucosylceramide synthase inhibitor that, in previous studies, reduced amounts of the glycosphingolipid. We aimed to assess the safety, efficacy, and target engagement of venglustat in people with early-stage Parkinson's disease carrying pathogenic *GBA1* variants.

Methods MOVES-PD part 2 was a randomised, double-blinded, placebo-controlled phase 2 study done at 52 centres (academic sites, specialty clinics, and general neurology centres) in 16 countries. Eligible adults aged 18–80 years with Parkinson's disease (Hoehn and Yahr stage ≥2) and one or more *GBA1* variants were randomly assigned using an interactive voice–response system (1:1) to 52 weeks of treatment with oral venglustat (15 mg/day) or matching placebo. Investigators, site personnel, participants, and their caregivers were masked to treatment allocation. The primary outcome measure was the change from baseline to 52 weeks in the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) parts II and III combined score (a higher score indicates greater impairment), and it was analysed in a modified intention-to-treat population (ie, all randomly assigned participants with a baseline and at least one post-baseline measurement during the treatment period). This study was registered with ClinicalTrials.gov (NCT02906020) and is closed to recruitment.

Findings Between Dec 15, 2016, and May 27, 2021, 221 participants were randomly assigned to venglustat (n=110) or placebo (n=111). The least squares mean change in MDS-UPDRS parts II and III combined score was 7·29 (SE 1·36) for venglustat (n=96) and 4·71 (SE 1·27) for placebo (n=105); the absolute difference between groups was 2·58 (95% CI −1·10 to 6·27; p=0·17). The most common treatment-emergent adverse events (TEAEs) were constipation and nausea (both were reported by 23 [21%] of 110 participants in the venglustat group and eight [7%] of 111 participants in the placebo group). Serious TEAEs were reported for 12 (11%) participants in each group. There was one death in the venglustat group owing to an unrelated cardiopulmonary arrest and there were no deaths in the placebo group.

Interpretation In people with *GBA*-associated Parkinson's disease in our study, venglustat had a satisfactory safety profile but showed no beneficial treatment effect compared with placebo. These findings indicate that glucosylceramide synthase inhibition with venglustat might not be a viable therapeutic approach for *GBA1*-associated Parkinson's disease.

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See Comment page 64

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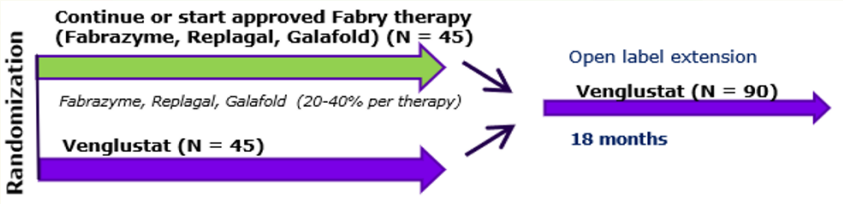
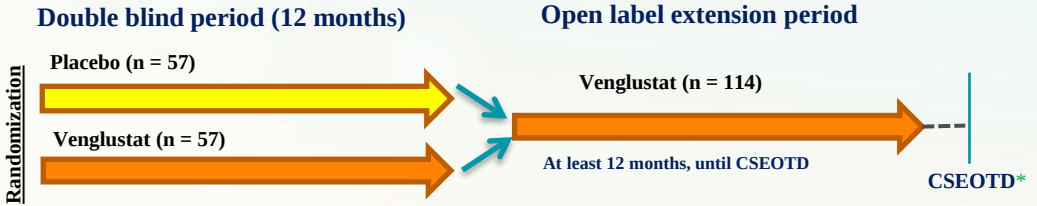
PERIDOT/EFC17045

CARdiac AssessmenT in Fabry Patients on Venglustat

Patient ExpeRIence in Fabry Disease On VenglustaT





Primary endpoint: Slope of left ventricular mass index (LVMI) on MRI in venglustat vs. standard therapy (non-inferiority)

Secondary:

- eGFR slope
- LVMI slope (superiority)
- T1 relaxation time (MRI)
- Global longitudinal strain (ECHO)
- Safety
- Pharmacokinetics
- Fabry symptoms (swelling, tiredness)

Exploratory:

- PRO endpoints, composite clinical events associated with FD, hs-TNT, pro-NT BNP, plasma GL-3 and lyso-GL3, FASTEX

Primary endpoint:

- Percent change from baseline in the most bothersome symptom selected by participant between three Fabry Disease Patient-Reported Outcome (FD-PRO)[1,2] items (neuropathic pain in upper extremities, neuropathic pain in lower extremities or abdominal pain)

Secondary:

- Biomarkers (plasma lyso-GL-3)
- Frequency of rescue pain medication use
- Other Fabry symptoms (diarrhea, tiredness)
- Proportion of responders in most bothersome symptom (response defined as ≥30% decrease from baseline)
- Safety
- Pharmacokinetics

Exploratory:

- Additional PRO endpoints; eGFR; urine ACR and PCR; plasma and urine Gb3; medical resource use