Le Venglustat dans la maladie de Gaucher type 3

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maladie de Gaucher

Mutations du gène GBA

Gène induisant la fabrication de la β-glucosidase acide

Déficit en β-glucosidase acide

Enzyme hydrolysant le glucosylcéramide

Accumulation de glucosylceramide

Dans les lysosomes de cellules, principalement les macrophages tissulaires

Macrophages gorgés de substrat (« cellules de Gaucher ») dans les organes touchés

Cerveau

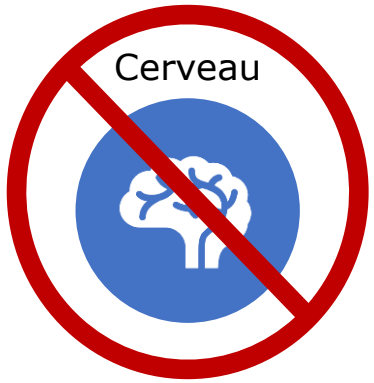
Maladie de Gaucher type 2 & 3 uniquement

*autres organes pouvant être affectés:
Coeur | Poumons | Ganglions lymphatiques

Grabowski GA, et al, Gaucher disease, in: D. Valle, A.L. Beaudet, et al (Eds.),OMMBID: The Online Metabolic and Molecular Bases of Inherited Disease, McGraw-Hill, New York, NY, 2013.

Besoin de traitement ayant une action au niveau cérébral

Aucun traitement approuvé pour traiter les manifestations neurologiques de la MG3



- Aucun traitement actuellement approuvé ne traverse la barrière hémato-encéphalique
- Aucun des traitements actuels n'a d'effet sur les symptômes neurologiques
- Les traitements qui traversent la barrière hémato-encéphalique sont nécessaires pour traiter les manifestations neurologiques

TES approuvés pour les manifestations systémiques de la MG3

Imiglucérase	Approuvé en Europe dont la France (AMM centralisée) pour indication MG3 et MG1
Vélaglucérase	Approuvé dans quelques pays mais pas en Europe pour indication MG3 (uniquement MG1 en Europe)
Taliglucérase	Approuvé dans quelques pays mais pas en Europe

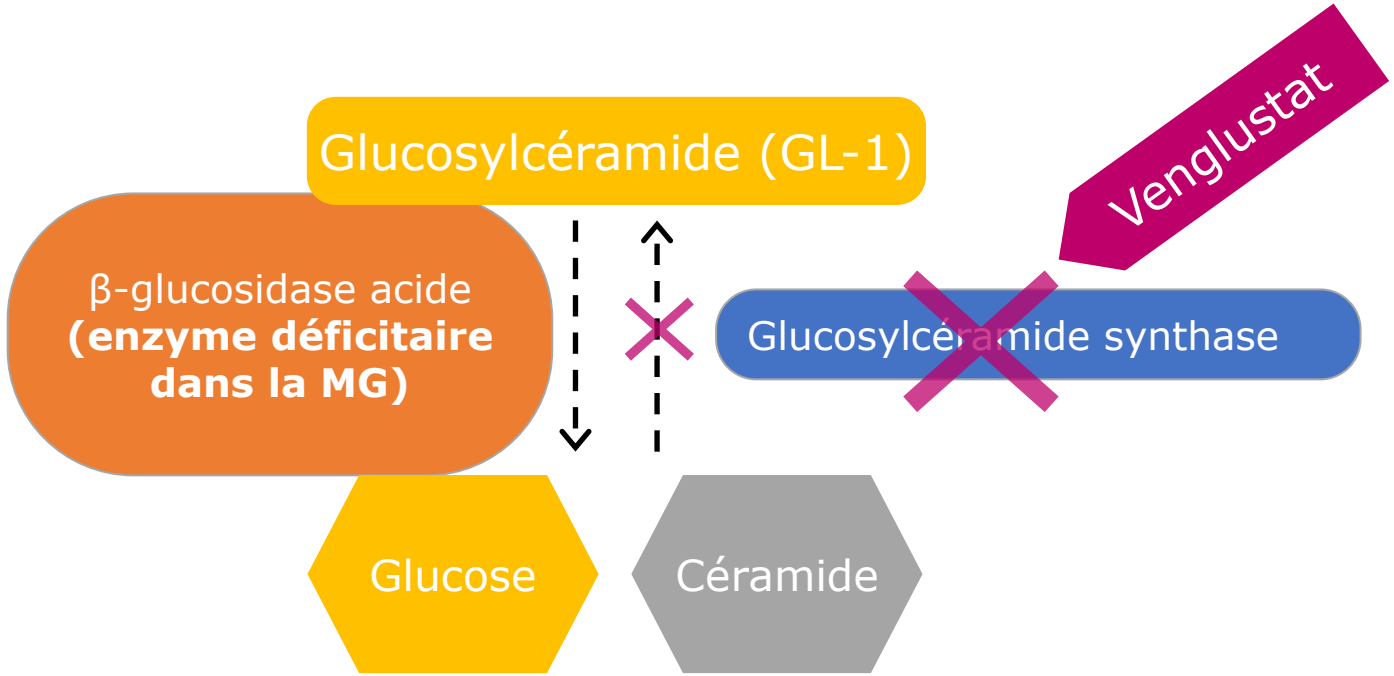
TES : traitement enzymatique substitutif ; MG : Maladie de Gaucher

Venglustat : Inhibiteur oral de la glucosylcéramide synthase

Inhibiteur experimental de la glucosylcéramide synthase, administré par voie orale, pénétrant dans le cerveau

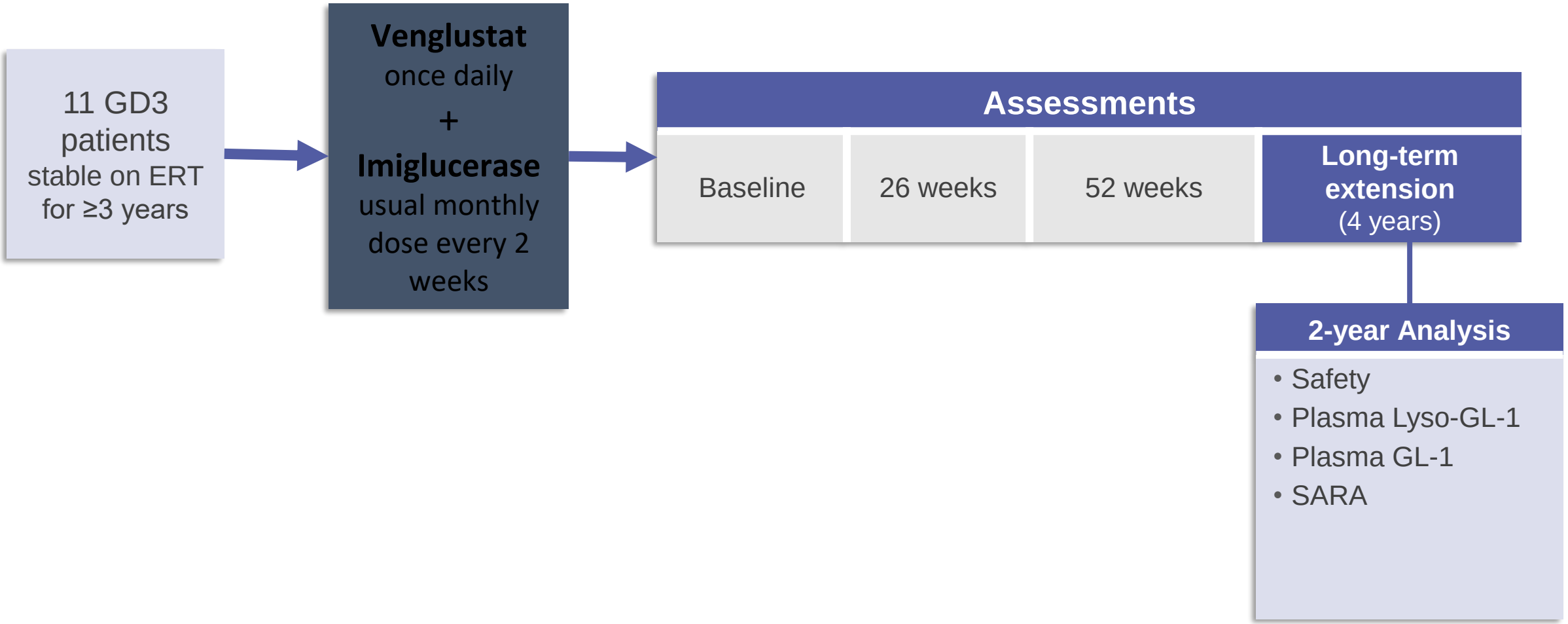
Dans des études précliniques chez des souris atteintes de la forme neuropathique de la maladie de Gaucher, le venglustat passe la barrière hémato-encéphalique, Réduit l'accumulation de glucosylcéramide dans le SNC

Mécanisme d'action du venglustat dans la maladie de Gaucher



MG : Maladie de Gaucher
Marshall J, et al. Mol Ther 2016 ;24 :1019–1029.

Ongoing Phase 2 trial of Oral Venglustat in Combination with Intravenous Imiglucerase in Adult GD3 Patients*, 2 years outcomes



*Trial also includes biomarker evaluation for differences between GD3 and GD1 patients (GD1 patients do not receive study medication).
†Scale for Assessment and Rating of Ataxia (SARA), brain functional MRI (fMRI) and trail-making test (TMT)
GD3: Gaucher disease type 3; GL-1: glucosylceramide; Lyso-GL-1: glucosylsphingosine

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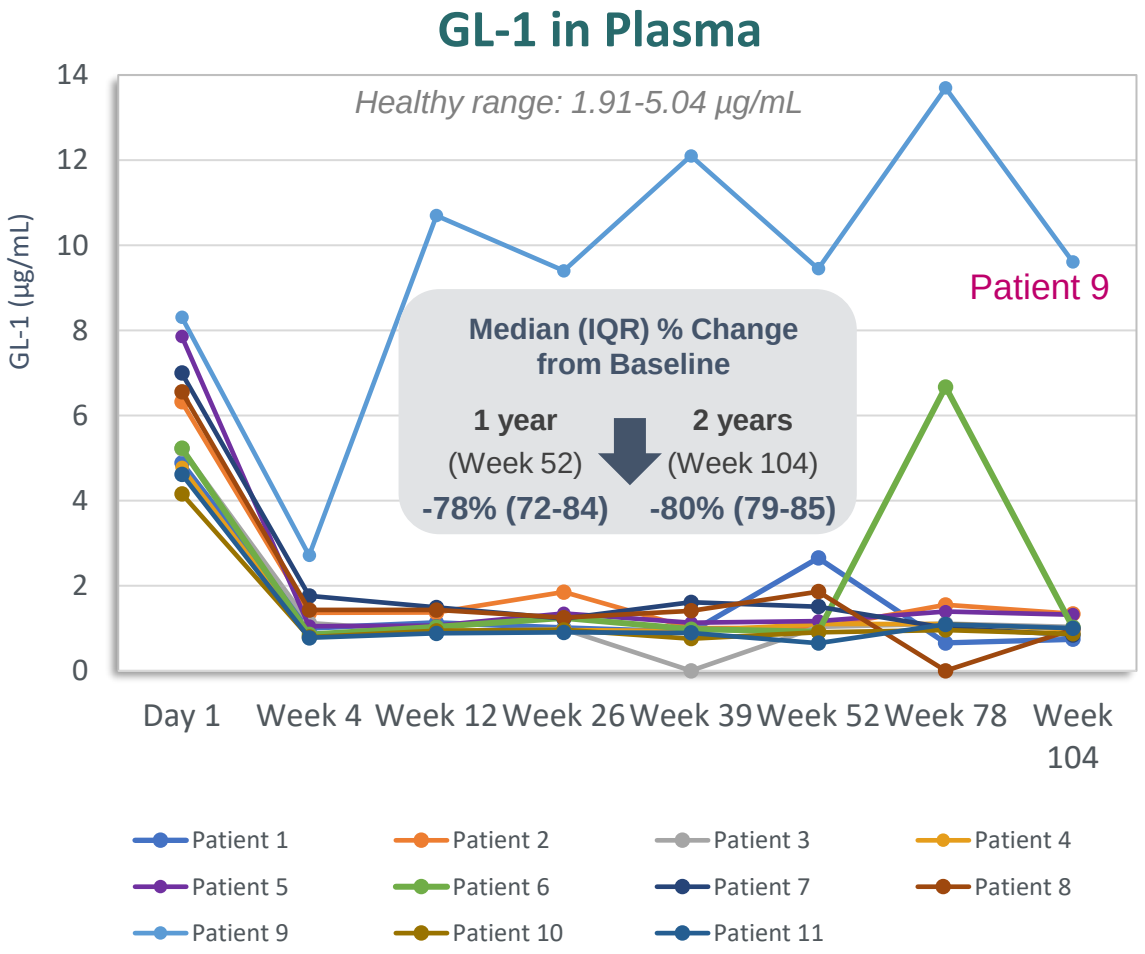
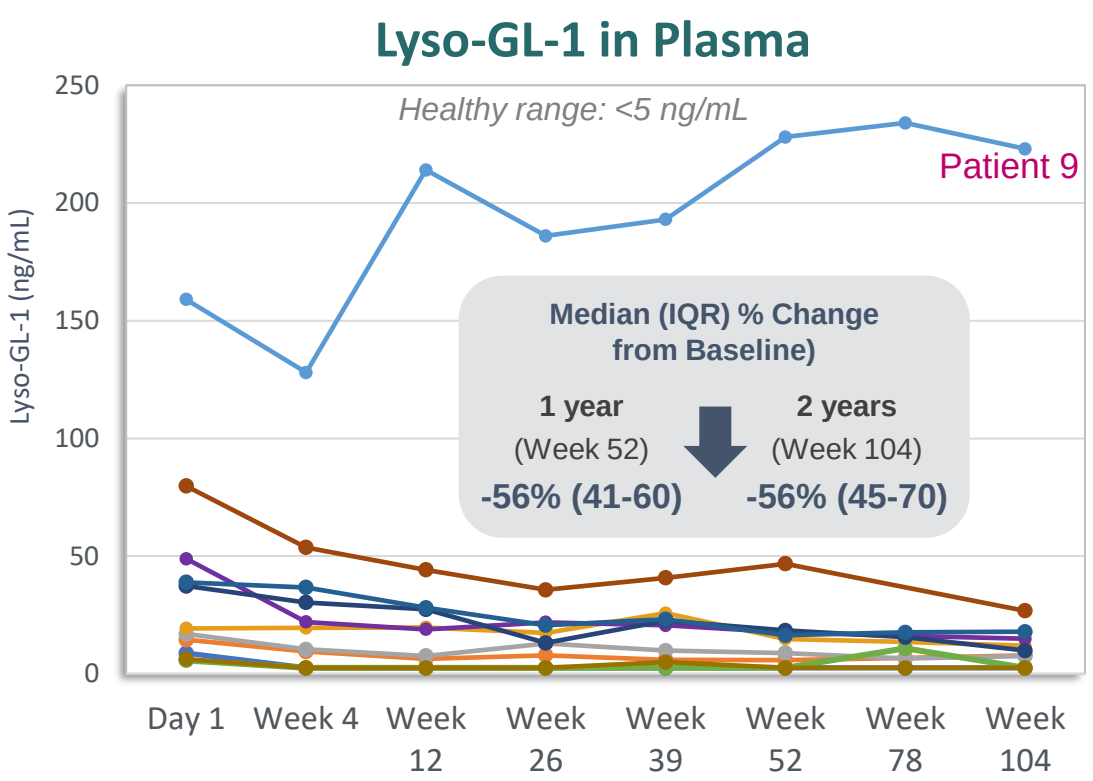
GL-1 and Lyso-GL-1 in Plasma at 2 Years (104 weeks)

Levels decreased for all patients, except Patient 9





LLOQ: plasma GL-1: 0.1 µg/mL; LLOQ: plasma lyso-GL-1: 5.0 ng/mL
GL-1: glucosylceramide; Lyso-GL-1: glucosylsphingosine; LLOQ: lower limit of quantification
Patient 9 had low-to-undetectable venglustat exposure at Weeks 26 and 52

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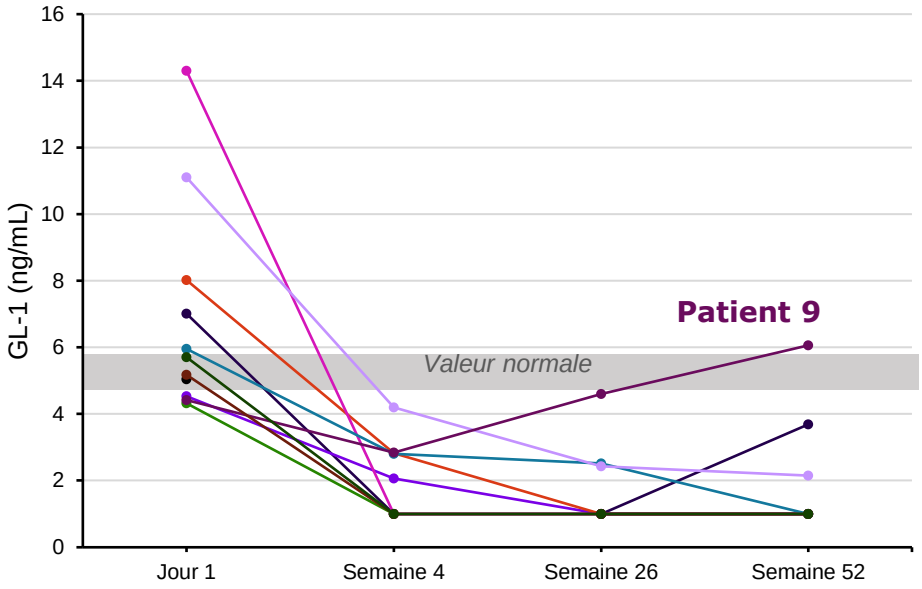
Diminution des **biomarqueurs dans le LCR** avec traitement par venglustat

NCT02843035 : Phase 2

% médian de réduction 81 %
(IQR : 83, 77)

GL-1 LCR

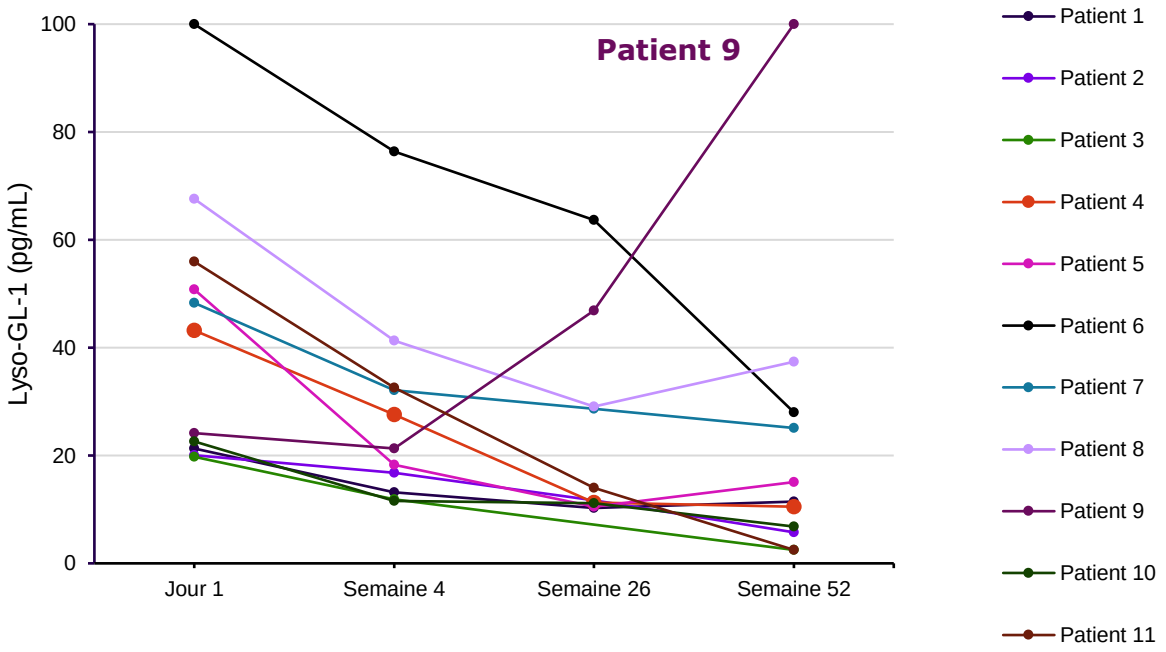
Valeurs normales : 4,5-5,9 ng/ml



% médian de réduction de 70 %
(IQR : 76, 46)

Lyso-GL-1 LCR

Nulle chez les personnes en bonne santé

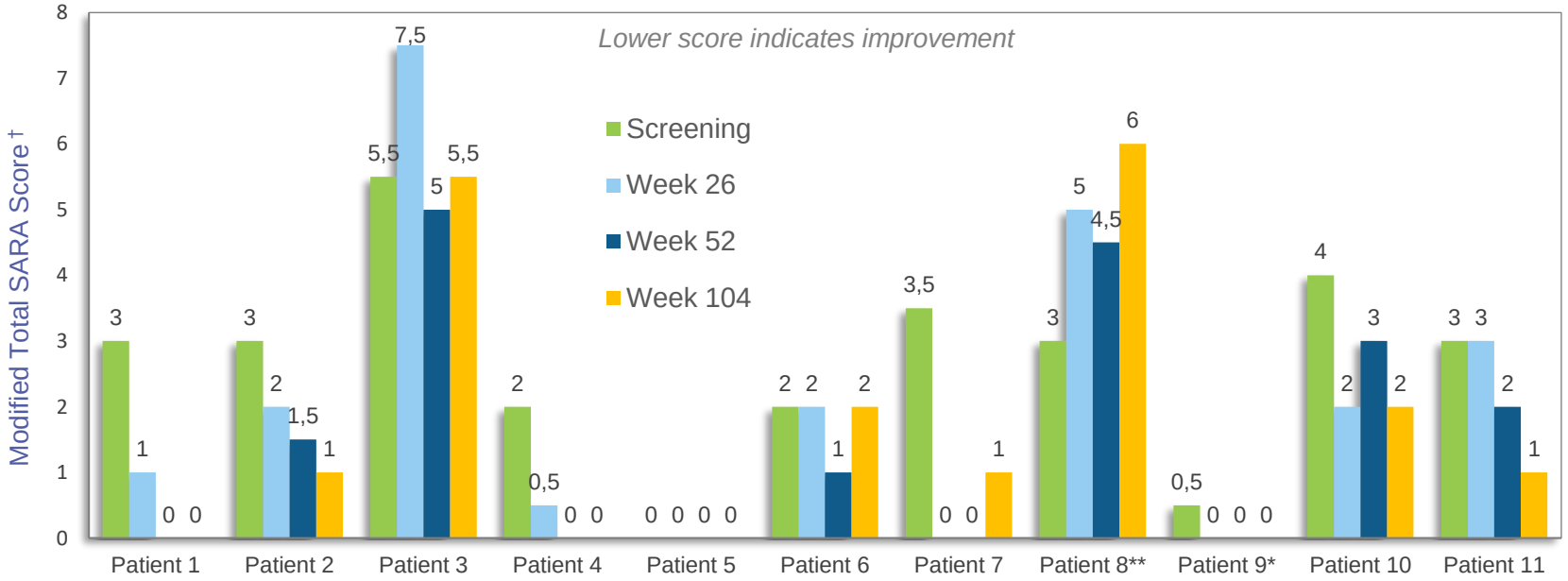


LIQ : GL-1 : 2,0 ng/ml, LCR lyso-GL-1 : 5 pg/ml
LCR : liquide céphalorachidien ; GL-1 : glucosylcéramide ; IQR : intervalle interquartile ; LIQ : limite inférieure de quantification ; Lyso-GL-1 : glucosylsphingosine
Schiffmann R. et al. Brain 2023: 146; 461-474 : doi : 10.1093/brain/awac379

Scale for Assessment and Rating of Ataxia (SARA) Score at 2 Years

91% of patients had improvement or no change at Week 52 and Week 104

Change in Total Modified SARA Score† at Week 26, Week 52 and Week 104



Mean (SD) Change from Baseline (excluding patient 9)	
1 year (Week 52)	**2 years** (Week 104)
-1.14 (1.38)	-1.0 (1.72)
P<0.05‡	P<0.10‡

*Patient 9 had low-to-undetectable venglustat exposure at Weeks 26 and 52. This participant discontinued study treatment after 96 weeks but remained in the study for assessment through Week 104.
**Patient 8 stance score of 5 at Week 52 was excluded. Patient had left knee pain at Week 52 and injured left great toe prior to the exam; the injury was considered resolved 11 days after the exam. Stance score at Week26 (score=2) was imputed at Week 52
†In the total modified SARA score, each item of the SARA scale is scored on a 0 to 4 scale.
‡ Ad-hoc analysis

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Summary: LEAP Trial Two-Year Results

At 2 years, venglustat added to imiglucerase in adult GD3 patients showed:

- Sustained reduction in plasma sphingolipids
- Potential to ameliorate neurological manifestations of GD3
  - Improvement or no change in ataxia at 1 year and 2 years (based on SARA)
  - Stabilization of whole brain volume at 1 and 2 years in patients with venglustat exposure
  - Enhanced connectivity across key brain regions (resting state networks) on functional MRI was among patients with venglustat exposure
- Stable systemic manifestation
- Favorable safety and tolerability

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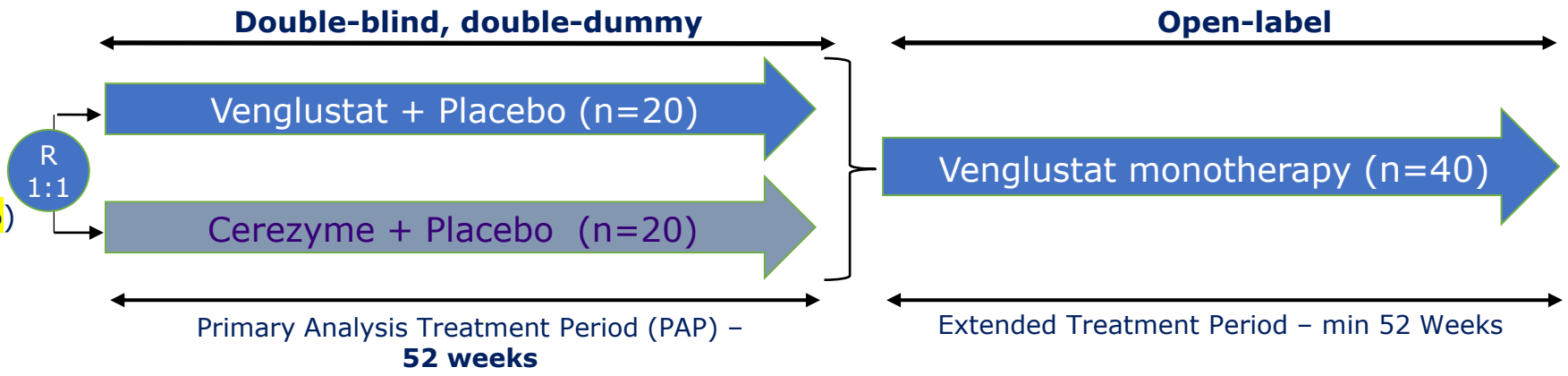
LEAP2MONO EFC17215, Phase 3 study

LEAP2MONO/EFC17215 (n=40)

- Adults GD3 patients (n=24)
- Paediatric GD3 patients 12-17 years (**n=16**)

All previously stabilized with ERT



Primary Endpoints

Change from **baseline to Week 52** on:

- Scale for Assessment and Rating of Ataxia **(SARA)** modified total score
- Repeatable Battery for the Assessment of Neuropsychological Status **(RBANS)** total scale index score

Superiority of venglustat vs Cerezyme®

Secondary endpoints

- Percent change from baseline in MRI liver volume
- Percent change from baseline in MRI spleen volume
- Change from baseline in hemoglobin level
- Percent change from baseline in platelet count

Non-inferiority of venglustat vs Cerezyme®

- Percent change from baseline in CSF GL-1 and lyso GL-1 levels to Week 52
- Percent change from baseline in plasma GL-1 and lyso GL-1 levels to Week 52

Superiority of venglustat vs Cerezyme®

Exploratory Endpoints

Include changes from baseline in:

-**Bone disease manifestations**
-Patient Quality of Life (EQ-5D)
-Observer-reported, clinician-reported, and patient-reported outcomes

- **Acting countries: 12**
- **Active sites 22**
- **#43 Ped:19 Adult: 24**
- **LPI: October 2024**
- **KRM November 2025**

Resultats attendus
début 2026

Merci pour votre écoute