Safety and efficacy of venglustat versus imiglucerase in patients with Gaucher disease type 3 (LEAP2MONO): A phase 3, randomized, double-blind multicenter trial

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CONCLUSIONS

LEAP2MONO is the first trial evaluating venglustat, an oral, brain-penetrant glucosylceramide synthase inhibitor, in pediatric and adult patients with GD3. Primary endpoint was met:

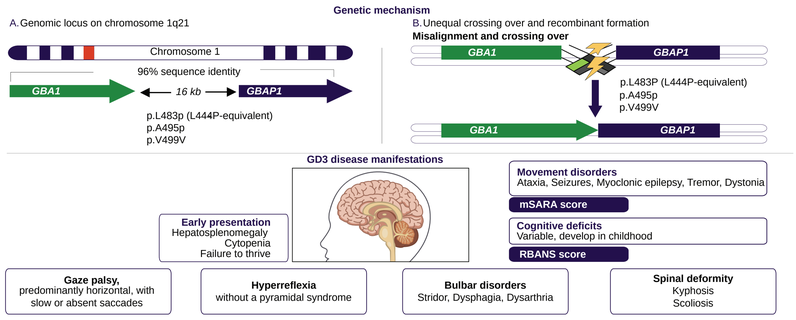
- **Neurologic efficacy demonstrated:** Superior and clinically meaningful improvement vs imiglucerase across motor (mSARA) and cognitive (RBANS) domains.
- **Stabilization of systemic disease:** for those who had reached therapeutic goals at baseline:
  - Met noninferiority for percent change in spleen volume and liver volume and absolute change in hemoglobin level.
  - For platelet count, 19 out of 20 participants in venglustat treatment group remained within platelet count therapeutic goals (>100,000 mm^3)
  - None required rescue ERT therapy during the 52-week PAP.
- **Robust disease biomarker reduction:** Rapid effect as evidenced by substantial reduction in disease-specific CSF and plasma biomarkers vs imiglucerase.
- **Extensive safety data:** from >650 patients exposed to venglustat with no identified safety risk, support a positive benefit risk profile.
- **Findings support a new therapeutic paradigm for neuronopathic GD:** interrupting lipid-driven cellular network injury modifies disease trajectory.

PLAIN LANGUAGE SUMMARY

- Gaucher disease type 3 is a rare inherited condition in which a fatty substance abnormally accumulates in cells throughout the body, including the brain. This causes symptoms affecting organs and blood (such as enlarged spleen and liver, blood problems and bone disease), as well as brain symptoms (such as eye movement, movement disorders, and thinking/ memory problems). Current treatments are intravenous infusions that control symptoms affecting organs and blood but can't reach the brain to address brain symptoms. Venglustat is an oral, once daily tablet designed to cross into the brain to treat both symptoms affecting organs and blood, and brain symptoms.
- In this study, venglustat was compared with imiglucerase in people with GD3 who had been receiving imiglucerase for at least 3 years with well-controlled symptoms affecting liver, spleen and blood but still had ongoing brain symptoms. The study included 43 people with GD3 (21 received venglustat and 22 received imiglucerase).
- The study results show that people taking venglustat demonstrated significant and clinically meaningful improvements in thinking/memory and movement/coordination compared with imiglucerase, alongside substantially reduced levels of fats that buildup in the blood and cerebrospinal fluid (the fluid surrounding the brain and spinal cord), while symptoms affecting organs and blood remained well controlled. Venglustat was well tolerated, with fewer serious side effects than imiglucerase (9.5% vs. 18.2%), and no participants stopped treatment due to side effects.

BACKGROUND

Gaucher disease type 3: The global, predominant neuronopathic form driven by gene conversion at the GBA locus

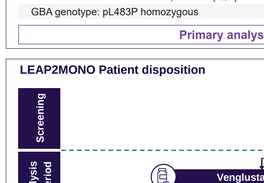


1. El-Beshlawy A, et al. *Mol Genet Metab.* 2017;120(1-2):47-56; 2. Nagral A. *J Clin Exp Hepatol.* 2014;4(1):37-50; 3. Weinreb NJ, et al. *J Inherit Metab Dis.* 2013;36(3):543-553; 4. Schiffmann R, et al. Brain. 2023;146(2):461–474; 5. Woo EG, et al. *Front Genet.* 2021 Jun 21;12:684067.

From substrate accumulation to cellular network injury — and how brain-penetrant glucosylceramide synthase inhibitor interrupts the cascade[1-4]

nGD: GBA deficiency and substrate accumulation

Brain-penetrant GCSi (GenZ 667161 and GZ161)



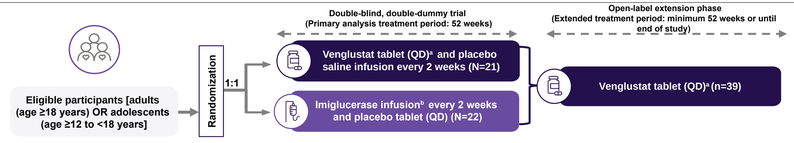
- Venglustat is an orally administered, brain-penetrant glucosylceramide synthase inhibitor that has shown therapeutic potential to address the CNS manifestations of GD[3,5]
- Phase 2 clinical trial data demonstrated preliminary efficacy across key neurological and functional outcomes in patients with GD[3,5]
- Across multiple clinical programs, including *GBA1*-associated Parkinson's disease, ADPKD, and GM2 gangliosidoses, venglustat was generally well tolerated, with no new or unexpected safety signals identified, supporting a consistent safety profile across diverse patient populations[6-8].

1.Blumenreich S, et al. *Mov Disord.* 2020 Dec;35(12):2150-2155; 2. Boddupalli CS, et al. *Elife.* 2022 Aug 16;11:e79830; 3. Marshall J, et al. *PLoS One.* 2010;5:e15033; 4. Marshall J, et al. *Mol Ther.* 2016;24:1019–1029; 5. Schiffmann R, et al. *Brain.* 2023 Feb 13;146(2):461-474; 6. Giladi N, et al. *Lancet Neurol.*2023 Aug;22(8):661-671; 7. GansevoortRT, et al. *Am J Kidney Dis.* 2023 May;81(5):517-527; 8. Tifft CJ, et al. *Genet Med.* 2026 Jan;28(1).

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STUDY DESIGN

LEAP2MONO (NCT05222906) is a Phase 3, randomized, double-blind, double-dummy, active-comparator, multinational, multicenter trial.



[a]Venglustat dose was 15 mg for adults and 12 or 15 mg for adolescents daily based on bodyweight at screening and continued at the same dose through Week 52.
[b]Imiglucerase dose was equivalent to each participant's pre-trial ERT dose.

OBJECTIVE

- The objective of this study was to compare oral venglustat to intravenous imiglucerase in pediatric (≥12 to <18 years) and adult patients with GD3 who have received ERT for ≥3 years prior to enrollment at a stable dose for ≥6 months and met predefined therapeutic goals.

METHODS

Study population

Key inclusion criteria:

- Diagnosis of GD3 with documented deficiency of acid β-glucosidase activity
- Received ERT for ≥3 years prior to enrollment at a stable dose for ≥6 months and met predefined therapeutic goals[a]
- Adults (age ≥18 years) or adolescents (age ≥12 to <18 years)
- Modified SARA score of 1 or above
- Presence of gaze palsy, predominantly horizontal with slow or absent saccades
- Body weight ≥30 kg

Key exclusion criteria:

- Progressive myoclonic epilepsy
- Total splenectomy prior to enrollment or partial splenectomy ≤3 years prior to randomization
- Blood transfusion dependence
- Prior/concomitant therapy with chaperone therapy or SRT other than venglustat within 6 months, venglustat therapy prior to enrollment, and other investigational drugs[b]
- Severe depression[c]

[a]Predefined goals were hemoglobin level of ≥11.0 g/dL for females and ≥12.0 g/dL for males, platelet count ≥100000/mm^3, spleen volume <10MN, liver volume <1.5 MN, and no bone crisis and free of symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathological fractures within 3 months prior to screening. [b]Investigational drugs within 30 days or 5 half-lives before screening, and strong or moderate inducers or inhibitors of CYP3A within 14 days or 5 half-lives before screening. [c]As measured by BDI-II >28 (for participants 13 years of age or above) or PHQ-9 ≥20 (for 12-year-old participants) and/or a history of a major affective disorder within one year of screening examination.

End-points/objectives

Primary objective

- To evaluate superiority of venglustat vs. imiglucerase from baseline to Week 52 on **neurologic efficacy** in adults and pediatric patients with GD3

Primary endpoint: Assessed with Global test of multiple endpoints (Prespecified O'Brien ordinary least square [OLS] test)

- **Motor function:** mSARA
- **Cognitive function:** RBANS

Key secondary objectives

- To ensure **systemic disease control** by evaluating non-inferiority of venglustat vs. imiglucerase from baseline to Week 52 on spleen volume, liver volume, hemoglobin and platelets
- To confirm **CNS and systemic biomarker reduction** and mechanism by assessing superiority of venglustat vs. imiglucerase from baseline to Week 52 on levels of:
  - CSF GL-1, CSF lyso-GL-1
  - Plasma GL-1, plasma lyso-GL-1

Additional secondary/exploratory objectives

- Safety

RESULTS

Demographic and baseline data

Parameters	Venglustat (N=21)	Imiglucerase (N=22)
Age		
Median (IQR)	19.0 (14.0-24.0)	18.5 (15.0-24.0)
<18 years, n (%)	9 (43%)	10 (46%)
Sex, females, n (%)	8 (38%)	14 (64%)
Age at GD diagnosis (years), Median (IQR)	2 (1–2)	2 (2-3)
Weight (kgs), Median (IQR)	56.4 (48–60)	52.6 (47–70.5)
SARA modified total score, Median (IQR)	4 (3–5.5)	5.75 (2.5–10)
RBANS total scale index score, Median (IQR)	79 (65–89)	65 (53–81)
GBA genotype: pL483P homozygous	11 (52.4)	15 (68.2)

Primary analyses were adjusted for baseline values using MMRM for primary endpoints

LEAP2MONO Patient disposition

Primary neurologic endpoint met at Week 52

Prespecified Global O'Brien test of mSARA and RBANS showed statistical superiority of venglustat vs imiglucerase

- O'Brien ordinary least square (OLS) test statistic = 2.17[b]
- One-sided p-value vs Imiglucerase[a] p= 0.0179[b]

Motor and Cognitive Components of Neurologic Benefit

mSARA

- Clinically meaningful improvement with venglustat (-1.35) compared with imiglucerase (-0.79)
- Magnitude of 1-point change directly relevant to the patient's everyday functioning and quality of life.[1,2]

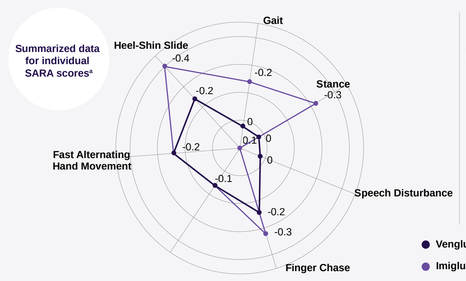
RBANS

- Improved by an average of 3.69 points in the venglustat arm and declined by an average of -4.63 points in the imiglucerase arm
- This treatment difference exceeded the minimum clinically important difference of 8 established in a separate study.[3]

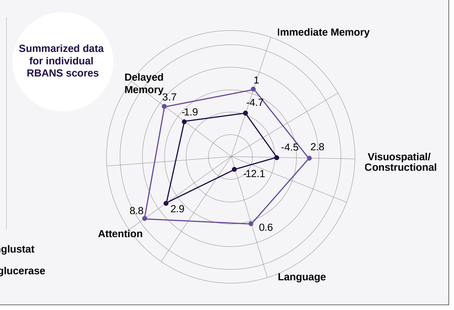
[a]One sided p-value is to compare with **pre-specified significance level of 0.05**; [b]Post-presentation correction to O'Brien OLS statistic and p-value. Updated value remains statistically significant.

Radar plot for individual items of SARA (item 1 to 8) & RBANS (domain 1 to 5) at Week 52

Improvements observed in gait, stance, and heel-to-shin slide: consistent with the predominance of lower limb gross motor involvement



Improvements across all domains



[a]Sitting disturbance not displayed because only 4 participated with non-zero change.

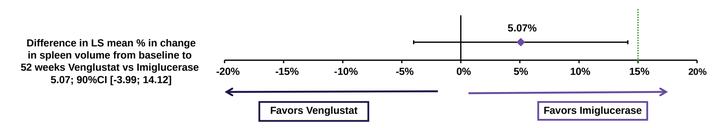
Systemic outcomes in patients treated with venglustat and imiglucerase from baseline to Week 52

	Venglustat		Imiglucerase	
	Baseline	Week 52*	Baseline	Week 52*
Spleen volume (MN), median (min, max), n	2.85 (1.1, 7.9), n=19	2.78 (1.1, 11.6) n=20	2.48 (0.7, 4.4), n=21	2.22 (0.7, 4.1) n=22
Liver volume (MN), median (mix, max), n	0.91 (0.7, 1.6), n=20	0.90 (0.7, 1.7) n=20	0.87 (0.6, 1.4), n=21	0.84 (0.6, 1.4) n=22
Hemoglobin (g/L), median (min, max), n	139.0 (111, 178), n=21	138.0 (118, 185) n=21	134.5 (112-161), n=22	135.3 (103,159) n=22
Platelet count (10^9/L), median (min, max), n	194.3 (133, 277), n=20	190.5 (99, 286) n=21	236.8 (100, 324), n=22	235.5 (139, 310) n=22

*While on-treatment estimand; Predefined goals were hemoglobin level of ≥11.0 g/dL for females and ≥12.0 g/dL for males, platelet count ≥100 000/mm^3, spleen volume <10MN, liver volume <1.5 MN

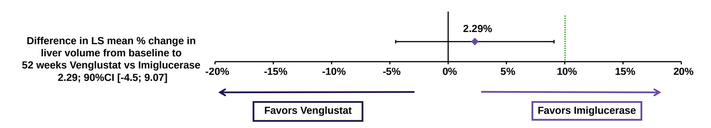
Venglustat maintained spleen & liver volume, as well as hemoglobin & platelet count in patients with GD3

Spleen volume (Meet non-inferiority, as upper bound of 90% CI is < Non-inferiority margin of 15%)



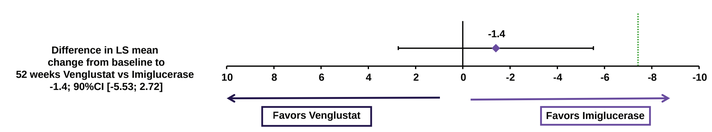
The green dot line denotes the NI margin 15%

Liver volume (Meet non-inferiority, as upper bound of 90% CI is < Non-inferiority margin of 10%)



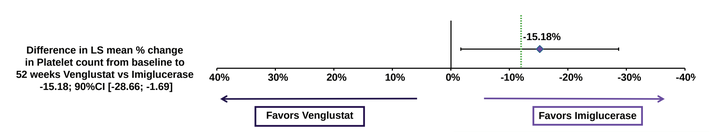
The green dot line denotes the NI margin 10%

Hemoglobin (Meet non-inferiority, as lower bound of 90% CI is > Non-inferiority margin of -7.5 g/L)



The green dot line denotes the NI margin 7.5 g/L

Platelet count (Did not meet non-inferiority, as lower bound of 90% CI was not > Non-inferiority margin of -12.5%)

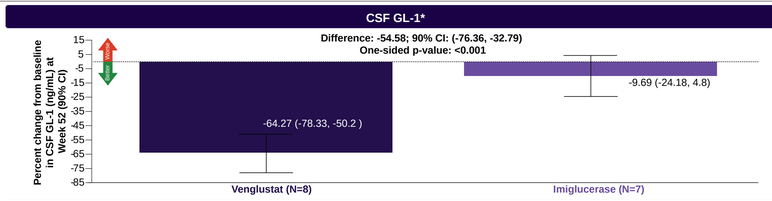


The green dot line denotes the NI margin 12.5%

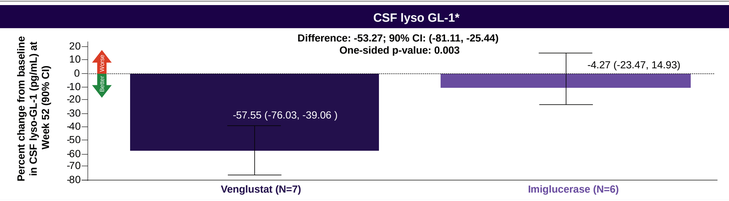
19/20 participants in venglustat group met the platelet count therapeutic goal (>100,000/mm^3)

Robust CNS and Systemic Biomarker Reduction

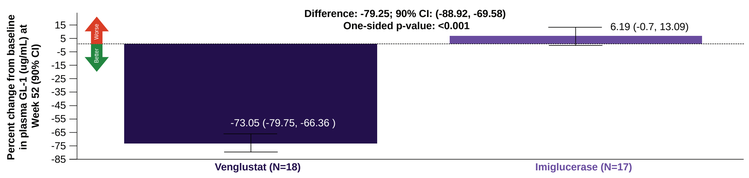
CSF GL-1*



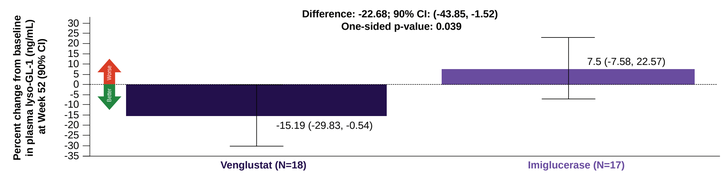
CSF lyso GL-1*



Plasma GL-1*



Plasma GL-1*

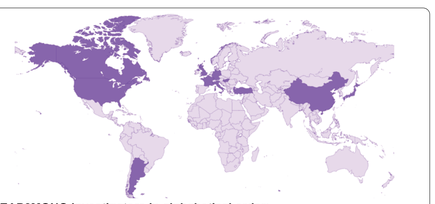


*Per protocol CSF GL-1 and CSF lyso GL-1 obtained only in adults; plasma GL-1 and Plasma lyso-GL-1 obtained in adult and pediatric participants

Safety: Number (%) of participants with TEAE(s) with a PT >5% in at least one group by primary SOC and PT during the Primary analysis treatment period - Primary Safety population

PRIMARY SYSTEM ORGAN CLASS Preferred Term n(%)	Venglustat (N=21)	Imiglucerase (N=22)
Any event	19 (90.5)	19 (86.4)
INFECTIONS AND INFESTATIONS	8 (38.1)	10 (45.5)
COVID-19	2 (9.5)	0
Gastroenteritis	2 (9.5)	0
Pharyngitis	2 (9.5)	1 (4.5)
Nasopharyngitis	1 (4.8)	3 (13.6)
Upper respiratory tract infection	1 (4.8)	4 (18.2)
Ear infection	0	2 (9.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	4 (19.0)	2 (9.1)
Splenomegaly	3 (14.3)	0
METABOLISM AND NUTRITION DISORDERS	3 (14.3)	4 (18.2)
Iron deficiency	1 (4.8)	2 (9.1)
Vitamin B12 deficiency	1 (4.8)	3 (13.6)
PSYCHIATRIC DISORDERS	3 (14.3)	1 (4.5)
Depression	2 (9.5)	0
NERVOUS SYSTEM DISORDERS	9 (42.9)	9 (40.9)
Headache	3 (14.3)	4 (18.2)
Dizziness	2 (9.5)	1 (4.5)
Epilepsy	1 (4.8)	2 (9.1)
EYE DISORDERS	1 (4.8)	3 (13.6)
Visual field defect	0	2 (9.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	5 (23.8)	4 (18.2)
Rhinitis allergic	1 (4.8)	2 (9.1)
GASTROINTESTINAL DISORDERS	5 (23.8)	6 (27.3)
Diarrhoea	3 (14.3)	0
Nausea	3 (14.3)	1 (4.5)
Vomiting	2 (9.5)	1 (4.5)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	4 (19.0)	3 (13.6)
Dermatitis	0	2 (9.1)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (9.5)	2 (9.1)
Fatigue	2 (9.5)	0
INVESTIGATIONS	3 (14.3)	8 (36.4)
Blood alkaline phosphatase increased	0	2 (9.1)
Weight increased	0	2 (9.1)

- Incidence of TEAEs was consistent with safety profile observed in all previous studies.
- There were no TEAEs leading to permanent study treatment discontinuation and no treatment emergent AESI.
- The most frequently reported TEAEs (occurring in ≥10% of participants in the venglustat treatment arm) by PT were splenomegaly, nausea, headache, and diarrhoea (3 [14.3%] participants for each). The incidence of TEAEs, at the PT level, was generally similar between treatment arms with the following exceptions (with a difference of ≥10%):
  - Splenomegaly and diarrhoea were reported more frequently in the venglustat arm than in the imiglucerase arm (14.3% versus 0%, respectively, for each PT).
  - Upper respiratory tract infection was reported less frequently in the venglustat arm than in the imiglucerase arm (4.8% versus 18.2%).
  - Depression PT was reported in 2 adult participants in the venglustat arm with no occurrences in the imiglucerase arm.
- None of the venglustat participants required rescue imiglucerase therapy during the randomized period of up to Week 52.



LEAP2MONO Investigators in alphabetical order:

- C. Balci, J. Bernat, A. Brassier, F.D. Bulut, G. Drelichman, M. Ghisoli, O. Goker-Alpan, C. Greenberg, D. Hughes, N. Ichinoi, N-C. Lee, X. Luo, M. Matsuda, E. Mengel, Pramod K. Mistry, I. Motta, Y. Nadjar, I. Okur, Z. Qiu, E. Rakoczi, D. Rendina, H. Zhang.

***LEAP2MONO:* Evidence for Disease Modification in GD3**

- **Neurologic efficacy demonstrated:** Coherent benefit across motor (mSARA) and cognitive (RBANS) domains based on a prespecified global analysis
- **Systemic Gaucher disease control preserved:** No trade-off between CNS benefit and core Gaucher management
- **Mechanism confirmed in humans:** Robust CNS and systemic glycosphingolipid reduction consistent with target engagement
- **Acceptable safety profile:** Supports chronic CNS-directed therapy
- **Implication:** Findings support a shift from an assumption of inevitable neurologic progression toward the possibility of modifying neurologic trajectory in neuronopathic GD

ABBREVIATIONS

ADPKD, Autosomal Dominant Polycystic Kidney Disease; AE, adverse event; AESI, AE of special interest; BBB, blood–brain barrier; BDI-II, Beck Depression Inventory–II; CI, confidence interval; CNS, central nervous system; CSF, cerebrospinal fluid; D, day; ECM, extracellular matrix; ERT, enzyme replacement therapy; GBA1, glucocerebrosidase 1 gene; GCSi, Glucosylceramide synthase inhibitors; GD, Gaucher disease; GD3, Gaucher disease type 3; GL-1, glucosylceramide; GM2, Ganglioside M2; GlcCer, glucosylceramide; GlcSph, glucosylsphingosine; IQR, interquartile range; lyso-GL-1, glucosylsphingosine; M, male; MH, medical history; MMRM, mixed model of repeated measures; MN, multiples of normal; mSARA, Modified Scale for the Assessment and Rating of Ataxia; NfL, neurofilament light chain; nGD, neuronopathic Gaucher disease; OLE, open-label extension;PAP, primary analysis treatment period; PT, preferred term; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SAE, serious adverse event; SARA, Scale for the Assessment and Rating of Ataxia; SOC, system organ class; SRT, substrate reduction therapy; TEAE, treatment-emergent adverse event; W, week

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DISCLOSURES

Pramod K. Mistry is a member of the International Collaborative Gaucher Group (ICGG) Gaucher Registry North American Advisory Board, and has received research support, and travel reimbursement from Sanofi; **Fatma Derya Bulut** has no conflict of interest; **Qi Zhang, Dmitry Cherkasov, Gabriela Perichon, and Kristina An Haack** are employees of Sanofi and may hold stock/stock options; **Riliang Zheng** is a former employee of Sanofi and may hold stock/stock options; **Eugen Mengel** has received research support, honoraria, and consulting fees from Sanofi.

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1. Park J, et al. *J Neurol.* 2024;271(10):6888-902.
2. Schmitz-Hübsch T, et al. *Neurology.* 2006;66(11):1717-20.
3. Phillips R, et al. Clin Neuropsychol. 2015;29(7):905-923.

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