First-in-Human Study of Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of SAR443820, a Central Nervous System Penetrant RIPK1 Inhibitor in Healthy Participants

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Disclosures

- **Agnes Hincelin-Mery, Cathy Cantalloube, Xavier Nicolas, Myriam Benamor, Robert Pomponio, Emmanuel Krupka, Dimitry Ofengeim, Li Xiong, and Nazem Atassi:** Employees of Sanofi and may hold stock and/or stock options in the company
- **Pascale Lewanczyk:** Employee of Ividata Life Sciences (contracted by Sanofi)
- **Amy Eastenson:** Nothing to disclose

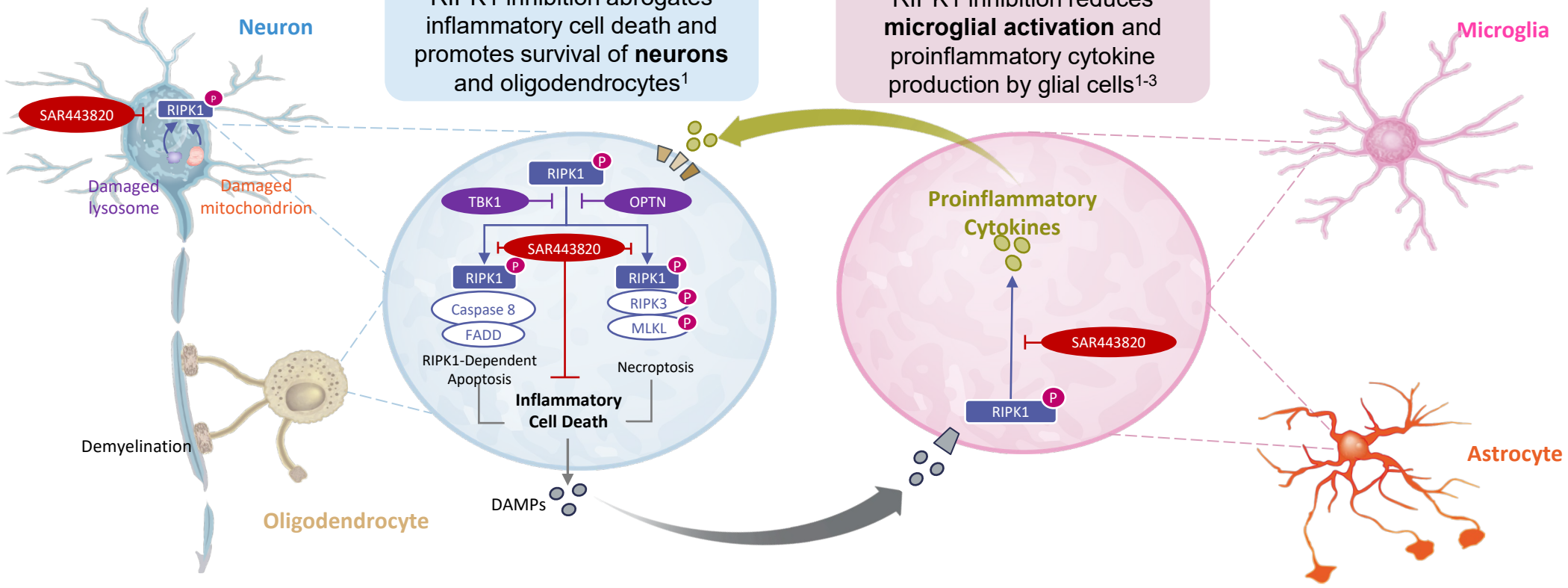
- **The study was funded by Sanofi**
- **The authors and Sanofi thank the participants and their families for their participation in the SAR443820 Phase 1 first-in-human trial**
- **SAR443820 (DNL788) is being developed by Sanofi in collaboration with Denali Therapeutics Inc.**
- **Jennifer Hsiao-Nakamoto from Denali contributed in running pS166-RIPK1 immunoassay for MAD samples**
- **Nian Tian provided global support in the study management**
- **Medical writing support for this presentation was provided by Akshada Deshpande, and reviewed by Roopali Gandhi and Aditya Garg, of Sanofi**

RIPK1 is a key target at the intersection of inflammation and cell death

Proposed mechanism of RIPK1 inhibition in the CNS

RIPK1 inhibition abrogates inflammatory cell death and promotes survival of **neurons** and oligodendrocytes[1]

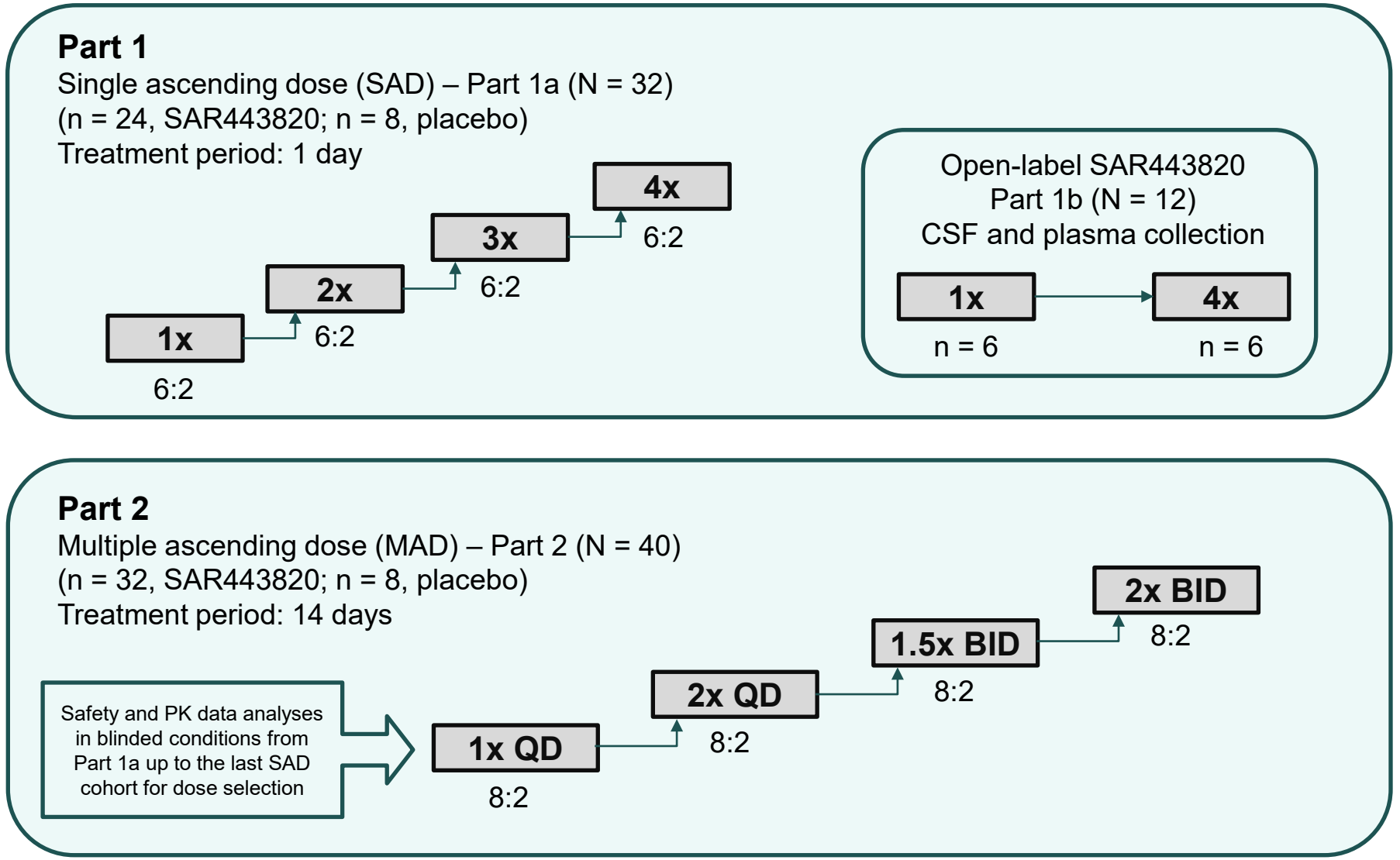
RIPK1 inhibition reduces **microglial activation** and proinflammatory cytokine production by glial cells[1-3]



SAR443820 (DNL788), a selective, orally bioavailable, CNS penetrant, small-molecule, reversible inhibitor of RIPK1, is currently under Phase 2 clinical development for MS and ALS

1. Ito Y, et al. Science. 2016;353:603-8; 2. Caccamo A, et al. Neurosci. 2017;20:123; 3. Degterev A, et al. PNAS. 2019;116:9714-22. ALS, amyotrophic lateral sclerosis; CNS, central nervous system; DAMPs: damage-associated molecular patterns; FADD: fas-associated death domain; MLKL: mixed-lineage kinase domain-like protein; MS, multiple sclerosis; OPTN: Optineurin; PD, pharmacodynamics; PK, pharmacokinetics; RIPK1, receptor-interacting serine/threonine protein kinase 1; RIPK3: receptor-interacting serine/threonine-protein kinase 3; TBK1: TANK-binding kinase 1.

Phase 1 study design



BID, twice daily; CSF, cerebrospinal fluid; MAD, multiple ascending dose; PK, pharmacokinetics; QD, once daily; SAD, single ascending dose.

Study objectives

Primary

- Assess safety and tolerability of SAR443820

Secondary

- Determine PK parameters of SAR443820 in plasma
- Determine SAR443820 concentrations in CSF after single dose (Part 1b)
- Assess the potential for CYP3A4 enzyme induction by SAR443820 after repeated doses (MAD)

Exploratory

- Evaluate the PD effect of SAR443820 on the inhibition of pS166-RIPK1 in PBMC lysates (SAD and MAD)
- Analyze exposure-QTcF between the change from time-matched baseline in centrally-read ECG intervals and corresponding drug concentrations (SAD and MAD)

CSF, cerebrospinal fluid; ECG, electrocardiogram; MAD, multiple ascending dose; PBMC, peripheral blood mononuclear cell; PD, pharmacodynamics; PK, pharmacokinetics; pS166, phosphorylated at Serine166; RIPK1, receptor-interacting serine/threonine protein kinase 1; SAD, single ascending dose.

SAR443820 was generally safe and well-tolerated in healthy participants

- No SAR443820-related SAEs
- No severe SAR443820-related TEAEs
- Two AESIs of asymptomatic ALT increase (<3-fold ULN) in SAR443820 groups: one after single lowest dose (1x) and one after multiple doses (1.5x BID)
- Most frequently reported TEAEs in SAR443820 groups:
  - SAD: Dizziness (33.3% 3x group; 16.7% 4x group; vs 12.5% placebo group)
  - Part 1b: Headache (50% 1x group; 66.7% 4x group)
  - MAD: Headache (25% 1x QD group; 12.5% each in 1.5x BID and 2x BID groups; vs 12.5% placebo group)
- A few potentially clinically significant abnormalities were noted in hematology, clinical chemistry, vital signs, and ECG parameters; none considered as clinically relevant

AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; BID, twice daily; ECG, electrocardiogram; MAD, multiple ascending dose; QD, once daily; SAD, single ascending dose; SAE, serious adverse event; TEAE, treatment emergent adverse event; ULN, upper limit of normal.

SAR443820 had a favorable PK profile

T_{max}	• Rapid absorption with median T_{max} between 1–1.5 h in SAD and 1–2 h in MAD
$T_{1/2z}$	• Mean plasma half-lives ($T_{1/2z}$) ranged between 6–8 h in SAD and 7–9 h in MAD
Dose proportionality	• No major deviation from dose proportionality for C_{max} and AUC over the range of SAR443820 doses
Lack of CYP3A4 induction	• No potential for CYP3A4 induction as indicated by 4β-hydroxycholesterol levels vs baseline (MAD)
High CNS penetrance	• Mean CSF-to-unbound plasma concentration ratio between 0.8 and 1.3 (Part 1b)

AUC, area under the plasma concentration versus time curve; C_{max}, maximum plasma concentration; CNS, central nervous system; CSF, cerebrospinal fluid; MAD, multiple ascending dose; PK, pharmacokinetics; SAD, single ascending dose; $T_{1/2z}$, terminal half-life; T_{max}, time to reach C_{max}.

SAR443820 showed a marked RIPK1 target engagement at peripheral level

- SAR443820 showed a marked RIPK1 target engagement at the peripheral level as measured by reduction in phosphorylation at Serine166 of RIPK1 (pS166-RIPK1) in human PBMCs
  - Median inhibition of at least 90% after multiple doses in all SAR443820 groups (MAD)

MAD, multiple ascending dose; PBMC, peripheral blood mononuclear cell; RIPK1, receptor-interacting serine/threonine protein kinase 1.

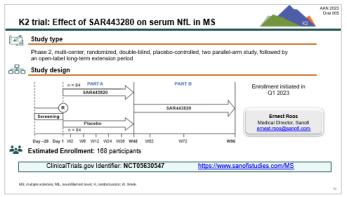
Conclusions

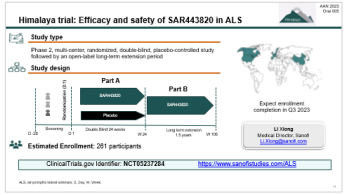
SAR443820 had a **good safety and tolerability** profile after single and 14 days multiple oral doses

SAR443820 showed **favorable PK** properties including **high CNS penetrance**

SAR443820 showed a **marked RIPK1 target engagement** at the peripheral level

Results of this first-in-human study support further development of SAR443820, in the **ongoing phase 2 trials in MS and ALS**





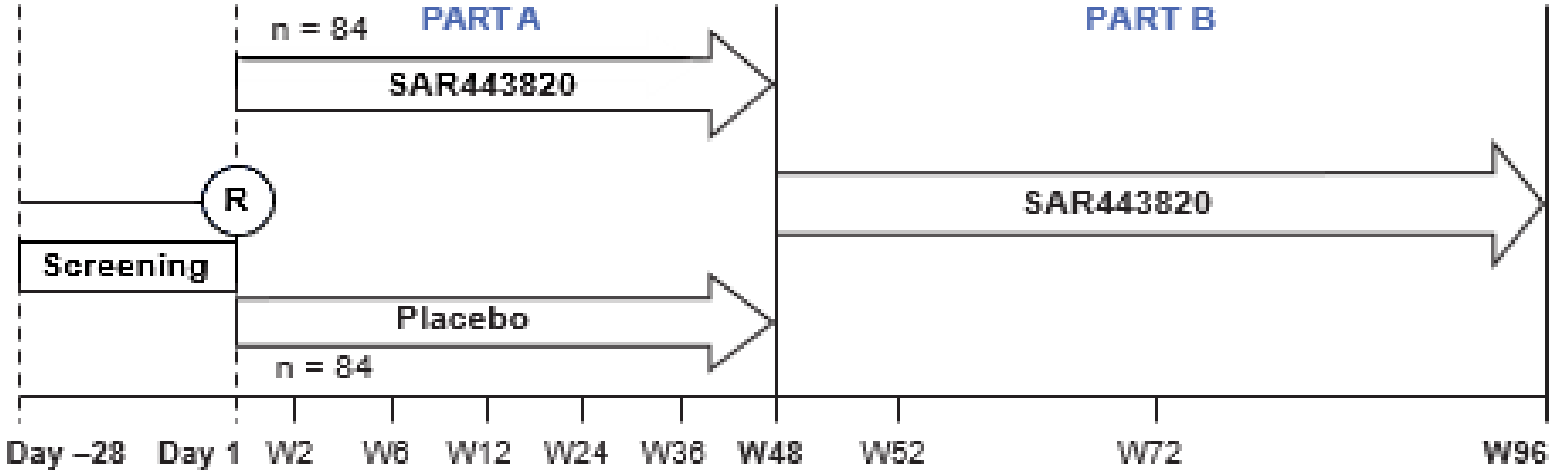
ALS, amyotrophic lateral sclerosis; CNS, central nervous system; MS, multiple sclerosis; PK, pharmacokinetics; RIPK1, receptor-interacting serine/threonine protein kinase 1.

K2 trial: Effect of SAR443280 on serum NfL in MS

Study type

Phase 2, multi-center, randomized, double-blind, placebo-controlled, two parallel-arm study, followed by an open-label long-term extension period

Study design



Enrollment initiated in Q1 2023

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Estimated Enrollment: 168 participants

ClinicalTrials.gov Identifier: **NCT05630547** https://www.sanofistudies.com/MS

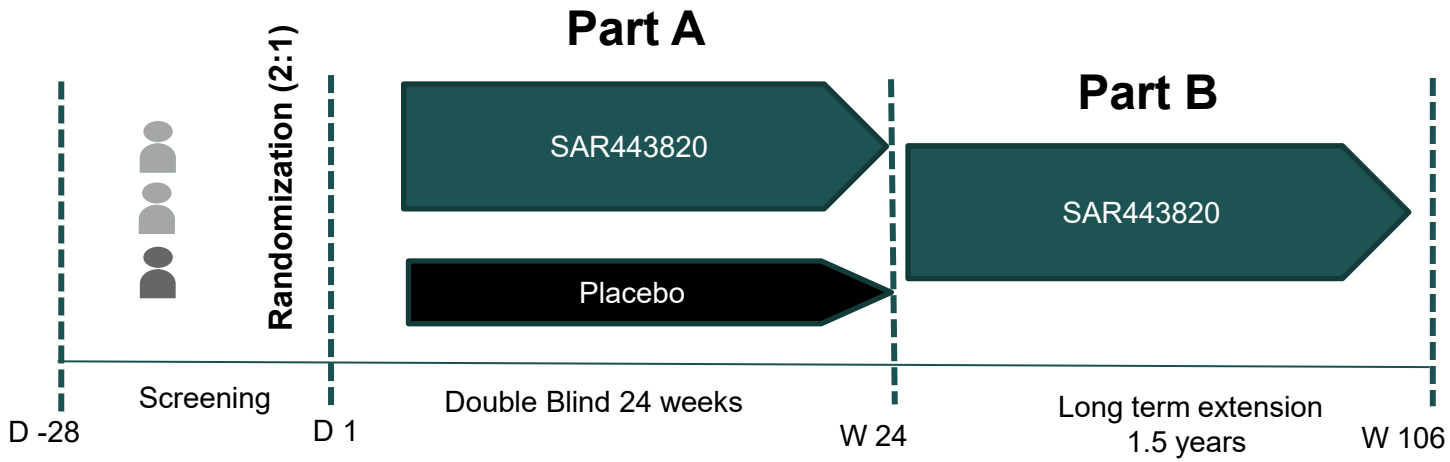
MS, multiple sclerosis; NfL, neurofilament level; R, randomization; W, Week.

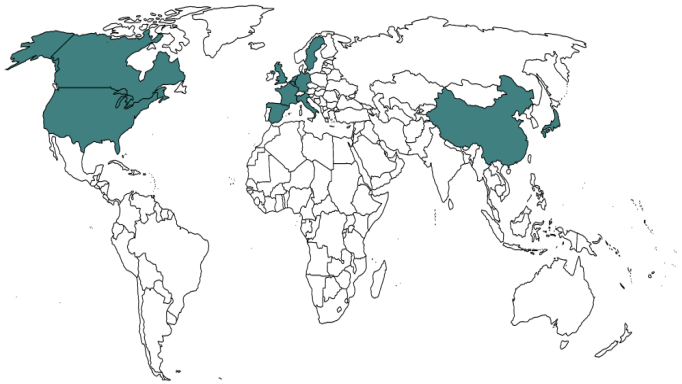
Himalaya trial: Efficacy and safety of SAR443820 in ALS

Study type

Phase 2, multi-center, randomized, double-blind, placebo-controlled study followed by an open-label long-term extension period

Study design





Expect enrollment completion in Q3 2023

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Estimated Enrollment: 261 participants

ClinicalTrials.gov Identifier: **NCT05237284** https://www.sanofistudies.com/ALS

ALS, amyotrophic lateral sclerosis; D, Day; W, Week.

Thank you