199M

STELLAR Phase 3 Studies to Evaluate the Efficacy and Safety of Salanersen in Infants with Spinal Muscular Atrophy

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Objective

- To evaluate whether salanersen, an investigational, intrathecal antisense oligonucleotide with a novel backbone chemistry enabling high potency and once-yearly dosing, can address the residual unmet needs that persist for individuals with SMA despite current transformative presymptomatic therapies.
- STELLAR-1 evaluates salanersen treatment in presymptomatic, treatment-naive infants.
- STELLAR-2 evaluates salanersen after presymptomatic treatment with OA.

Background and Unmet Need

- DMTs have transformed outcomes in SMA, particularly for individuals who are treated presymptomatically.
- Nonetheless, unmet needs remain. Outcomes are not consistently within the normal range, and deficits persist compared with individuals without SMA.[1–3]

Overview of Salanersen

- Salanersen (BIIB115) is a novel, intrathecally administered antisense oligonucleotide in development for SMA.
- Salanersen corrects splicing of *SMN2* pre-mRNA by binding to a region also targeted by nusinersen and is designed to increase SMN protein.
- Salanersen has a new backbone chemistry that leads to high potency, enabling the potential for high efficacy with once-yearly dosing.

Rationale and Study Designs

- Phase 1 salanersen study (NCT05575011/EudraCT 2022-000956-12) is ongoing.
- Interim results show that in children with SMA who were previously treated with intravenous onasemnogene abeparvovec (OA), salanersen is well tolerated, drives sustained reductions of plasma NfL, and demonstrates consistent functional improvements (see associated oral presentation at MDA 2026 for further details*).

STELLAR-1 (Salanersen Monotherapy)

- The primary objective of STELLAR-1 is to evaluate the efficacy of once-yearly, intrathecal salanersen initiated presymptomatically in treatment-naive infants (**Figure 1**).
- STELLAR-1 (NCT07221669) is a two-part, open-label, single-arm study evaluating salanersen in treatment-naive, presymptomatic infants (aged ≤ 6 weeks) with 2 or 3 *SMN2* copies (N = 30: 15 with 2 *SMN2* copies, 15 with 3 *SMN2* copies) (**Figure 2**).
- Participants will receive annual doses of salanersen 80 mg: 2 doses in Part 1 (at Days 1 and 365) and 3 doses in Part 2 (at Days 730, 1095, and 1460). After the fifth dose at Day 1460, participants will enter a 1-year follow-up period (**Figure 3A**).
- Endpoints assess multidomain clinical function (motor, respiratory, bulbar, and neurodevelopment), biomarkers, PK, and safety/tolerability (**Figure 1**).

STELLAR-2 (Salanersen After OA)

- The primary objective of STELLAR-2 is to evaluate whether the addition of once-yearly intrathecal salanersen treatment after presymptomatic treatment with OA can further address remaining unmet need (**Figure 1**).
- STELLAR-2 (NCT07444450) is a randomized, double-blind, sham-controlled study evaluating salanersen in infants with 2 *SMN2* copies who received presymptomatic OA therapy at ≤ 6 weeks of age (participants can enter screening at any time within 6 months of OA therapy) (**Figure 2**).
- Participants (N = 42) will be randomized 1:1 to an early-start cohort (salanersen 80 mg administered 6 months after OA, then once-yearly thereafter) or a delayed-start cohort (a single sham LP procedure 6 months after OA, followed by initiation of salanersen 80 mg 1 year post-sham dose, and then annually thereafter) (**Figure 3B**).
- Endpoints include safety/tolerability, multidomain clinical function, biomarkers, and PK (**Figure 1**).

Recruitment

- STELLAR-1 and STELLAR-2 will be conducted globally at approximately 40 and 35 sites, respectively (see ClinicalTrials.gov for an up-to-date list of study sites).
- The planned start dates are Q1 2026 (STELLAR-1) and Q3 2026 (STELLAR-2).

Figure 1. Study Endpoints

STELLAR-1

Primary objective: to evaluate the short- and long-term clinical efficacy of salanersen in infants with SMA

Secondary objectives: to evaluate the short- and long-term safety, tolerability, and PK after treatment with salanersen in presymptomatic infants with SMA

Primary endpoints: efficacy

2 *SMN2*-copy group: WHO motor milestone of sitting without support at 12-month follow-up

3 *SMN2*-copy group: WHO motor milestone of walking alone at 18-month follow-up

Attainment and maintenance of WHO motor milestones

Secondary and exploratory endpoints: efficacy

Motor: WHO motor milestones, HINE-2 motor milestones, CHOP-INTEND, HFMSE,[a] RULM[a]

Respiratory and survival: overall survival, time to death or permanent ventilation,[b] ventilation use

Biomarker and electrophysiology: plasma and CSF NfL,[c] CMAP amplitudes

Bulbar: bulbar endpoints

Neurodevelopment and QoL: motor and cognitive development scales, QoL assessment

Other clinical: no SMA symptoms,[d] development of SMA subtypes[e]

Secondary endpoints: safety and PK

Safety: AEs and SAEs

PK: CSF and serum salanersen concentrations

STELLAR-2

Primary objective: to evaluate the safety and tolerability of salanersen in infants with SMA who received presymptomatic treatment withonasemnogene abeparvovec (OA)

Secondary objectives: to evaluate the efficacy, effect on biomarkers, and PK of adding salanersen 6 months after OA in infants with SMA who received presymptomatic OA treatment

Primary endpoint: safety and tolerability

Safety: incidence of AEs and/or SAEs

Secondary and exploratory endpoints: efficacy

Motor: WHO motor milestones, HINE-2 motor milestones, CHOP-INTEND, HFMSE, RULM

Respiratory and survival: overall survival, time to death or permanent ventilation,[b] ventilation use

Biomarker and electrophysiology: plasma and CSF NfL,[c] CMAP amplitudes

Bulbar: bulbar endpoints

Neurodevelopment and QoL: motor and cognitive development scales, QoL assessment

Other clinical: no SMA symptoms,[f] development of SMA subtypes[e]

Secondary endpoint: PK

PK: CSF and serum salanersen concentrations

[a]Total score and change from Part 2 baseline on Day 730. [b]Permanent ventilation is defined as a tracheostomy or ≥ 16 hours of ventilation per day continuously for > 21 days in the absence of an acute reversible event. [c]NfL is a disease-relevant treatment response biomarker. [d]Proportion of participants who remain free of clinically manifested SMA (clinically manifested SMA will be determined by a decrease of ≥ 2 major weight growth curve percentiles [3rd, 5th, 10th, 25th, or 50th], percutaneous gastric tube placement for nutritional support, and failure to achieve all 6 WHO motor milestones) after completion of Part 1 (Day 365) or study termination with no alternative cause (non-SMA-related) as identified by the Investigator. [e]As assessed by the Investigator. SMA subtypes assessed will be 'sitters', 'standers', and 'walkers'.[4,5] [f]Proportion of participants who remain free of clinically manifested SMA at 12- or 18-month follow-up with no alternative cause (non-SMA-related) as identified by the Investigator.

Figure 2. Key Eligibility Criteria

STELLAR-1

Salanersen monotherapy, N = 30

Inclusion criteria

- Genetically diagnosed 5q SMA[a]
- 2 or 3 *SMN2* copies[b]
- First dose of salanersen at ≤ 42 days of age
- Ulnar CMAP amplitude ≥ 2 mV at Screening and Day 1 predose
- Body weight ≥ 3rd percentile (WHO) at informed consent

Exclusion criteria

- Clinical signs/symptoms suggestive of SMA at Screening or Day 1 in the opinion of the Investigator
- Areflexia at biceps, knee, or ankle at Screening or Day 1 predose
- Any prior SMA DMT (e.g., nusinersen, OA, or risdiplam) or investigational SMA therapy

STELLAR-2

Salanersen after OA, N = 42

Inclusion criteria

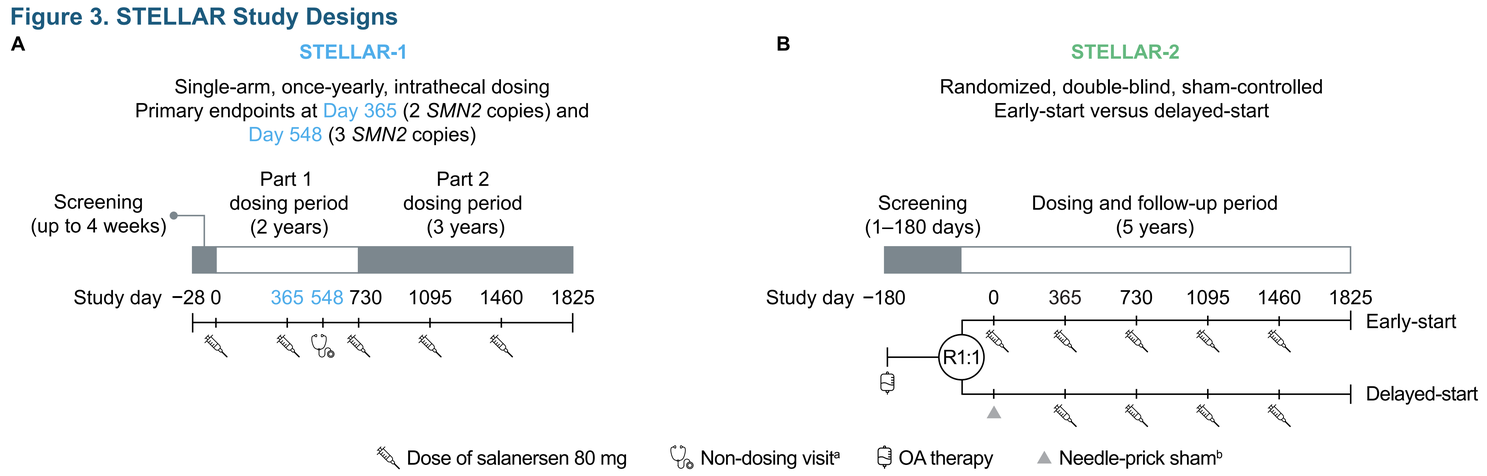
- Genetically diagnosed 5q SMAa and prior OA dose given at ≤ 42 days of age[a]
- 2 *SMN2* copies
- OA dose given at ≤ 42 days of age, and screening initiated < 6 months from OA dosing
- Presymptomatic at OA dosing[c]
- ALT and AST < 2 × ULN off corticosteroids within 30 days prior to Day 1 dose

Exclusion criteria

- Ongoing steroid treatment following OA within 14 days prior to Day 1 dosing/Sham
- Clinically significant abnormal laboratory test values that remain unresolved after screening period, or history of DILI, liver failure, or thrombotic microangiopathy
- Any prior SMA DMT other than OA (e.g., nusinersen or risdiplam) or investigational SMA therapy

Additional eligibility criteria apply.
[a]Genetic documentation of 5q SMA homozygous gene deletion or mutation or compound heterozygous mutation. [b]STELLAR-1 aims to recruit 15 participants with 2 *SMN2* copies and 15 participants with 3 *SMN2* copies. [c]Presymptomatic is defined as: no clinical signs or symptoms at the time of OA dosing that are strongly suggestive of OA; reflexes are present at the time of OA dosing and supported by clinical documentation; ulnar CMAP amplitude ≥ 2 mV.

Figure 3. STELLAR Study Designs



In panel A, after completion of Part 1, participants will continue to Part 2.
In panel B, after receiving OA, participants will attend 2 follow-up clinic visits during the 180-day observation period. After completion of the observation period, participants will be randomized 1:1 into 1 of the 2 treatment arms: early-start of salanersen and delayed-start of salanersen.
[a]Additional non-dosing visits were conducted (not shown). [b]The sham LP procedure will consist of a superficial needle prick on the lower back at the typical LP injection site. The needle will puncture the skin, but will not be inserted further, and no LP injection will be administered.

Acronyms
AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound action muscle potential; CSF = cerebrospinal fluid; DILI = drug-induced liver injury; DMT = disease-modifying therapy; HFMSE = Hammersmith Functional Motor Scale Expanded; HINE-2 = Hammersmith Infant Neurological Examination Section 2; LP = lumbar puncture; NfL = neurofilament light chain; OA = onasemnogene abeparvovec; PK = pharmacokinetics; Q = quarter; QoL = quality of life; R = randomized; RULM = Revised Upper Limb Module; SAE = serious adverse event; SMA = spinal muscular atrophy; *SMN2* = *survival motor neuron 2*; ULN = upper limit of normal; WHO = World Health Organization.

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Disclosures
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Clinical Trial Registration
STELLAR-1, NCT07221669; STELLAR-2, NCT07444450.

*Oral presentation title: Phase 1 Interim Results Evaluating the Safety, Tolerability, Pharmacokinetics, and Exploratory Efficacy of Salanersen for Spinal Muscular Atrophy

STELLAR-1 STUDY STELLAR-2 STUDY

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