
High-dose nusinersen for spinal muscular atrophy: a phase 3 randomized trial

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Supplementary Notes: Methods

Study design

Safety data from DEVOTE Part A were assessed before Part B was initiated, and safety data from Part B were assessed before Part C was initiated.

Participants

In terms of participant eligibility, their age was anchored to the day of their signed informed consent.

Participants in Part C comprised two cohorts. Cohort 1 included individuals of any age, and those at least 18 of age had to be ambulatory. Cohort 2 included individuals at least 18 years of age who were ambulatory or non-ambulatory, had a Hammersmith Functional Motor Scale Expanded (HFMSE) score of at least 4 points and Revised Upper Limb Module (RULM) score entry Item A of at least 3 points at screening, and did not have evidence of severe scoliosis.

Part B inclusion criteria

All participants

1. Signed informed consent of parent or guardian and signed informed assent of the participant, if indicated per participant's age and institutional guidelines.
2. Genetic documentation of 5q spinal muscular atrophy (SMA; homozygous gene deletion, mutation, or compound heterozygote).
3. Ability of the participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.
4. Able to complete all study procedures, measurements, and visits and parent(s) or legal guardian(s)/participant has adequately supportive psychosocial circumstances, in the opinion of the Investigator.

5. Must be compliant with the study travel policy.
6. Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures (as assessed by the Investigator and either anesthesiologist or pulmonologist).
7. All female participants of childbearing potential (defined as any female physiologically capable of becoming pregnant) and all male participants of reproductive age must practice contraception.

Participants with SMA symptom onset ≤ 6 months (≤ 180 days) of age (infantile-onset)

8. Age >1 week to ≤ 7 months (≤ 210 days) at the time of informed consent.
9. *Survival motor neuron 2 (SMN2)* copy number = 2.
10. Onset of clinical signs and symptoms consistent with SMA at ≤ 6 months (≤ 180 days) of age.
11. At Screening, receiving adequate nutrition and hydration, in the opinion of the Investigator.
12. Body weight in at least the third percentile for age using appropriate country-specific guidelines.
13. Gestational age of 37 to 42 weeks for singleton births and 34 to 42 weeks for twins. Infants with a lower gestational age may be considered for enrollment if there are no complications due to prematurity and approval by the Medical Monitor has been granted.

Participants with SMA symptom onset >6 months (>180 days) of age (later-onset)

14. Onset of clinical signs and symptoms consistent with SMA at >6 months (>180 days) of age.
15. Age 2 to <10 years at the time of informed consent.
16. Can sit independently but has never had the ability to walk independently.
17. HFMSE score ≥ 10 and ≤ 54 at Screening.
18. Estimated life expectancy >2 years from Screening, in the opinion of the Investigator.

Part B exclusion criteria

All participants

1. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening period.

2. History of brain or spinal cord disease that would interfere with the lumbar puncture procedures, cerebrospinal fluid (CSF) circulation, or safety assessments.
3. History of bacterial meningitis, viral encephalitis, or hydrocephalus.
4. Presence of an implanted shunt for the drainage of CSF or of an implanted central nervous system (CNS) catheter.
5. Permanent tracheostomy or on permanent ventilation at Screening.
6. Clinically significant abnormalities in hematology or blood chemistry parameters, as assessed by the Investigator, at Screening that would render the participant unsuitable for inclusion.
7. History of systemic hypersensitivity reaction to the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study.
8. Prior scoliosis surgery that would interfere with the lumbar puncture injection procedure.
9. Prior injury (e.g., upper or lower limb fracture) or surgical procedure that affects the participant's ability to perform any of the outcome measure testing required in the protocol and from which the participant has not fully recovered or achieved a stable baseline.
10. Treatment with an investigational drug including but not limited to the treatment of SMA (e.g., oral albuterol/salbutamol, riluzole, carnitine, sodium phenylbutyrate, valproate, and hydroxyurea), biological agent, or device within 30 days or 5 half-lives of the agent, whichever is longer, prior to Screening or anytime during the study; any prior or current treatment with any *SMN2*-splicing modifier or gene therapy; or prior anti-sense oligonucleotide treatment (e.g., nusinersen) or cell transplantation.
11. The participant's parent(s) or legal guardian(s) is unable to understand the nature, scope, and possible consequences of the study or does not agree to comply with the protocol-defined Schedule of Activities.
12. The participant's parent(s) or legal guardian(s) is not willing or able to meet guidelines in the consensus statement for standard of care in SMA or provide nutritional and respiratory support throughout the study, per the Investigator's judgment. Note: Routine vaccinations and respiratory syncytial virus (RSV) prophylaxis are recommended per consensus guidelines on standard of care but are not required for study enrollment. Participants who are not currently on vaccinations or who are not receiving RSV prophylaxis but otherwise meet study inclusion criteria will be considered eligible for study enrollment.

13. Ongoing medical condition that, according to the Investigator, would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the participant to undergo study procedures.
14. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the participant unsuitable for enrollment.

Participants with SMA symptom onset ≤ 6 months (≤ 180 days) of age (infantile-onset)

15. Hypoxemia (O_2 saturation [awake or asleep, without ventilation support] $< 96\%$ at an altitude of < 1500 meters, $< 92\%$ at an altitude of 1500 to 2000 meters, or $< 90\%$ at an altitude > 2000 meters) at Screening.
16. Signs or symptoms of SMA present at birth or within the first week after birth.

Participants with SMA symptom onset > 6 months (> 180 days) of age (later-onset)

17. Hospitalization for surgery (i.e., scoliosis surgery or other surgery), pulmonary event, or nutritional support within 2 months prior to Screening or planned within 12 months after the participant's first dose.
18. Respiratory insufficiency, defined by the medical necessity for invasive or noninvasive ventilation for > 6 hours during a 24-hour period, at Screening.
19. Medical necessity for a gastric feeding tube, where the majority of feeds are given by this route, as assessed by the Investigator.
20. Severe scoliosis evident on X-ray examination at Screening (with the participant in a sitting or supported sitting position). For sites with local regulation on use of X-ray (e.g., Germany), the Investigator may assess scoliosis based on physical examination without imaging.
 - Cobb's angle $> 40.0^\circ$: exclusionary for severe scoliosis.
 - Cobb's angle $< 33.0^\circ$: not exclusionary for severe scoliosis.
 - For participants with a Cobb's angle between 33.0° and 40.0° , inclusive, discussion with the Medical Monitor must occur before determining eligibility.
21. Severe contractures evident at Screening, as determined by clinical judgment of the Investigator (with the participant supine, not in a supported sitting position).

22. Participants who are pregnant or currently breastfeeding, and those intending to become pregnant during the study.

Part C inclusion criteria

All participants

1. Signed informed consent of parent or guardian and signed informed assent of the participant, if indicated per participant's age and institutional guidelines.
2. Currently on nusinersen treatment at the time of Screening, with the first dose being at least 1 year prior to Screening.
3. Genetic documentation of 5q SMA (homozygous gene deletion, mutation, or compound heterozygote).
4. Ability of the participant and/or his/her legally authorized representative (e.g., parent, spouse, or legal guardian), as appropriate and applicable, to understand the purpose and risks of the study, to provide informed consent, and to authorize the use of confidential health information in accordance with national and local privacy regulations.
5. Able to complete all study procedures, measurements, and visits and parent(s) or legal guardian(s)/participant has adequately supportive psychosocial circumstances, in the opinion of the Investigator.
6. Must be compliant with the study travel policy.
7. Meets age-appropriate institutional criteria for use of anesthesia/sedation, if use is planned for study procedures (as assessed by the Investigator and either anesthesiologist or pulmonologist).
8. All female participants of childbearing potential (defined as any female physiologically capable of becoming pregnant) and all male participants of reproductive age must practice contraception.
9. Postmenopausal female participants must be amenorrheic without an alternative medical cause and have a serum follicle-stimulating hormone level >40 mIU/mL for ≥ 12 months prior to Screening or ≥ 6 weeks postsurgical bilateral oophorectomy (with or without hysterectomy) prior to Screening.

Participants in Cohort 1

10. Males and females of any age (individuals ≥ 18 years of age at Screening must be ambulatory).

Participants in Cohort 2

11. Males and females ≥ 18 years of age at Screening (can be ambulatory or nonambulatory).
12. HFMSE total score ≥ 4 points at Screening.
13. RULM entry item A score ≥ 3 points at Screening.

Part C exclusion criteria

All participants

1. Presence of an untreated or inadequately treated active infection requiring systemic antiviral or antimicrobial therapy at any time during the Screening period.
2. History of brain or spinal cord disease that would interfere with the lumbar puncture procedures, CSF circulation, or safety assessments.
3. History of bacterial meningitis, viral encephalitis, or hydrocephalus.
4. Presence of an implanted shunt for the drainage of CSF or of an implanted CNS catheter.
5. Permanent tracheostomy or on permanent ventilation at Screening.
6. Clinically significant abnormalities in hematology or blood chemistry parameters, as assessed by the Investigator, at Screening that would render the participant unsuitable for inclusion.
7. History of systemic hypersensitivity reaction to nusinersen, the excipients contained in the formulation, and if appropriate, any diagnostic agents to be administered during the study.
8. Prior scoliosis surgery that would interfere with the lumbar puncture injection procedure.
9. Prior injury (e.g., upper or lower limb fracture) or surgical procedure that affects the participant's ability to perform any of the outcome measure testing required in the protocol and from which the participant has not fully recovered or achieved a stable baseline.
10. Hospitalization for surgery (i.e., scoliosis surgery or other surgery), pulmonary event, or nutritional support within 2 months prior to Screening or planned within 12 months after the participant's first dose.
11. Participants who are pregnant or currently breastfeeding, and those intending to become pregnant during the study.
12. Concurrent or previous participation and/or administration of nusinersen in another clinical study.

13. Concomitant or previous administration of any *SMN2*-splicing modifier (excluding nusinersen) or gene therapy, either in a clinical study or as part of medical care.
14. Concurrent or previous participation in any interventional investigational study for any other drug or device within 30 days or 5 half-lives of the agent, whichever is longer, prior to Screening.
15. Ongoing medical condition that, according to the Investigator, would interfere with the conduct and assessments of the study. Examples are medical disability other than SMA that would interfere with the assessment of safety or would compromise the ability of the participant to undergo study procedures.
16. The participant or the participant's parent(s) or legal guardian(s) is unable to understand the nature, scope, and possible consequences of the study or does not agree to comply with the protocol-defined Schedule of Activities.
17. The participant or the participant's parent(s) or legal guardian(s) is not willing or able to meet guidelines in the consensus statement for standard of care in SMA or provide nutritional and respiratory support throughout the study, per the Investigator's judgment. Note: Routine vaccinations and RSV prophylaxis are recommended per consensus guidelines on standard of care but are not required for study enrollment. Participants who are not currently on vaccinations or who are not receiving RSV prophylaxis but otherwise meet study inclusion criteria will be considered eligible for study enrollment.
18. Other unspecified reasons that, in the opinion of the Investigator or Sponsor, make the participant unsuitable for enrollment.

Participants in Cohort 2

19. Severe scoliosis evident on X-ray examination at Screening (with the participant in a sitting or supported sitting position). For sites with local regulation on use of X-ray (e.g., Germany), the Investigator may assess scoliosis based on physical examination without imaging.
 - Cobb's angle >40.0°: exclusionary for severe scoliosis.
 - Cobb's angle <33.0°: not exclusionary for severe scoliosis.
 - For participants with a Cobb's angle between 33.0° and 40.0°, inclusive, discussion with the Medical Monitor must occur before determining eligibility.

Procedures

To maintain treatment blinding and ensure the same dosing visit schedule for all groups in Part B, one sham procedure was administered in the 12/12 mg control groups on day 135, three sham procedures were administered in the 50/28 mg groups on days 29, 64, and 183, and day 279 was adjusted in both arms (24 days early for the 12 mg group and 24 days late for the 50/28 mg group). Participants in Part B remained at the clinic for at least 24 hours after treatment administration on days 1 and 15, and inpatient stays at other visits were permitted at the investigator's discretion. Participants in Part C remained at the clinic for at least 24 hours after the bolus dose to allow study assessments to be completed.

Outcomes

The list and ordering of the secondary endpoints was amended in version 7.0 of the protocol in June 2024, based on final negotiations with regulators. These changes included moving analyses comparing high dose nusinersen with the 12/12 mg regimen from exploratory to secondary, despite being underpowered to detect statistical significance, recognizing detection of even trends favoring high dose nusinersen across these analyses would provide important context. These changes were made prior to database lock and analysis of study data.

For NfL assays, NfL concentrations in plasma and CSF were measured using a quantitative Simoa immunoassay validated at Quanterix (Billerica, MA, USA) and CRL (Shrewsbury, MA, USA).

Other secondary endpoints reported for the 50/28 mg group include: Clinical Global Impression of Change (CGIC) at day 302 (responders versus DEVOTE 12/12 mg), number and duration of hospitalizations due to serious adverse events, number of serious respiratory events, ventilation support at day 302 (time and number on ventilation versus DEVOTE 12/12 mg), Parental Assessment of Swallowing Ability (PASA) at day 302 (change from baseline versus DEVOTE 12/12 mg), change in CSF NfL levels over time, and safety (clinical and laboratory assessments).

The pharmacokinetics of nusinersen in plasma and CSF were assessed as an exploratory outcome. Pre-specified and *post hoc* sensitivity analyses were conducted for CHOP-INTEND and HINE-2 results, in order to consider alternative matching approaches and implementations of the joint-rank test (JRT). A *post hoc* exploratory analysis compared 50/28 mg with DEVOTE 12/12 mg for change in swallowing ability using the HINE section 1 (HINE-1)

suck/swallow assessment. A *post hoc* exposure-adjusted analysis using standardized MedDRA queries for pneumonia infective and pneumonia aspiration was conducted.

Statistical analysis

Methods of analysis for efficacy endpoints

Within Part B, to control the overall type 1 error at a 2-sided alpha level of 0.05, a sequential testing procedure ranked in the order of the primary and secondary endpoints was utilized (**Extended Data Table 2**). In this procedure, the primary endpoint of change in CHOP-INTEND total score from baseline to day 183 for the 50/28 mg group compared to the matched sham control group from ENDEAR was tested. If this is statistically significant, then the first secondary endpoint of the proportion of motor milestone responders at day 183 for the 50/28 mg group compared to the matched sham control group from ENDEAR was tested, and so forth in the order of the remaining endpoints. Inferential conclusions about each successive analysis required statistical significance of the prior one.

The primary endpoint compared the 50/28 mg group to the matched sham control group from ENDEAR. The pool of subjects from ENDEAR consisted of N=37 participants who had the opportunity to reach day 183 in ENDEAR.¹ An exhaustive algorithm was utilized to evaluate each combination of selecting X from 37 sham participants and matching to the N=50 in the 50/28 mg arm. The algorithm started with X=37 and if this was unsuccessful, stepped down to X=36 and so on and the lowest allowed was X=20. The similarity between samples was assessed using the absolute standardized mean difference (ASMD).² If the ASMD of sham compared to 50/28mg was ≤ 0.3 for disease duration and baseline CHOP INTEND then this was considered acceptable. If, for a given number of sham patients a number of combinations satisfied the criteria then the robust Mahalanobis distance³ was considered and the one with the smallest distance selected. A total of N=20 Sham control participants from ENDEAR were successfully matched to the 50/28 mg group using this algorithm and were used for the analysis of the primary endpoint and a subset of secondary endpoints.

CHOP-INTEND (primary endpoint): The primary efficacy endpoint of change from baseline to day 183 in CHOP-INTEND total score was analyzed using the joint-rank methodology to account for mortality.⁴ This joint-ranking procedure allowed for a statistical test of the treatment effect on the CHOP-INTEND total score while accounting for loss of data due to deaths. In this analysis, a participant's Combined Assessment of Function and

Survival score was calculated by comparing each participant to every other participant in the study, resulting in a score of +1 if the outcome was better than the participant being compared, -1 if worse, and 0 if the same. The participant's score was then calculated by summing up their comparison to all the other participants in the study. For example, if two participants completed the study up to day 183, their comparison score would be based on the change from baseline in CHOP-INTEND total score at day 183. A participant who died prior to the day 183 visit would rank lower than any participant who completed the study up to day 183. Two participants who both died prior to the day 183 visit would be ranked based on the time of death with a longer time to death corresponding to the higher rank. Hence, in general, these comparisons would result in participants who died being assigned the worst scores and ranked according to the time of death.

Multiple imputation was utilized to impute a missing day 183 value of CHOP-INTEND for participants who discontinued for a reason other than death or where it was not assessed. Participants who have an imputed or available day 183 score were ranked more favorably than participants who died. The ranked scores were analyzed using an analysis of covariance model with treatment included as a fixed effect and adjusted for baseline CHOP-INTEND total score and disease.

Missing data was handled using multiple imputation. 100 complete datasets were produced. Each dataset was analyzed using an ANCOVA model with treatment group as a factor and disease duration and baseline CHOP-INTEND as covariates for the primary endpoint. The estimates from the 100 datasets were combined to provide an overall estimate with corresponding confidence intervals (CIs) and P value.

The trimmed-means method⁵ was performed as a supplementary analysis. The analysis was performed treating all dropouts and deaths as bad outcomes and trimming them out with other observed bad outcomes to form balanced comparison groups. In the trimmed mean approach, response scores were ranked from best to worst, and participants who died were considered as having worse outcomes than those who survived and completed the study. All response scores in the treatment group with high mortality/dropout rate were retained. In the treatment group with the higher survival/completion rate, only the same proportion (as the survival rate in the high-mortality group) of the top response scores were retained. The trimmed-mean difference can be interpreted as the difference between the top fraction of responses between the two groups. The *P* value associated with the difference test statistics was calculated using a reference distribution generated by a rerandomization procedure.

CHOP-INTEND sensitivity analyses (Part B infantile-onset): Sensitivity analyses were pre-specified to consider alternative matching approaches and implementations of the JRT. Three alternative matching approaches were implemented: i) the same algorithm used for the primary approach was implemented using all 75 participants in the intent-to-treat set as the target to match, rather than the 50 participants who received 50/28 mg nusinersen, ii) a greedy matching algorithm was used and managed to match 1:1, 25 participants receiving sham with 25 participants receiving 50/28 mg, iii) all 37 available sham participants were utilized.

Sensitivity analyses to explore different implementations of the JRT, summarized in Forest plots, included:

- Adjustment of the JRT implementation to consider withdrawals not due to death as a third group which is ranked lower than those who did not die or withdraw.
- Adjustment of the JRT implementation to consider participants who reached permanent ventilation as a third group, ranked lower than those who did not die or get permanent ventilation.

HINE-2 motor milestone responders: The difference in the proportion of responders between treatment groups was compared using logistic regression with the number of motor milestones at baseline, age at symptom onset, and disease duration at screening as covariates. Should the number of responders be less than five in either group, Fisher's exact test was used instead. If Fisher's exact test was used, the unconditional confidence interval for the difference in response rates was provided.⁶

Total HINE-2: Motor milestones change from baseline to day 183 for 50/28 mg versus matched sham and change from baseline to day 302 for 50/28 mg versus 12/12 mg were analyzed using the same methodology as described for the primary endpoint and summarized in Forest plots.

Plasma neurofilament: For plasma NfL, if the baseline assessment is missing, then the first available assessment post dose within day 2 was used instead as baseline. Values that were below the limit of quantification were set to half of the diluted lower limit of quantification. Change in plasma NfL from (ratio to) baseline to day 183 was analyzed for 50/28 mg versus matched sham and change in plasma NfL from baseline to day 29 was analyzed for 50/28 mg versus 12/12 mg using the same method as for the primary endpoint.

CHOP-INTEND: Change in CHOP-INTEND from baseline to day 302 was analyzed for 50/28 mg versus 12/12 mg using the same methodology as described for the primary endpoint.

Time to death or permanent ventilation (event-free survival, EFS): Permanent ventilation is defined as tracheostomy or ≥ 16 hours of ventilation/day continuously for >21 days in the absence of an acute reversible event. An independent Endpoint Adjudication Committee determined, in a blinded fashion, the date at which a participant was considered to have met the definition of an event. The procedures for reviewing and adjudicating events were described in a charter. The time to death or permanent ventilation (tracheostomy or ≥ 16 hours of ventilation/day continuously for >21 days in the absence of an acute reversible event) and time to death (overall survival) were analyzed using the log-rank test stratified by disease duration at screening. The null hypothesis was that the comparison groups (i.e., 50/28 mg dose and matched sham) have the same “survival” function. Participants who did not meet the endpoint definition were censored at the last occasion the participant was seen (either in-person visit or by telephone contact), irrespective of whether the participant had completed the full course of treatment and whether the participant had completed the study or permanently withdrawn. The exception was time to death or permanent ventilation in cases in which a participant had begun a ventilator diary, in which case the latest entry in the diary would be used as the date of censoring. The proportion of participants meeting an event at time points of interest were estimated using the Kaplan–Meier method. The analysis would also be performed for the comparison of 50/28 mg versus matched sham and the comparison of 50/28 mg versus 12/12 mg doses.

Time to death: Overall survival was analyzed in the same way as time to death or permanent ventilation.

Later-onset matching

As part of the study design, the eligibility criteria and endpoints for participants with later-onset SMA in DEVOTE were harmonized to be consistent with participants in the CHERISH trial. Owing to the different dosing schedules between the trials, efficacy data were collected at slightly different time points. For the purposes of data presentations from the DEVOTE trial, data at day 183 and day 279 will be utilized and the corresponding days for CHERISH are day 169 and day 274.

The approach to matching DEVOTE participants with later-onset SMA with the CHERISH trial was pre-specified. The first step was attempting to find a matching group using optimal matching. Covariates included in the propensity score model included age, age at onset, and *SMN2* copy number. Sex, baseline HFMSE, and a caliper width of 0.25 times the propensity score was selected. These matching attempts were not successful and the pre-specified alternative method which was optimal matching with an ASMD ≤ 0.3 for age and baseline function was

attempted and achieved successful matches. Matching attempts were as follows: matching to 12/12 mg, 3:1, 2:1, and 1:1; matching to sham, 2:1 and 1:1.

Sample size

The sample size for the 50/28 mg comparison to sham control was based on simulations using data generated from a joint model of survival and functional change. In order to estimate the sample size required to demonstrate statistical difference between 50/28 mg and 12/12 mg, a similar model was used. The parameter estimates were based on the 12 mg CS3B results, and the 50/28 mg arm assumed a 5-point benefit in CHOP-INTEND and 4% survival benefit at day 302. It was estimated that a sample size of N=180 would be required to achieve 80% power with a two-sided alpha of 0.05.

Study investigators

DEVOTE **Principal Investigators** and study site personnel who enrolled participants are listed by country below:

Brazil: **Jonas Alex Morales Saute, MD**, Ana Leticia Amorim de Albuquerque, MD, Michele Becker, MD, Fernanda Brenda Possetto, Vitória Brum Silva Nunes, Renato Chagas Ribeiro, Edlus Colares, Larissa Pozzebon da Silva, Karina Donis, MD, Bruno Dorr, Daniel Fasolo, Ana Luiza Fonseca Siqueira, MD, Esteban Gonzales, Gerson Guerra, Mariana Horn Scherer, MD, Ana Luisa Fernandes Dubiela, Thais Martins, MD, Elaine Miglorini, MD, Márcia Narcizo Rodrigues, Johanna Nehm, Karen Daniela Picolli Lucas, Ana Lucia Portella Staub, MD, Rodrigo Rosa de Stefani, MD, Marina Bauer Zambrano, Joao Henrique Zucco Viesi, MD; **Juliana Gurgel Giannetti, MD**, Maria Eduarda Amaral Pinto, Marina Belisario Carvalhais, Vanilda Borges, Arianne Caroline Rocha, Mariana Ferreira Bizzi, Patricia Ferreira Fonseca, Baltazar Leao Reis, Márcia Maria Leonardo, Hannelore Maciel, Bruna Magalhaes, Ana Carolina Monteiro Lessa de Moura, Beatriz Vilela Moraes de Azevedo, MD, Josyene Simão, Sabrina Stephanie Lana Diniz, Gilzani Teixeira da Cunha, Alexandre Varella Gianetti; **Edmar Zanoteli, MD**, Mariana Artilheiro, MD, Juliana Caires de Oliveira Achili Ferreira, Umbertina Conti Reed, MD, Rodrigo de Holanda, MD, Ana Cristina dos Santos Monteiro, Clara Gontijo Camelo, MD, Juliana Iannicelli, MD, Luiz Henrique Libardi, MD, Ciro Matsui, MD, Fernanda Nunes, Helio Rodrigues Gomes, MD, Thais Tiemi Araki;

Canada: **Craig Campbell, MD**, Sulaiman Al-Mobarak, MD, Chantal Cacciotti, Melissa Greenwood, Cara Grobbeck, Rhiannon Hicks, Mona Hnaini, MD, Teresa Longfield, Michael Mayich, Cheryl Scholtes, Mona ElWanni, Kayleigh Tam;

Chile: **Claudia Castiglioni, MD**, Damaris Colicheo, Marianela De la Fuente, Jose Miguel Guanipa, Javiera Figueroa Jofre Ines, MD, Valeria Jorquera, Jaime Lara Sasso, Constanza Larraguibel, Pamela Andrea Lolas Mutis, Valentina Martínez, Marcia Ocares, Maria Angelica Palomino Montenegro, MD, Gonzalo Rivera, MD, Valentina Seguel, Bernardita Isabel Suarez Squadritto, MD; **Ricardo Erazo, MD**, Patricia Acuña, Rudy Clavero Bocca, MD, Sebastian Eulufi Munoz, MD, Pamela Alejandra Figueroa Ojeda, MD, Jorge Ignacio Galecio Moraga, MD, Patricio Lacaux, MD, Daniela Constanza Mistretta Solorza, MD, Mariana Munoz, Salomé Rivera, Constanza Ruiz;

China: **Hui Xiong, MD**, Wenzhu Li, MD, Lun Qin, Cuijie Wei, Jingyao Xu, Xinyu Zhao; **Shanshan Mao, MD**, Tingting Chen, Guoxia Sheng, Lu Xu, Zihao Yang, Congying Zhao, MD; **Li Liu, MD**, Rong Du, MD, Yuyu Feng, MD, Minyan Jiang, MD, Duan Li, MD, Cuili Liang, MD, Ruizhu Lin, MD, Zhikun Lu, MD, Huifen Mei, MD, Xiaoyue Wang, Kaishou Xu, Wen Zhang, MD, Yani Zhang, MD, Ruidan Zheng, MD;

Colombia: **Edna Julieth Bobadilla Quesada, MD**, Fernando Suarez Obando, MD, Angelica Maria Amador Gutierrez, Angelica Maria Arango Gutierrez, Nixon Giovany Archila Rodriguez, Stela del Pilar Baracaldo Gomez, MD, Diana Carol Benitez Ramirez, MD, Maria Alejandra Betancur Diaz, MD, Juliana Andrea Bravo Gallego, Diego Alberto Caicedo Callejas, Angie Kares Cardona Camacho, Paula Cordon, Martha Beatriz Delgado Ramirez, MD, Edy Yesenia Diaz Garrido, MD, Christian Javier Duarte Parra, Veronica Echeverry Mallarino, MD, Lady Gonzales, Viviana Marcela Mendez Calderon, Luis Morillo, MD, Ivonne Katherine Sabogal Alfaro, Diana Ximena Salgado, Alejandra Sanin Hoyos, MD, Diana Pilar Soto Pena, MD, Jenny Marcela Velasco Ramirez, Natalia Velasquez Leon;

Germany: **Astrid Pechmann, MD**, Stefanie Ajayi, Sabine Borell, MD, Simone Bürklin, Matthias Eckenweiler, MD, Juliane Hug, Janbernd Kirschner, Stefanie Koelble, Thorsten Langer, MD, Inka Lotz, Beate Lubrich, MD, Nadja Mingirulli, MD, Cornelia Mueller, MD, Bianca Rippberger, David Schorling, MD, Marleen Schulz, Sabine Stein, Pirmin Tritschler, Sibylle Vogt, Silke Wehrle, Anja Wehrle, Sabine Wider, Barbara Wirth, Theresa Woltering; **Andreas Hahn, MD**, Thea Beatrice Abele, MD, Katharina Biesgen, Bodo Fleischer, Andrea Hackemer, Renate Hepp, MD, Mareike Hohmann, Christina Lampe, MD, Annina Lang, Kyriakos Martakis, MD, Evelyn Morbitzer, Kathy Rausch, Verena Rolz, Lena Russ, Annabell Schantz, Doris Stahl;

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Russian Federation: **Dmitry Vladmirovich Vlodavets, MD**, Svetlana Artemyeva, MD, Antonina Grigorieva, MD, Tatyana Okhapkina, MD, Yulia Papina, MD, Olga Shidlovskaya, MD, Irina Shulyakova, MD; **Olga Lvova, MD**, Kristina Nevmerzhtskaya, MD, Elena Sapego, MD, Inna Tuktareva;

Saudi Arabia: **Ali Al Shehri, MD**, Mahmoud Abu Riash, Musaad Abukhalid, MD, Fatima Ahmed, Nouf Al Ashwal, Abdullah Ali Al Nowaiser, Weaam Alammar, MD, Mohammad Al-Muhaizea, MD, Riyadh Al-Okaili, MD, Haya Alothaimeen, Mashael Alsaud, MD, Dalal Ghouth Alsayed, Joti Bhattacharya, MD, Marjorie Dador, Rozeena Huma, MD, Francis Limjuico, Ghaliah Omar Alzaid, Samar Talal Nouri; **Fouad Alghamdi, MD**, Walaa Abdulgader, Walaa Khaled AI-Abdulqader, MD, Tasneem Al Atwi, Lamees Algain, MD, Fatema Almatrook, Manar Saud Al-Otaibi, MD, Fawzia Amer, MD, Mahammad Awadalla, Zakaria Basbous, Amina Bukhamsin, Shaikha Dossary, Reem Gaw, Mona Ibrahim Mohammed Ali, MD, Abdullah Ahmed Saadi AlGhamdi, MD, Merhana Sahi; **Nahla Alshaikh, MD**, Hisham Aburjeila, Mushtaha Ahmed, Mona Al Jehani, Hani Al Sawadi, MD, Khaled Algarny, Mohammed Alharbi, Maha Gashlan, MD, Alaa Rasool, Raneem Sedayou, Mohammad Tamboosi;

Spain: **Gloria Lopez Sobrino, MD**, Samuel Ignacio Pascual Pascual, MD, Sofia Bueno, Paul Burnham, Jose Manuel Caballero, MD, Cristina Cardenas Sarralde, Cristina Contreras Olmedo, Milagros Coso, Maria del Rio Durango, Maria Espinosa, MD, Ariadna Fernandez, Janire Fernandez Cuenca, María García Romero, MD, Pilar Gomez Salcedo, Yaqing Huang, Jose Lopez Araujo, Isabel Malpartida Jimenez, Mercedes Martinez Moreno, Fatima Mendoza Duran, Carmen Munoz Jimenez, Anaïs Sevillano Blanco, Andrea Tejedor Perez, Nuria Torre Buxalleu; **Andres Nascimento Osorio, MD**, Marta Sanchez, MD, Laura Sole Heuberger, Alicia Rodriguez Ramirez, Laura Carrera Garcia, MD, Alba Martinez, Obdulia Moya Arcos, Sandra Roca Urraca, Maria Valle Saez, Daniel Natera de Benito, MD, Jesica Maria Exposito Escudero, MD, Carlos Ignatio Orteiz Gonzalez, MD, Julia Medina Cantillo, MD,

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United States: **John Day, MD**, Tiffany Chang, Steven Chinn, MD, James Cutler, Genevieve D Souza, MD, Sally
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Changes during the study were as follows: Dr. Edna Julieth Bobadilla Quesada assumed responsibility of Principal Investigator from Dr. Fernando Suarez Obando; Dr. Astrid Pechmann assumed responsibility of Principal Investigator for the study from Dr. Sabine Borell; Dr. Juan Carlos Garcia Beristain assumed responsibility of Principal Investigator for the study from Dr. Eduardo Javier Barragan Perez; Dr. Gloria Lopez Sobrino assumed responsibility of Principal Investigator from Dr. Samuel Ignacio Pascual Pascual; Dr Susan Iannaccone assumed responsibility of Principal Investigator from Dr. Diana Castro.

The Physical Therapist Advisory Board comprised: Matt Civitello, Giorgia Coratti, Sally Dunaway Young, Richard Gee, Allan Glanzman, Kristin Krosschell, Anna Mayhew, Elena Mazzone, Jacqueline Montes, Leslie Nelson, Kristy Rose, Elise Townsend, and Chris Yun.

Owing to operational considerations, samples from participants at sites in China were tested locally. As pre-specified in the statistical analysis plan, data from these participants were excluded from this analysis as the samples were not tested in the same batch as the global samples.

Ethics approval

List of ethics committees / institutional review boards that approved the protocol for Part B:

Akdeniz University School of Medicine Clinical Trials Ethics Committee; Ann & Robert H. Lurie Children's Hospital of Chicago Institutional Review Board; Azienda Socio Sanitaria Territoriale Niguarda (Grande Ospedale Metropolitano Niguarda); Boston Children's Hospital IRB; CEIm Iislafe (Instituto de Investigación Sanitaria La Fe); Centrale Commissie Mensgebonden Onderzoek; CEP da Faculdade de Medicina da Universidade de São Paulo - FMUSP/SP; CEP da Universidade Federal de Minas Gerais; Children's Health Ireland (CHI) at Crumlin-Ethics (Medical Research) Committee; Clinical Trial Ethical Committee of West China Second Hospital, Sichuan University; Comitato Etico del l'Università Cattolica del Sacro Cuore e annesso Policlinico "A. Gemelli"; Comité de Ética de Investigación en Seres Humanos (CEISH); Comité de Ética de la Investigación Fundación; Comité de Ética en Investigación del Hospital Civil de Guadalajara Fray Antonio Alcalde; Comité de Ética en Investigación del Instituto Nacional de Pediatría; Comité de Ética en Investigación Hospital Infantil de México Federico Gómez; Comité de Investigaciones y Ética Institucional (CIEI); Copernicus Group IRB; CPP Ile de France 5, Hôpital Saint-Antoine; EC of Beijing Children's Hospital; EC of Children's Hospital of Chongqing Medical University; EC of Peking University First Hospital; EC of Qilu Hospital of Shandong University; Ethics Committee for Clinical Trials of Medicinal Products (Latvia); Ethics Committee of King Faisal Specialist Hospital and Research Centre; Ethics Committee of National Guards Health Affairs (Riyadh); Ethik-Kommission der medizinischen Fakultät der Albert-Ludwigs-Universität Freiburg i. Br.; Great Ormond Street Hospital for Children NHS Trust; Guangzhou Women and Children's Medical Center; Hospital de Clínicas de Porto Alegre CEP; Institutional Review Board of Hyogo College of Medicine College Hospital; IRB for Saint George Hospital (Beirut); IRB of Kyungpook National University Chilgok Hospital; IRB of Seoul National University Hospital; Johns Hopkins University IRB; Joint Institutional Review Board / Sanyo Kochi; Kaohsiung Medical University Chung-Ho Memorial Hospital Institutional Review Board; KFSH-D Institutional Review Board; Komisja Biotyczna przy Instytucie – Pomnik-Centrum Zdrowia Dziecka; LEC at Regional Pediatric Clinical Hospital #1; LEC at SBEI HPE " Russian National Research Medical University n.a. N.I. Pirogov" of the MoH; Medical Ethics Committee of The Children's Hospital Zhejiang University School of Medicine; Medical Ethics Committee of Xiangya Hospital of Central South University; Medical Research Council of Ethics Committee for Clinical Pharmacology (Hungary); National Ethics

Committee (Athens Greece); National Taiwan University Hospital, Research Ethics Committee; Rabin MC EC Committee; Research Ethics Committee of the National Institute for Health Development (Estonia); Research Western (Ontario, Canada); Royal Children's Hospital Human Research Ethics Committee; St. Jude Children's Research Hospital IRB; Stanford IRB Research Compliance Office; Tel-Aviv Sourasky; Tokyo Women's Medical University Institutional Review Board; UBC Children's & Women's REB; Western Institutional Review Board (WIRB).

List of ethics committees / institutional review boards that approved the protocol for Part C:

Ann & Robert H. Lurie Children's Hospital of Chicago Institutional Review Board; Azienda Socio Sanitaria Territoriale Niguarda (Grande Ospedale Metropolitano Niguarda); Boston Children's Hospital IRB; CEIm Iislafe (Instituto de Investigación Sanitaria La Fe); Comitato Etico del l'Università Cattolica del Sacro Cuore e annesso Policlinico "A. Gemelli"; Copernicus Group IRB; Ethik-Kommission der medizinischen Fakultät der Albert-Ludwigs-Universität Freiburg i.Br.; Institutional Review Board of Hyogo College of Medicine College Hospital; Johns Hopkins University IRB; Joint Institutional Review Board / Sanyo; Research Western (Ontario, Canada); St. Jude Children's Research Hospital IRB; Stanford IRB Research Compliance Office; Tokyo Women's Medical University Institutional Review Board; Western Institutional Review Board (WIRB).

Supplementary Notes: Results

Pharmacokinetics of nusinersen (exploratory outcome)

In Part B, plasma concentrations of nusinersen increased approximately linearly with dose, with no evidence of accumulation after multiple doses (**Supplementary Fig. 2 and 3**). On day 1, area under the concentration–time curve from 0 to 24 hours (AUC_{0-24h}) increased 5- and 7.4-fold from 12 to 50 mg in participants with infantile-onset SMA and later-onset SMA, respectively, whereas C_{max} increased 4.6- and 9.3-fold, respectively (**Extended Data Table 3**). A substantially higher increase in exposure for participants with later-onset SMA can be attributed to the relatively small number of participants in this cohort.

Dose proportionality in plasma was also supported by the individual C_{trough} across the entire duration of Part B (**Supplementary Fig. 3**). Plasma C_{trough} values were approximately 4- to 5-fold higher in the 50/28 mg group compared with the 12/12 mg group on day 15 (**Extended Data Table 3**). On day 279, plasma trough concentrations of nusinersen were approximately 2-fold higher in the 50/28 mg group (geometric mean: 2.0 ng/mL; the preceding dose of 28 mg was administered 144 days earlier) than in the 12/12 mg group (geometric mean: 0.9 ng/mL; the preceding dose of 12 mg was administered 96 days earlier) in participants with infantile-onset SMA (**Extended Data Table 3**). A <2-fold ratio between plasma trough concentrations in the 50/28 mg group (geometric mean: 0.8 ng/mL) and the 12/12 mg group (0.6 ng/mL) was observed on day 279 in participants with later-onset SMA (**Extended Data Table 3**). Lower-than-dose-proportional increase in plasma concentration between 12 mg and 28 mg on day 279 is associated with a 48-day longer follow-up period in the 50/28 mg group compared with the 12/12 mg group, and with highly variable plasma concentration readouts at trough points.

In Part B, a less-than-dose-proportional increase in CSF C_{trough} levels was observed over the range of 12 to 50 mg doses. As illustrated in **Supplementary Fig. 4**, in participants with infantile-onset SMA, CSF C_{trough} of nusinersen was approximately 2-fold higher following the 50 mg dose compared with the 12 mg dose on day 15 (geometric mean: 7.9 versus 3.4 ng/mL). About the same 2-fold difference in CSF trough levels was also observed in participants with later-onset SMA (geometric mean: 7.8 versus 4.5 ng/mL). Higher variability was observed in the 50/28 mg group compared with the 12/12 mg group.

CSF C_{trough} of nusinersen on day 15 in the 50/28 mg group were similar to those observed in the 12/12 mg group before the last loading dose of the standard dosing regimen (day 64) for both SMA-onset types (**Supplementary Fig. 5**). Although the increase in CSF exposures is less-than-dose-proportional, the 50/28 mg dose regimen achieves higher CSF C_{trough} levels faster (one dose of 50 mg versus three doses of 12 mg). In the 50/28 mg dose regimen including two loading doses of 50 mg, mean CSF C_{trough} levels after each loading dose and subsequent maintenance doses remained similar, at least for the duration of Part B study (**Supplementary Fig. 5**). CSF C_{trough} levels were similar between the two groups on day 279 (**Supplementary Fig. 5**) in both SMA-onset types. It should be noted that over the duration of Part B, proportionality of CSF trough exposures with dose cannot be evaluated based on side-by-side comparison of time-dependent profiles from the two dosing regimens owing to different dosing schedules. Moreover, the absence of significant difference in CSF C_{trough} on day 279 between the 12/12 mg and 50/28 mg groups can be partially explained by matching the schedules for the two groups on day 279: this pre-dose measurement was 24 days (20%) earlier than the target trough point for the 12/12 mg group and 24 days (20%) later than the target trough point for the 50/28 mg group. Since the day 279 observation was made within the elimination phase of trough CSF concentration, the 20% shorter follow-up in the 12/12 mg group caused higher concentration readouts, whereas the 20% longer follow-up in the 50/28 mg group resulted in lower concentration readouts.

In Part C, the baseline geometric mean (95% confidence interval [CI]) plasma nusinersen concentration was 0.2154 (0.174, 0.266) ng/mL. Plasma nusinersen pre-dose concentrations slightly increased but remained low over the duration of Part C.

Part C enrolled participants who were currently on 12/12 mg nusinersen at the time of screening, with the first dose being at least 1 year prior to screening. The median time on 12/12 mg nusinersen at baseline was 3.9 years. In participants with prior 12/12 mg nusinersen exposure of <3.9 years, baseline geometric mean (95% CI) CSF concentration of nusinersen was 13.447 (11.295, 16.009) ng/mL, with a median CSF concentration of 14.020 ng/mL. In participants with prior 12/12 mg nusinersen exposure of ≥ 3.9 years, the baseline geometric mean (95% CI) CSF concentration of nusinersen was 16.819 (13.118, 21.564) ng/mL, with a median CSF concentration of 15.010 ng/mL. For all participants, baseline CSF concentrations of nusinersen increased rapidly following the 50 mg loading dose on day 1 and the higher concentrations were maintained during the maintenance dose period of Part C. In participants with prior 12/12 mg nusinersen exposure of <3.9 years, the day 241 (pre-dose) geometric mean

(95% CI) CSF concentration of nusinersen was 15.593 (12.542, 19.386) ng/mL, with a median of 17.730 ng/mL. In participants with prior 12/12 mg nusinersen exposure of ≥ 3.9 years, the day 241 (pre-dose) geometric mean (95% CI) CSF concentration of nusinersen was 20.53 (16.392, 25.713) ng/mL, with a median of 18.480 ng/mL.

Post hoc or sensitivity analyses

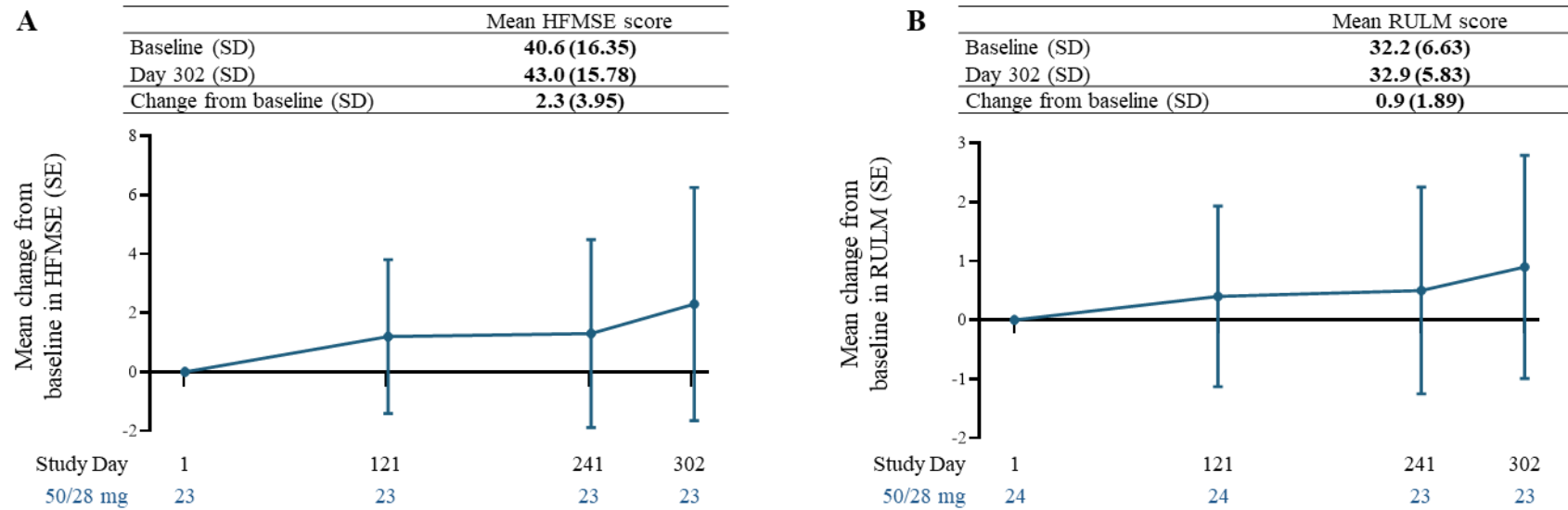
In the Part B infantile-onset cohort, given possible differences in exposure time between the 50/28 mg and ENDEAR matched sham groups since participants receiving treatment lived longer, a *post hoc* exposure-adjusted analysis was performed utilizing the standardized MedDRA queries for pneumonia infective and pneumonia aspiration. The exposure-adjusted incidence per 100 person-years for pneumonia infective was lower in the 50/28 mg group (117.5 events per 100 person-years) compared with the ENDEAR matched sham group (203.2 events per 100 person-years). However, the exposure-adjusted incidence per 100 person-years for pneumonia aspiration was higher in the 50/28 mg group (21.8 events per 100 person-years) compared with the ENDEAR matched sham group (8.5 events per 100 person-years).

In pre-defined sensitivity analyses of the primary endpoint using different matched sets/approaches for handling withdrawals, the results were consistent with those from the main analysis. Post hoc sensitivity analyses were conducted to assess different approaches to handle missing data and deaths for the 50/28 mg comparison versus 12/12 mg for CHOP-INTEND and HINE-2 (**Extended Data Fig. 7 and Supplementary Fig. 6**). Although consistent with the main analysis, none of these were statistically significant. It was noted that the HINE-2 results consistently favored 50/28 mg, whereas CHOP-INTEND results varied depending on the analysis.

In a post hoc exploratory analysis, compared with the DEVOTE 12/12 mg group, the 50/28 mg group was associated with greater swallowing ability as per HINE-1 suck/swallow assessment (**Extended Data Table 1**).

Supplementary Figures

Supplementary Figure 1. Part C – HFMSE (A) and RULM (B) in adult participants aged ≥ 18 years (n=24)

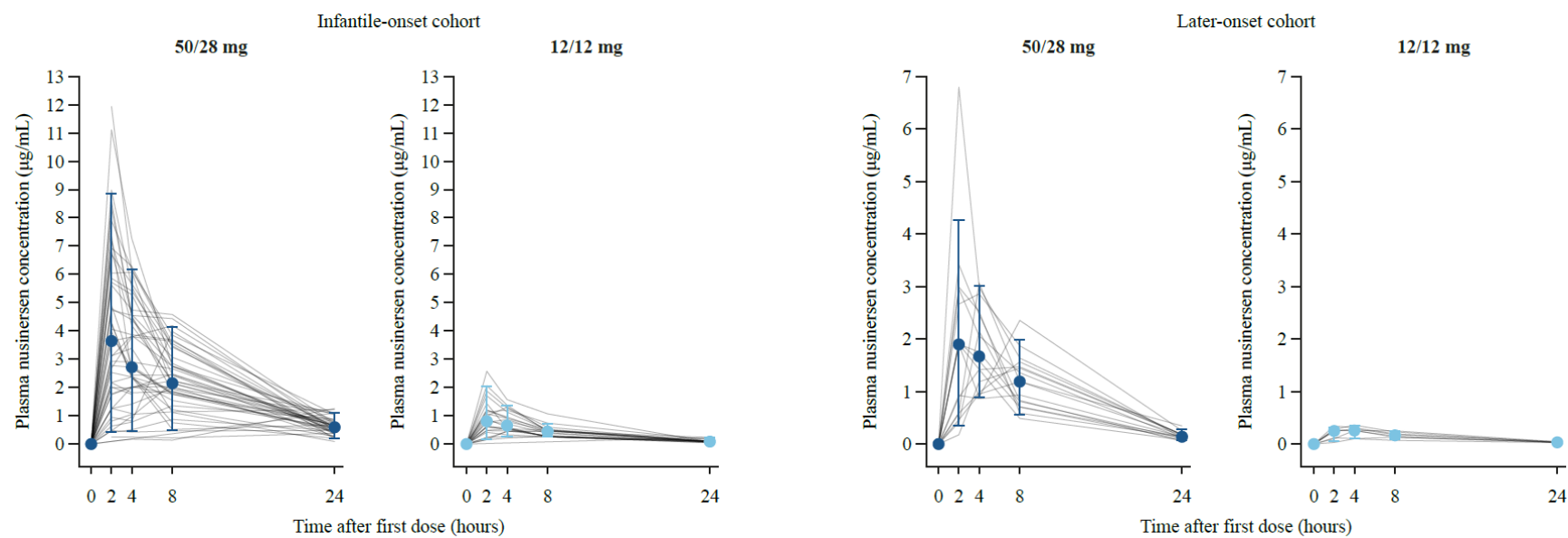


Study day 1 is baseline.

Observed data and mean change are shown.

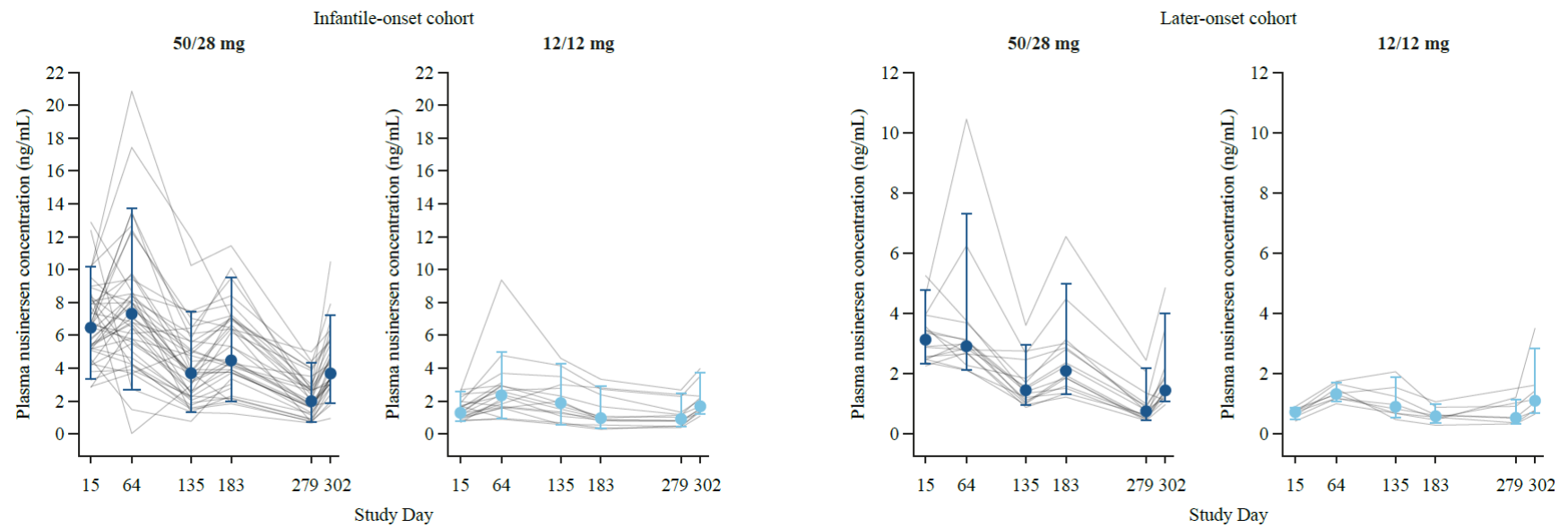
HFMSE, Hammersmith Functional Motor Scale Expanded; RULM, Revised Upper Limb Module; SD, standard deviation; SE, standard error.

Supplementary Figure 2. Part B – Individual plasma concentration profiles over 24 hours after the first dose of 12 mg and 50 mg nusinersen



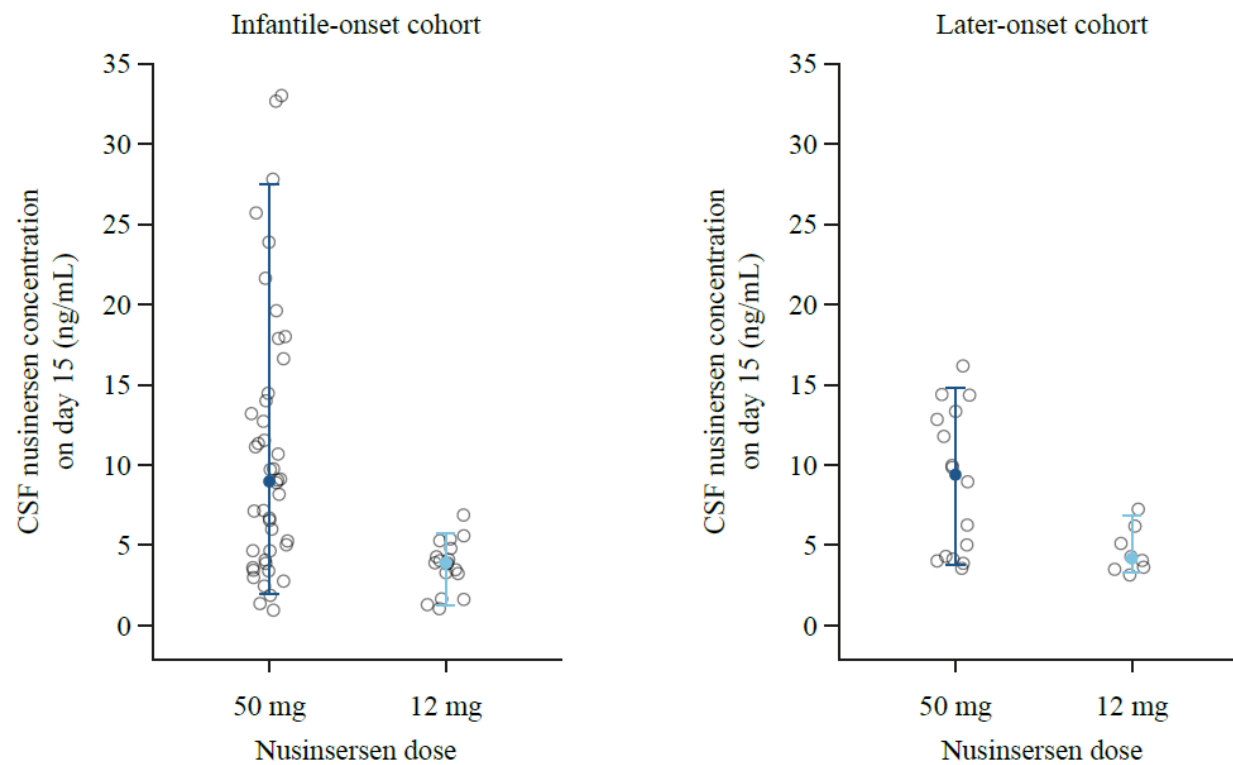
Summary data represent median with 5th and 95th percentiles. Lines represent individual participants.

Supplementary Figure 3. Part B – Plasma C_{trough} levels by visit day



Summary data represent median with 5th and 95th percentiles. Lines represent individual participants.

Supplementary Figure 4. Part B – Comparison of CSF C_{trough} levels after the first dose (day 15) of 12 mg and 50 mg nusinersen

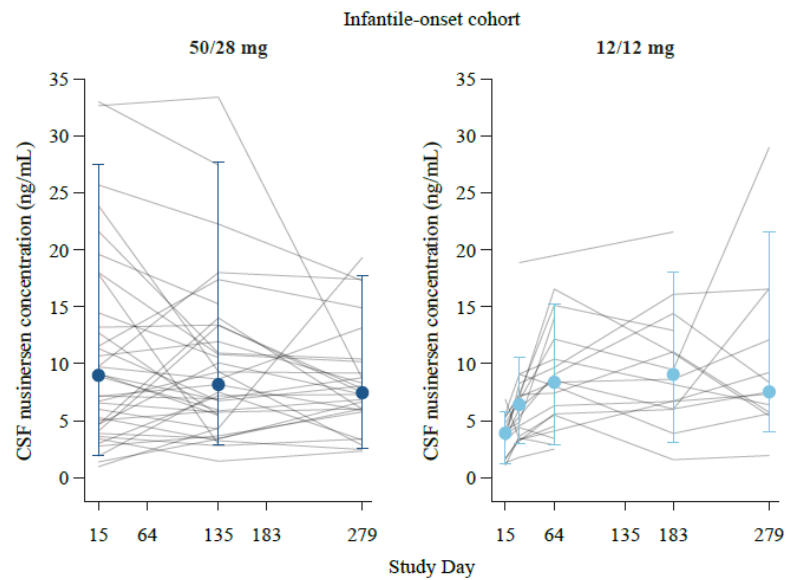


Summary data represent median with 5th and 95th percentiles. Circles represent individual participants.

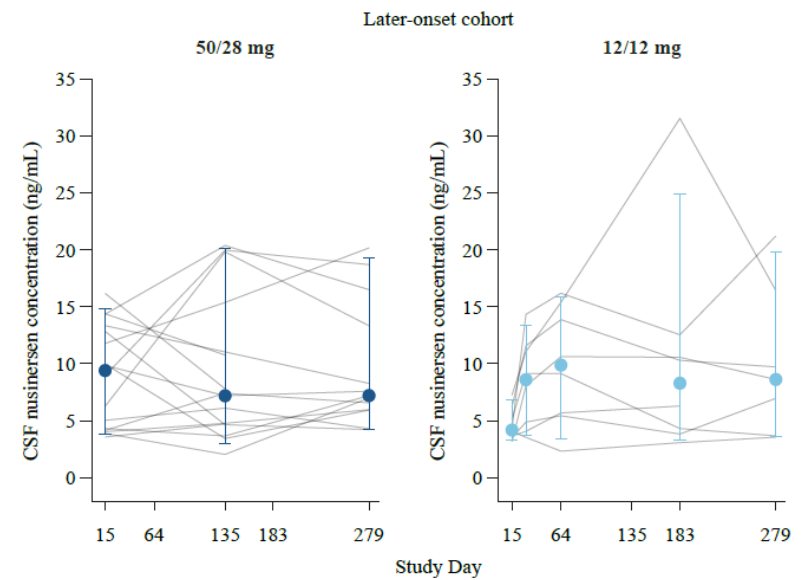
CSF, cerebrospinal fluid.

Supplementary Figure 5. Part B – CSF C_{trough} levels by visit day

A



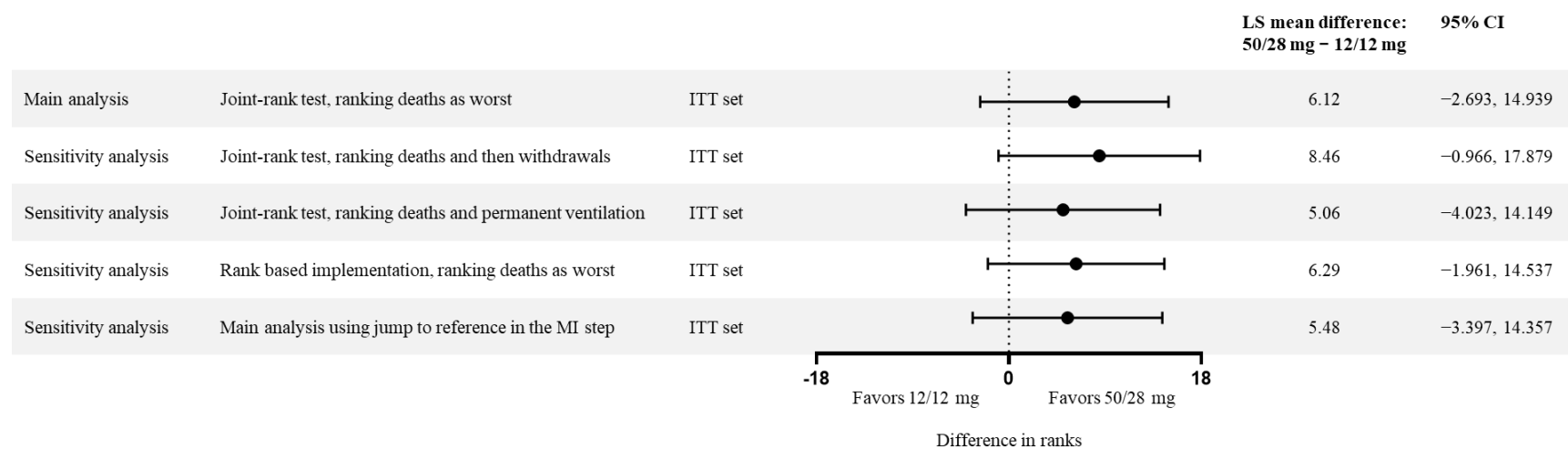
B



Summary data represent median with 5th and 95th percentiles. Lines represent individual participants.

CSF, cerebrospinal fluid.

Supplementary Figure 6. Part B infantile-onset cohort – HINE-2 sensitivity analyses



CI, confidence interval; HINE-2, Hammersmith Infant Neurological Exam section 2; ITT, intent-to-treat; LS, least-squares; MI, multiple imputation.

Supplementary references

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3. Rosenbaum, P.R. *Design of Observational Studies* (Springer-Verlag New York Inc. Press, 2010).
4. Berry, J.D., et al. The Combined Assessment of Function and Survival (CAFS): a new endpoint for ALS clinical trials. *Amyotroph Lateral Schler Frontotemporal Degener* 14, 162–168 (2013).
5. Permutt, T. and Li, F. Trimmed means for symptom trials with dropouts. *Pharm Stat* 16, 20–28 (2017).
6. Santner, T.J. and Snell, M.K. Small-sample confidence intervals for $p_1 - p_2$ and p_1/p_2 in 2×2 contingency tables. *J Am Statist Assoc* 75, 386–394 (1980).