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Exploring Higher Doses of Nusinersen in Spinal Muscular Atrophy: Final Results From Parts B and C of the 3-Part DEVOTE Study

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Objective

- To examine the safety and efficacy of a novel higher-dose regimen of nusinersen in:
  - treatment-naïve participants with infantile-onset and later-onset SMA enrolled in DEVOTE Part B
  - participants who transitioned from the currently approved 12/12mg regimen[1,2] in DEVOTE Part C.

Conclusions

- The 50/28mg regimen was well tolerated with a safety profile broadly consistent with the 12/12mg regimen.
- The 50/28mg regimen led to greater plasma NfL reductions at earlier time points than the 12/12mg regimen, indicating a more rapid slowing of neurodegeneration.
- In treatment-naïve infantile-onset participants, the 50/28mg group demonstrated clinically and statistically significant ($p < 0.0001$) improvement over the prespecified matched sham group for 6-month change in CHOP-INTEND score from baseline (primary endpoint).
- Infantile-onset results generally favored the 50/28mg group over the 12/12mg group and the matched sham group across secondary endpoints, including event-free survival.
- Results for treatment-naïve later-onset participants at Day 302 trended in favor of the 50/28mg group over the DEVOTE 12/12mg group, as well as the matched 12/12mg and sham groups from CHERISH, for HFMSE and RULM.
- Improvements in HFMSE and RULM scores were observed in a diverse cohort (aged 4–65 years) who transitioned to the 50/28mg regimen after several years on the 12/12mg regimen.

Introduction

- Nusinersen has shown clinically meaningful and sustained efficacy across the SMA spectrum, with a well-established safety profile of the 12/12mg regimen from over 10 years of study.[3–5]
- Recognizing the remaining unmet need across available therapies, a novel, higher-dose regimen was evaluated in the DEVOTE study.
- DEVOTE was a global 3-part (A, B, and C) Phase 2/3 study designed to evaluate the efficacy, safety, tolerability, and PK of 50/28mg nusinersen administered intrathecally. Part A results have been published.[6]

Methods

DEVOTE Parts B and C Study Design

- **Part B** was a randomized, double-blind evaluation of the safety and efficacy of 50/28mg nusinersen in treatment-naïve infantile-onset (pivotal) and later-onset (supportive) participants (**Figure 1**).
  - Part B was powered to assess change in CHOP-INTEND at Day 183 (primary endpoint) in infantile-onset participants for the 50/28mg group vs. a prespecified matched sham group from ENDEAR.
  - For infantile-onset, a hierarchical testing procedure was used for the primary and secondary endpoints.
  - Inclusion of the 12/12mg regimen was intended to provide supportive evidence; Part B was not sufficiently powered to detect statistical differences between those randomized to 50/28mg and 12/12mg nusinersen.
- **Part C** (supportive) was an open-label, safety and efficacy evaluation in children and adults with infantile-onset or later-onset SMA who transitioned from the 12/12mg to the 50/28mg regimen (**Figure 1**).
- **See supplement** for information on matching, hierarchical testing strategy and analytical methods.

Figure 1. DEVOTE Parts B and C Study Design

Part	Participants		Treatment	Key Efficacy Endpoints (Study Day)[a]	Comparator
B (treatment-naïve)	Infantile-onset SMA (N = 75)	Aged **> 1 week to ≤ 7 months** Symptom onset, **≤ 6 months** *SMN2* copies, **2 copies**	Participants were randomized (double-blind) within infantile- and later-onset cohorts to the **50/28mg** or 12/12mg regimen **50/28mg** **2 × 50mg loading dose** — **2 × 28mg maintenance dose** Day 1 (50) (50) 15 29 64 28 135 183 28 279 302 **12/12mg** **4 × 12mg loading dose** — **2 × 12mg maintenance dose** Day 1 (12) (12) (12) (12) 15 29 64 135 12 183 12 279 302 ▲ Sham procedure	Primary: CHOP-INTEND (183) HINE-2 (responder, change) (183) Plasma NfL (183) CHOP-INTEND (302) HINE-2 (change) (302) Plasma NfL (64) EFS/OS	*ENDEAR matched sham[3,b]* *ENDEAR matched sham[3,b]* *ENDEAR matched sham[3,b]* *DEVOTE 12/12mg* *DEVOTE 12/12mg* *DEVOTE 12/12mg* *ENDEAR matched sham,[3,b] and DEVOTE 12/12mg*
	Later-onset SMA (N = 24)	Aged **2 to < 10 years** Symptom onset, **> 6 months** Can sit independently, but never walked independently		Plasma NfL HFMSE (302) RULM (302)	*All compared with DEVOTE 12/12mg, CHERISH matched sham,[7,b] and CHERISH matched 12/12mg[b]*
C (prior 12/12mg nusinersen)	Infantile- and later-onset SMA (N = 40)	Any age, ambulatory or non-ambulatory Prior treatment with 12/12mg nusinersen ≥ 1 year	Participants transitioned from the 12/12mg to the **50/28mg** regimen open-label **1 × 50mg loading dose** — **2 × 28mg maintenance dose** Day 1 (50) 121 (28) 241 (28) 302	HFMSE/RULM (302)	*None*

[a]A hierarchical testing procedure was used for the primary and secondary endpoints for Part B infantile-onset (**see supplement**). [b]ENDEAR matched sham, CHERISH matched sham and CHERISH matched 12/12mg indicate prespecified subsets of participants matched to characteristics of the DEVOTE 50/28mg group (**see supplement**).

Results

Participants

- *Part B infantile-onset (pivotal):* Participants had 2 *SMN2* copies and were aged 15–232 days at first dose. While key characteristics were generally comparable between groups after matching, DEVOTE participants had shorter disease duration and lower baseline CHOP-INTEND scores relative to the sham group (**Table S1; see supplement**).
- *Part B later-onset:* Participants had 2 to 4 *SMN2* copies (primarily 3 copies) and were aged 2–9.8 years at first dose. Baseline HFMSE and RULM scores were higher in the 50/28mg group vs. the 12/12mg group (**Table S2**).
- *Part C:* Participants had 1 to 4 *SMN2* copies, were aged 4–65 years at first dose, and had received the 12/12mg regimen for a median 3.9 years prior to transitioning to the 50/28mg regimen (**Table S3**).

Safety

- Across cohorts and study parts, the 50/28mg regimen was generally well tolerated, with reported AEs generally consistent with SMA and the known safety profile of nusinersen (**Table S4**).

Efficacy

Part B Treatment-Naïve Infantile-Onset (Pivotal)

Neurodegeneration

- The 50/28mg group experienced 94% reduction in plasma NfL from baseline at Day 183, as compared with a 30% reduction in the sham group ($p < 0.0001$) (**Figure 2**).
- The 50/28mg group experienced greater reductions in plasma NfL at Day 64 relative to the 12/12mg group (LSGM ratio to baseline: 0.51; $p < 0.0050$*) (**Figure 2**).

Clinical Function

CHOP-INTEND

- Scores improved by 15.1 points from baseline at Day 183 in the 50/28mg group vs. an 11.1 point decline in the sham group (LSM difference: 26.19; $p < 0.0001$) (**Figure 3**).
- At Day 302, mean improvement was higher in the 12/12mg group compared to the 50/28mg group (LSM difference: −1.94; $p = 0.8484$) (**Figure 3**).

HINE-2

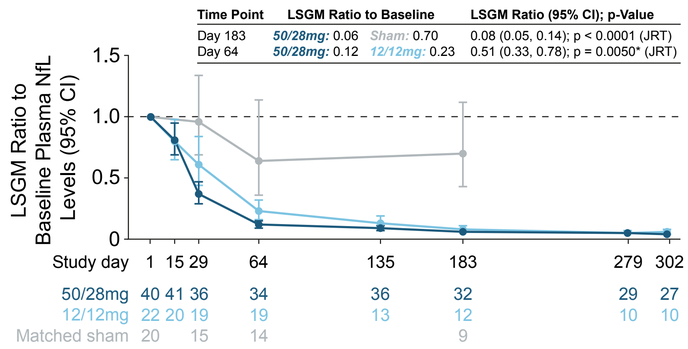
- A significantly greater proportion of participants receiving 50/28mg nusinersen vs. sham met the definition of a HINE-2 responder** at Day 183 (58% vs. 0%; $p < 0.0001$).
- The 50/28mg group had significantly greater improvements in change in HINE-2 score from baseline at Day 183 vs. the sham group ($p < 0.0001$); at Day 302, mean improvement was higher in the 50/28mg group compared to the 12/12mg group (LSM difference: 0.58; $p = 0.1734$) (**Figure 4**).

Survival and Related Events

- Risk of death or permanent ventilation (EFS) was reduced by 67.8% in the 50/28mg group vs. sham group (HR: 0.322; $p = 0.0006$*) and by 29.9% vs. the 12/12mg group (HR: 0.701; $p = 0.2775$) (**Figure 5**). Results for OS were consistent (**Figure S1**).

Figure 2. Change in Plasma NfL (Part B Infantile-Onset)

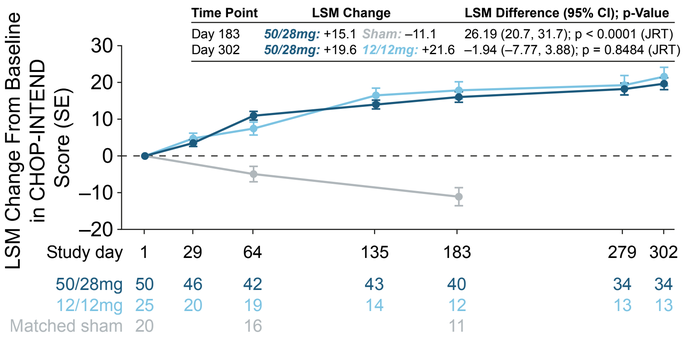
Time Point	LSGM Ratio to Baseline	LSGM Ratio (95% CI); p-Value
Day 183	*50/28mg:* 0.06 *Sham:* 0.70	0.08 (0.05, 0.14); p < 0.0001 (JRT)
Day 64	*50/28mg:* 0.12 *12/12mg:* 0.23	0.51 (0.33, 0.78); p = 0.0050* (JRT)



Study Day 1 is baseline. Multiple imputation was performed based on log transformed plasma NfL. Results shown are from an ANCOVA model with adjustment for participants' disease duration, baseline log plasma NfL, and baseline CHOP-INTEND score. The comparisons between 50/28mg and 12/12mg nusinersen, and between 50/28mg nusinersen and matched sham were performed as separate analyses. LSM difference from ANCOVA; p-value from joint-rank test.

Figure 3. Change in CHOP-INTEND (Part B Infantile-Onset)

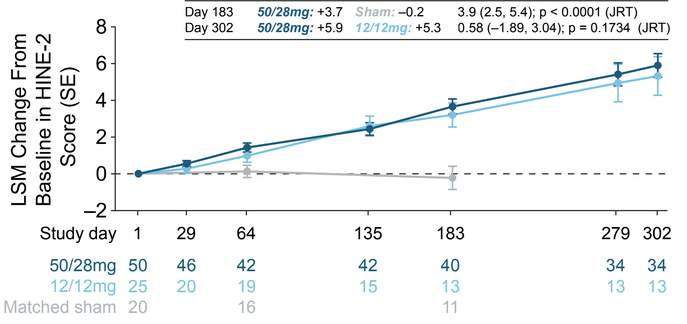
Time Point	LSM Change	LSM Difference (95% CI); p-Value
Day 183	*50/28mg:* +15.1 *Sham:* –11.1	26.19 (20.7, 31.7); p < 0.0001 (JRT)
Day 302	*50/28mg:* +19.6 *12/12mg:* +21.6	–1.94 (–7.77, 3.88); p = 0.8484 (JRT)



Study Day 1 is baseline. Results shown are from multiple imputation and an ANCOVA model with adjustment for participants' disease duration and baseline CHOP-INTEND score. The comparisons between 50/28mg and 12/12mg nusinersen, and between 50/28mg nusinersen and matched sham were performed as separate analyses. LSM difference from ANCOVA; p-value from joint-rank test.

Figure 4. Change in HINE-2 (Part B Infantile-Onset)

Time Point	LSM Change	LSM Difference (95% CI); p-Value
Day 183	*50/28mg:* +3.7 *Sham:* –0.2	3.9 (2.5, 5.4); p < 0.0001 (JRT)
Day 302	*50/28mg:* +5.9 *12/12mg:* +5.3	0.58 (–1.89, 3.04); p = 0.1734 (JRT)



Study Day 1 is baseline. Results shown are from multiple imputation and an ANCOVA model with adjustment for participants' disease duration, baseline HINE-2 score, and baseline CHOP-INTEND score. The comparisons between 50/28mg and 12/12mg nusinersen, and between 50/28mg nusinersen and matched sham were performed as separate analyses. LSM difference from ANCOVA; p-value from joint-rank test.

- In the 50/28mg group, the proportion of participants undergoing a hospitalization, time in hospital, and the proportion of participants experiencing a serious respiratory event were lower as compared with the 12/12mg group (**Table S5**).

Part B Treatment-Naïve Later-Onset

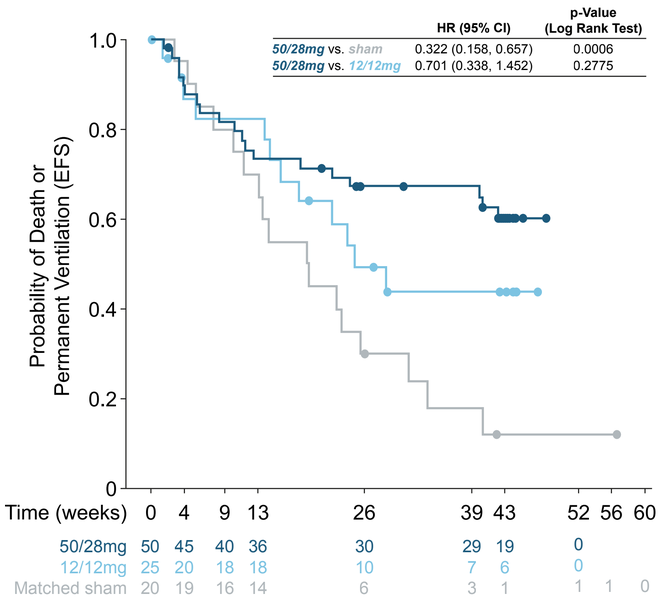
- The 50/28mg group achieved faster lowering of plasma NfL levels, with greater reductions at Day 64 relative to the 12/12mg group in DEVOTE (LSGM ratio to baseline: 0.58; $p = 0.0495$*) (**Figure S2**).
- The 50/28mg group had greater mean change in HFMSE and RULM scores at Day 302 compared to the DEVOTE 12/12mg group, and achieved greater improvements vs. the matched CHERISH 12/12mg and sham groups (**Figures S3 and S4**).

Part C Prior 12/12mg Nusinersen Transition Cohort

- Participants experienced improvements in motor function after transitioning to the 50/28mg regimen, with mean increases from baseline at Day 302 of 1.8 (SD 3.99) points on HFMSE and 1.2 (SD 2.14) points on RULM (**Figure 6**).
  - In later-onset adults (≥ 18 years of age; n = 24), improvements of 2.3 (SD 3.95) points on HFMSE and 0.9 (SD 1.89) points on RULM were observed.

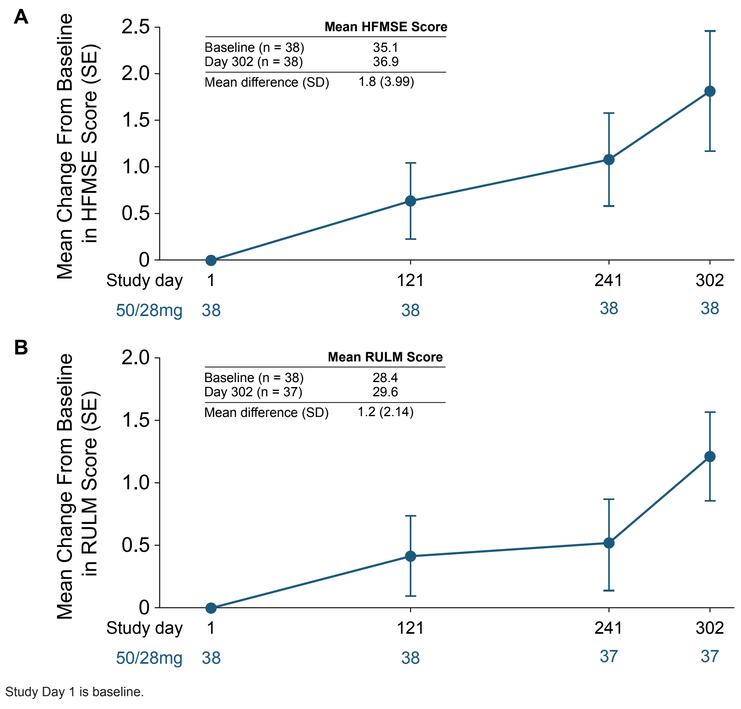
Figure 5. Event-Free Survival (Part B Infantile-Onset)

	HR (95% CI)	p-Value (Log Rank Test)
50/28mg vs. *sham*	0.322 (0.158, 0.657)	0.0006
50/28mg vs. *12/12mg*	0.701 (0.338, 1.452)	0.2775



p-value is from log rank test stratified by disease duration (≤ 12 weeks or > 12 weeks).

Figure 6. Change in HFMSE (A) and RULM (B) in Participants Who Transitioned from 12/12mg to 50/28mg Nusinersen (Part C)



Study Day 1 is baseline.

Acronyms and Abbreviations
AE = adverse event; ANCOVA = analysis of covariance; CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CI = confidence interval; EFS = event-free survival; HFMSE = Hammersmith Functional Motor Scale Expanded; HINE-2 = Hammersmith Infant Neurological Exam section 2; HR = hazard ratio; JRT = joint rank test; LSGM = least-squares geometric mean; LSM = least-squares mean; NfL = neurofilament light chain; OS = overall survival (death); PK = pharmacokinetics; RULM = Revised Upper Limb Module; SD = standard deviation; SE = standard error; SMA = spinal muscular atrophy; *SMN2* = survival of motor neuron 2.

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Disclosures
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Clinical Trial Registration
DEVOTE: ClinicalTrials.gov, NCT04089566; EudraCT number, 2019-002663-10.

*Indicates nominally significant. **See supplement** for additional information.
**See supplement for definition of HINE-2 responder.

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