COVER PAGE

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STATISTICAL ANALYSIS PLAN

Final Analysis

Version No.: V2.0

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Study Title: A Phase 4 Study of Nusinersen (BIIB058) Among Patients With Spinal Muscular Atrophy Who Received Onasemnogene Abeparvovec

Name of Study Treatment: Spinraza

Protocol No.: 232SM404

Study Phase: 4

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APPROVAL

This document has been reviewed and approved by:

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VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
V1.0	02 NOV 2023	
V2.0	06 OCT 2025	Protocol was updated from V3.0 to V4.0, therefore SAP was updated to align with protocol

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LIST OF ABBREVIATIONS

Abbreviation	Definition
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
AE	adverse event
[redacted]	[redacted]
[redacted]	[redacted]
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	confidence interval
[redacted]	[redacted]
CRF	case report form
CSF	cerebrospinal fluid
ECG	electrocardiogram
HINE	Hammersmith Infant Neurological Examination
HFMSE	Hammersmith Functional Motor Scale - Expanded
IT	intrathecal(ly)
IV	intravenous(ly)
LP	lumbar puncture

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NF-L	neurofilament light subunit
[redacted]	[redacted]
PD	pharmacodynamic(s)
[redacted]	[redacted]
[redacted]	[redacted]
pNF-H	phosphorylated neurofilament heavy subunit
[redacted]	[redacted]
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SMA	spinal muscular atrophy
SMN2	survival motor neuron 2
RBC	red blood cell
RULM	Revised Upper Limb Module
WBC	white blood cell
WHO	World Health Organization
[redacted]	[redacted]

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1. Introduction

An earlier version (V1.0) of SAP was developed on 02NOV2023 based on protocol V3.0 dated 15Jun2022, and this version (V2.0) of SAP was updated based on the new protocol (V4.0 dated 08Nov2023).

Nusinersen is an approved drug of Biogen for the treatment of 5q spinal muscular atrophy (SMA). The purpose of this study is to evaluate the clinical outcomes and safety of nusinersen in SMA patients who previously received onasemnogene abeparvovec. It is hypothesized that patients who received onasemnogene abeparvovec with suboptimal clinical status may gain additional clinical benefits with nusinersen treatment.

This SAP will reiterate the study design and primary, secondary, [redacted] and safety endpoints in the protocol and describe the analysis methods for each endpoint as well as associated analysis elements (such as definition of baseline etc.).

2. Study Overview

2.1. Study Objectives and Endpoints

Primary Objective	**Primary Endpoints**
To evaluate the clinical outcomes following treatment with nusinersen in participants with SMA who previously received onasemnogene abeparvovec	Total HINE Section 2 motor milestones score
Secondary Objectives	**Secondary Endpoints**
To evaluate the safety and tolerability of nusinersen in participants with SMA who previously received onasemnogene abeparvovec	Incidence of AEs and SAEs during the treatment period
	Change from baseline in clinical laboratory parameters, ECGs, vital signs, and other safety assessments
To evaluate clinical outcomes following treatment with nusinersen in participants with SMA who previously received onasemnogene abeparvovec	WHO motor milestones
	Change from baseline in applicable motor function assessments: CHOP INTEND, HFMSE, and RULM
	Time to death or permanent ventilation (tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event; APPENDIX A.)
To evaluate the PD of nusinersen in participants who previously received onasemnogene abeparvovec	Change from baseline in CSF and plasma levels of NF-L

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[redacted]

2.2. Study Design

This is an open-label, single-arm, interventional study to evaluate the efficacy and safety of nusinersen in approximately 46 participants who previously received IV onasemnogene abeparvovec in a clinical practice setting. The study will be conducted at approximately 20 sites globally. The total study duration for each participant will be up to 115 weeks. The participants are determined by the Investigator to have suboptimal clinical status and the potential for additional clinical improvement with nusinersen. Participants must have received

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onasemnogene abeparvovec at least 2 months prior to the first nusinersen dose. All participants will be aged ≤ 36 months at first nusinersen dose, have an SMN2 copy number of ≥ 1, and have received onasemnogene abeparvovec either when symptomatic or presymptomatic for SMA. One month is defined as 30 days in Protocol V4.

Of the approximately 46 participants to be recruited in total, approximately 28 will be recruited into Subgroup A or Subgroup B. Approximately 18 participants will be recruited into the Broader Group.

It is hypothesized that younger participants who receive onasemnogene abeparvovec and then nusinersen may derive the most benefit compared to onasemnogene abeparvovec alone. In order to optimize the evaluation of the benefit of nusinersen after receiving onasemnogene abeparvovec, participants with an SMN2 copy number of 2 and first dose of nusinersen at <300 days of age will be enrolled in Subgroup A or Subgroup B. The maximum age of <300 days at first nusinersen dose for participants in these subgroups will ensure adequate time to assess suboptimal clinical status after onasemnogene abeparvovec and ensure sufficient time on nusinersen to evaluate the benefit during the critical window for motor milestone achievement.

Subgroup A

Participants who meet the following additional criteria may enroll in Subgroup A:

- Received IV onasemnogene abeparvovec at > 6 weeks to ≤ 6 months (43 days to 180 days) of age.
- <300 days of age at the time of first nusinersen dose.
- SMN2 copy number of 2.
- SMA symptom onset ≤ 4 months (120 days) of age.
- Must have received IV onasemnogene abeparvovec after SMA symptom onset.

Subgroup B

Participants who meet the following additional criteria may enroll in Subgroup B:

- Received IV onasemnogene abeparvovec at ≤ 6 weeks (42 days) of age.
- <300 days of age at the time of first nusinersen dose.
- SMN2 copy number of 2.

2.3. Sample Size Considerations

It is planned that approximately 46 participants will be dosed, which is considered sufficient to characterize the safety, tolerability, [redacted] of 12 mg nusinersen in participants previously dosed with onasemnogene abeparvovec.

A formal sample size calculation was not performed. A sample size of 40 participants in Subgroup A and B will allow the 95% CI for the primary endpoint of total HINE Section 2 motor milestones score to be estimated with a halfwidth ± 2.05, assuming a standard deviation of 6.4.

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3. Definitions

3.1. Dates and Points of Reference

- Study Day 1: the date of the first dose of nusinersen
- Study Day
  - For a date on or after Study Day 1

    Study Day = (Date of Interest) – (date of Study Day 1) + 1
  - For a date before Study Day 1

    Study Day = (Date of Interest) – (date of Study Day 1)
- The baseline, throughout the analysis, will be defined as the closest available assessment prior to the first dose of nusinersen, unless otherwise specified for individual analysis. For endpoints that are introduced based on age or ability during the study, it may be necessary to define a different baseline as the first evaluable assessment in order to allow summaries over time to be presented.

3.2. Study Treatment

All participants will receive open label nusinersen 12 mg administered IT.

3.3. Study Periods

This study includes screening (up to 21 days), treatment (95 weeks) and follow-up (17 weeks, approximately 4 months) periods. The total study duration for each participant will be up to 115 weeks.

For treatment period, each participant will receive 4 loading doses of 12 mg of nusinersen administered IT by LP on Days 1, 15, 29, and 64. Maintenance dosing of 12 mg of nusinersen will be administered IT on Days 183, 302, 421, 540, and 659.

Follow up occurs on Day 778 (+/- 14 days).

All assessments (with the exception of coagulation testing) that were performed at Screening within 7 days prior to the Day 1 dosing visit do not need to be repeated on Day 1 unless results at Screening require reassessment (e.g., abnormal ECG, physical examination findings, out of range laboratory results, etc.) and will be windowed to Day 1. Visits up to Day 29 should be performed ± 1 day from the nominal visit day, the visit on Day 64 should be performed ± 7 days from the nominal visit day, and visits from Day 183 onward should be performed ± 14 days from the nominal visit day. All assessments for various endpoints in treatment and follow-up periods occur on the same visit days as dosing days and the endpoints will be analyzed accordingly as applicable. Age-based visits are required only for participants <300 days of age at the time of first nusinersen dose and visits based on participant age should be performed ± 14 days from the nominal visit day. If the window for an age-based visit overlaps with another scheduled visit, the visits may be combined.

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3.4. Key Derived Variables

Efficacy

Total HINE Section 2 motor milestones score: This primary endpoint will be derived as sum of 8 category scores (voluntary grasp, ability to kick, head control, rolling, sitting, crawling, standing, walking).

Safety

Treatment emergent adverse event (TEAE): An adverse event will be regarded as treatment-emergent if it was present prior to receiving the first dose of nusinersen and subsequently worsened in severity or was not present prior to receiving the first dose of nusinersen but subsequently appeared.

For events with missing or partial missing start or stop dates, the following criteria will be used for the purpose of identifying treatment-emergent adverse events in most conservative way:

- If both the start and stop dates for a particular event are completely missing, then the event is considered to be treatment emergent.
- If the start date for a particular event is missing and the stop date is not missing which falls after the first treatment date, then the event is considered treatment emergent.
- If only start day is missing for a particular event and the month and year are the same as or after the first treatment start year or month, then the event is considered treatment-emergent.
- If both start month and day are missing for a particular event and the year is the same as or after the treatment start year, then the event is considered treatment-emergent.
- If it cannot be determined whether an event has occurred on or after dosing due to a missing or partial date, then the event will be assumed to have occurred on or after the first dose for the purpose of identifying treatment-emergent adverse events.

Concomitant medications/non-drug procedures

For the purposes of analysis, a concomitant therapy (including medication or non-drug procedure) is defined as any therapy administered between screening and the final study visit/telephone call in the study. This includes therapies which are started prior to the initiation of nusinersen in the study if their use continues on or after the date of the first study dose. If the dates for concomitant medications or procedures are missing or partially missing, the following additional criteria will be used:

- if both the start and stop dates of a particular therapy are missing, that therapy is considered concomitant.
- if the start date of a therapy is missing and the stop date of that therapy fell on or after the date of dosing, that therapy is considered concomitant;
- if the start date of a therapy is prior to the date of dosing and the stop date of that therapy is missing and the therapy is ongoing, that therapy is considered concomitant;
- if the start date of a therapy is prior to the date of dosing and the stop date of that

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therapy is missing and the therapy is not ongoing, that therapy is considered concomitant, or

- if the start/stop date of a therapy is partial and it is not possible to rule out that it was not taken concomitantly it will be considered concomitant.

Denote the end date of medication as CMENDT and the date of the first dose of nusinersen in the study as TRTSTDT. The medication is classified concomitant provided any of the following is NOT true:

- CMENDT is complete and CMENDT is less than TRTSTDT.
- Day of CMENDT missing and year/month of CMENDT is strictly before year-month of TRTSTDT.
- Month of CMENDT is missing and year of CMENDT is strictly before year of TRTSTDT.

3.5. Stratification Factors and Subgroup Variables

3.5.1. Stratification Factors

Not applicable. This study does not include randomization. Therefore, there are no study randomization stratification factors.

3.5.2. Subgroup Variables

Not applicable. No formal subgroup analysis with statistical testing will be planned for this study. The subgroup variables (SMN2 copy number, age at first nusinersen dose, age at onasemnogene abeparvovec dose etc.) used in Display 1 and Display 2 described in Section 3.6 below are for presentation purpose only.

3.6. Analysis Sets and Main Displays

ITT Set: The ITT (Intent-to-Treat) set will be defined as all participants who received at least 1 dose of nusinersen in the study. The data in this set will be used for analysis of all clinical endpoints including efficacy, safety, demography, baseline characteristics, study drug exposure, concomitant medication, protocol deviation etc.

Per-Protocol Set: The Per-Protocol set will include all participants in the ITT set after excluding any efficacy assessments impacted by the use of any disallowed concomitant therapy. The data in this set will be used for a supplementary analysis of the primary efficacy endpoint (HINE-2 motor milestones).

Although Protocol V4 of the study defines the Safety Set for non-efficacy analysis and Evaluable Set for efficacy analysis, the ITT Set, with same definition as Safety Set, will be used in this SAP and reporting.

[redacted]

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The analysis for Pharmacodynamic (PD) will be performed on the ITT set.

The **Immunogenicity Set** is defined as all participants who were dosed for which there is at least 1 evaluable post-dose immunogenicity sample in the study.

Interim Evaluable sets will be defined and used for interim analyses during the study. For example, an Interim Day 64 Evaluable Set will be defined for all patients using the subset of patients in the ITT set who:

- have at least one post baseline efficacy assessment at Day 64 or later after removing any data impacted by the use of any disallowed concomitant therapy, OR
- discontinue due to AE or death provided the time difference between the date of first nusinersen dose and the clinical cutoff date is greater than 64+7 days, i.e., 64 days plus a 7-day window.

Interim Evaluable sets will be defined for other timepoints such as Day 183 or Day 302 etc. The window used will be per protocol so for Day 64 +/- 7 days and for other timepoints +/- 14 days.

Two displays as shown below will be used for analyses, in particular, Display 1 will be used for all endpoints, while Display 2 (for 2 SMN2 copy subjects aged <300 days at first nusinersen dose) will be used for selected analyses e.g., demographic, SMA history, primary efficacy endpoint (i.e., HINE-2 motor milestones).

- Display 1:

2 SMN2 Copy			3 SMN2 copy	Overall Total
Age <300 days at first nusinersen dose	Age >=300 days at first nusinersen dose	Total	Age >=300 days at first nusinersen dose	

- Display 2 (for 2 SMN2 copy subjects aged <300 days at first nusinersen dose):

Age <300 days at first nusinersen dose		Total
Age >6 weeks at onasemnogene abeparvovec dose	Age <=6 weeks at onasemnogene abeparvovec dose	

4. List of Planned Analyses

4.1. Interim Analysis

The first interim analysis will be conducted with clinical cut-off date of November 15, 2021. Future interim analyses may take place annually for internal or publication purposes if needed. Presentations from the interim analyses are a subset of those to be included in the final analysis.

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The interim analyses will be performed on the ITT set (previously defined as Safety set in SAP V1.0) as defined in Section 3.6 for presentations of study subjects and safety endpoints, and on the Interim Evaluable set for presentations of efficacy endpoints.

4.2. Final Analysis

The final analysis will take place when the last subject completes their last assessment.

5. Statistical Methods for Planned Analyses

5.1. General Principles

Summary statistics will be presented throughout for planned analyses.

For continuous endpoints, descriptive summary statistics include n, mean, median, standard deviation, standard error (or confidence intervals), interquartile range (25th percentile, 75th percentile), and range (minimum, maximum).

For categorical endpoints, counts and percentages will be used to summarize most data and the summary statistics will generally include number of participants dosed, number of participants with data, and the percentage of those with data in each category. Frequency distributions will be presented as appropriate.

Visit Windows for Analysis

Data from post-baseline unscheduled assessments and early termination visits will be assigned to an appropriate scheduled post-baseline visit using a windowing scheme for assessments that are tabulated or summarized by visit. If more than one observation is within the same window, data from the regular scheduled visit will be used for that visit. If there is more than one observation in the window, the observation from the day of dosing will be chosen. Scheduled visits will not be windowed.

The visit windowing will be performed for efficacy and safety endpoints.

For safety endpoints the following windows will be utilized.

Table: Visit windows for Safety Endpoints in 232SM404

Visit	Lower Bound	Upper Bound	Target Day
Baseline			<=1
Day 15	2	22	15
Day 29	23	47	29
Day 64	48	124	64

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Day 183	125	243	183
Day 302	244	362	302
Day 421	363	481	421
Day 540	482	600	540
Day 659	601	719	659
Day 778	720	792	778

For efficacy endpoints, if the actual study day falls within +/-7 days of visit Day 64, or +/- 14 days of visit Day 183/302/421/540/659/778, then it will be considered for windowing. The age-based visits (15 months, 18 months, 24 months) that are not initially collected will be derived by age at visit +/- 14-days, for example, a visit will be mapped as "15 months" visit if the participant's age at the visit is within the 15-months +/- 14-days range.

The following rules will be implemented for windowing of these visits for both safety and efficacy:

- If more than one observation is within the same window, data from the regular scheduled visit will be used for that visit.
- If neither of the observations are from a regular scheduled visit the observation closest to the planned target date will be used. However, if both the observations are equidistant from the target date, the latest one will be used; if repeated measurements are on the same day, then the last measurement will be used.
- If windowing safety data and there is more than one observation in a window for a dosing visit the observation on the day of dosing will be chosen over the observation where dosing did not occur on the same day.
- In windowing laboratory data, if a central and local result is available within the window then the central laboratory result will be chosen.

Missing Efficacy Endpoints

In certain situations, item-level imputation for efficacy endpoints such as HINE-2, CHOP INTEND and HFMSE total score using linear interpolation may be applied.

Missing or Partial Adverse Event Start Date

If an AE start date is missing or partially missing, it will be imputed as below:

- The AE start date can be imputed as first treatment date for the scenarios listed below
  - if the start date is completely missing or the year is missing
  - If only start day is missing and the month and year are the same as the first treatment start year and month

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  - If both start month and day are missing and the year is the same as the treatment start year
- If only start day is missing and the month and year are different from the first treatment start year or month, then impute the missing day to the first day of the month.
- If both start month and day are missing and the year is different from the treatment start year, then impute the missing month and day as January 01.

Note that the imputed date will not be used for calculations such as onset and duration of an adverse event. The imputation algorithm will only be used to identify treatment emergent adverse events. Due to the long half-life of nusinersen, analyses of treatment-emergent adverse events will include all events reported during the study.

The statistical software, SAS® version 9.3 or above, will be used for all summaries and statistical analyses.

5.2. Participant Accountability

The number of participants who were screened, who were enrolled, who were dosed, completed treatment, and completed the study, along with the number of participants who discontinued treatment and/or withdrew from study will be presented.

Listings of those participants discontinued treatment and/or withdrew from the study and the reasons for discontinuation/withdrawal will be presented. Subjects who died during the study will be listed separately.

5.3. Demographic and Baseline Characteristics

Baseline data (demography and baseline characteristics) will be summarized using descriptive statistics for the ITT Set. Baseline will generally be defined as the closest non-missing measurement before the first dose.

Demography

Demography including age, sex, ethnicity, and race will be summarized. Demography data will be presented in listing(s) as well.

Race and ethnicity may be unavailable for certain subjects due to regulatory restrictions on collection of such data in certain countries. In such cases, 'Not reported' will be presented in demography summary tables or listing(s).

Baseline Characteristics

SMA History

SMA history will be summarized and the summary contents may include the following:

- gestational age at birth;
- birth weight;
- age at symptom onset and at SMA diagnosis;

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- the number of copies of the SMN1 and SMN2 gene;
- feeding status prior to onasemnogene abeparvovec administration;
- prior ventilator use;
- motor functions ever achieved and still maintained:
  - sat without support;
  - stood without support;
  - walked with support;
  - walked without support/brace;

  If a motor function is achieved or if maintenance is lost, age of achievement or loss will also be summarized.

- ever used or using a device:
  - wheel chair;
  - walker;
  - crutches;
  - braces;
  - other device.

  If a device is used, the starting age and part time or fulltime use will also be summarized.

Age units may be unified for age summaries depending on display and data. SMA history data will be presented in listing(s) as well.

SMA History Prior to Onasemnogene Abeparvovec Administration and SMA History Prior to Informed Consent

SMA history prior to onasemnogene abeparvovec administration related to feeding and ventilator use will be presented in listing if available. SMA history prior to informed consent will be presented in listing(s) if available and the contents may include the following:

- growth parameters;
- HINE-2 motor milestones;
- other scores available:
  - CHOP INTEND
  - RULM
  - HFMSE
- [redacted]

Onasemnogene Abeparvovec Dosing History and Prior Steroid History

Onasemnogene abeparvovec dosing history will be summarized for age at onasemnogene abeparvovec dosing, time from onasemnogene abeparvovec dose to first dose of nusinersen, weight, participant symptomatic/pre-symptomatic at time of onasemnogene abeparvovec dose.

The onasemnogene abeparvovec dosing history data will also be presented in listing along with prior steroid history.

[redacted]

Medical History

Medical history will be coded in MedDRA, and the number and percentage of participants with each medical history will be presented by system organ class and/or preferred term. Medical history data will be presented in listing(s) as well.

Baseline disease characteristics will also be assessed, when appropriate, by HINE-2 motor milestones, CHOP INTEND total score, WHO motor milestones, [redacted] and growth parameters – these assessments are further described in Section 5.6.

5.4. Protocol Deviations

Protocol deviations identified during site monitoring will be captured in a protocol deviation log and categorized as major or minor deviations. These deviations will be listed. Major protocol deviations will be summarized.

5.5. Study Treatment Exposure and Concomitant Medications/Procedures

Study treatment exposure

The number of nusinersen doses received will be displayed using frequency distributions as well as summary statistics. Dosing administration will be provided in listing.

Overall time on study will be defined as the total number of days a subject is known to be followed on study calculated as follows:

Overall time on study = (Last date on study) – (Date of first dose of nusinersen) + 1.

The last date on study is defined as the date of the latest visit or evaluation or telephone contact, or time of death from all available data for a given subject, whichever is latest.

Time on study will be categorized into intervals and summarized by defined groups in Section 3.6. Given the long half-life of nusinersen, subjects are considered to be exposed to study drug from the time the first dose is administered to the last day of follow-up. Essentially, exposure is equivalent to time on study.

Concomitant medications/ non-drug procedures

A concomitant therapy is any drug or substance other than study drug administered between Screening and the final study visit/telephone call.

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All concomitant medications will be coded using the World Health Organization drug dictionary (WHODrug Global 2025-03_B3 or a more recent version).

A concomitant non-drug procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the participant is enrolled in the study and the final study visit/telephone call. These are referenced as ancillary procedures in the protocol.

The number and percentage of participants taking each type of concomitant medication at baseline and during the study will be presented by preferred name. The number and percentage of participants who underwent each type of non-drug procedure during the study will be presented by system organ class and preferred term.

For the purposes of analysis, a concomitant therapy (including medication or non-drug procedure) is defined as any therapy that was taken on or after the first dose of nusinersen in the study. This includes therapies which are started prior to the initiation of nusinersen in the study if their use continues on or after the date of the first study dose. Details of identifying concomitant therapies with missing start or stop dates are described in Section 3.4.

5.6. Efficacy Endpoints

The efficacy assessments are based on the following criteria.

Assessment	**Criteria**
Total HINE Section 2 motor milestones	All participants through end of study.
WHO motor milestones[1] [redacted]	All participants.
[redacted]	[redacted]

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Assessment	Criteria
CHOP INTEND	Participants < 2 years of age at the time of informed consent Participants 2 to ≤ 3 years of age at the time of informed consent if they did not achieve independent sitting prior to Screening[12]. Participants may discontinue these assessments after Day 421 once they have demonstrated a maximum score at one visit.
HFMSE RULM [redacted]	Participants ≥ 2 years of age (Note: The HFMSE and RULM will be performed in addition to the CHOP INTEND and HINE Section 2 motor milestones if those assessments are continued beyond 2 years of age [see above]).
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[1] WHO motor milestone assessments will be performed by appropriately trained sites personnel, including a physical therapist.
[2] Sitting independently is defined as able to sit without support per WHO motor milestones (Test Item No. 1 – Sitting Without Support).

[redacted]

Regular assessment schedule of efficacy endpoints: The majority of efficacy endpoints are assessed at pre-dose of Day 1, pre-dose at 4th loading dose visit Day 64 and maintenance dosing visits starting at Day 183, and follow-up visit Day 778/ET unless specified otherwise in subsections below.

5.6.1. General Analysis Methods for Efficacy Endpoints

The displays for analyses on efficacy endpoints are summarized in Section 3.6.

For analyses, continuous variables will be summarized by descriptive statistics, including number, mean, median, standard deviation, 25th percentile, 75th percentile, minimum, and

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maximum. Categorical variables will be presented with the number and percentage in each category. Ninety five percent CIs will be reported for point estimates as appropriate, such as means or proportions.

5.6.2. Primary Efficacy Endpoint

Hammersmith Infant Neurological Examination Section 2 – Motor Milestones

Section 2 of the HINE is composed of 8 motor milestone categories as follows: voluntary grasp, ability to kick in supine position, head control, rolling, sitting, crawling, standing, and walking. Within each motor milestone category, there are 3 to 5 levels that can be achieved. All 8 motor milestones should be tested during each assessment. A participant whose results after testing all appear in the first column (no grasp, no kicking, unable to maintain head upright, etc.) has not achieved any motor milestone. Motor milestone achievement is depicted by movement from the left side of the table to the right side of the table, as denoted by the Milestone Progression arrow in the table (Haataja 1999). The 8 categories of HINE Section 2 can be summed to give a total score that ranges from 0 to 26.

Total HINE Section 2 are assessed when participants are aged at 15, 18 and 24 months in addition to regular assessment schedule.

Missing values

If not all motor milestones test items were performed at a visit, the approach described below will be used for the handling of missing data. Missing data will be imputed on an individual item level. Age-based visits will be pooled together with regular visits for imputation.

If a subject has baseline defined at Day 1 but has a missing milestone, then an imputation will be performed using the screening value. If the screening value is missing, then the missing value will be imputed as the median of the non-missing baseline values of the group to which the subject belongs: SMA onset status at onasemnogene abeparvovec administration (pre-symptomatic, symptomatic onset <= 6 months, symptomatic onset > 6 months) by age at nusinersen dose (<= 12 months, > 12 months). Specifically, SMA onset status at onasemnogene abeparvovec administration is defined as:

- If "Was Patient symptomatic at time of dosing?" = No, then status = pre-symptomatic
- Else, calculate age at zolgensma dose = (date of zolgensma dosing – birth date)/30.4375
    - if age at zolgensma dose <= 6 months, then symptomatic onset <=6 months
    - if age at zolgensma dose > 6 months, then symptomatic onset >6 months

If for the subject with the missing value, the corresponding visit is flanked by visits with non-missing milestones, the missing value will be imputed using linear interpolation with the result rounded to the nearest integer score. Otherwise, if the imputation is the last visit for the subject the missing test will be imputed as the last observed value carried forward (LOCF) for the subject. In the specific situation where the missing test is at the age-based visit and the subject has another regular scheduled visit at the same date, then the same

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imputed values (from the regular scheduled visit) will be utilised for the age-based visit to maintain consistency.

Of note, only observed data will be utilized for imputation purposes. Missing motor milestone items will be imputed first prior to any analysis.

Hammersmith Infant Neurological Examination Section 2 - Motor Milestones

Motor Milestone Category	Milestone Level (Age Expected in Heathy Infants) Progression Score Improvement →				
	0	1	2	3	4
Voluntary grasp	No grasp	Uses whole hand	Finger and thumb/immature grasp	Pincer grasp	
Ability to kick (in supine)	No kicking	Kicks horizontal; legs do not lift	Upward (vertically) [3 months]	Touches leg (4 to 5 months)	Touches toes (5 to 6 months)
Head control	Unable to maintain upright (< 3 months)	Wobbles (4 months)	All the time upright (5 months)		
Rolling	No rolling	Rolls to side (4 months)	Prone to supine (6 months)	Supine to prone (7 months)	
Sitting	Cannot sit	Sits with support at the hips (4 months)	Props (6 months)	Stable sit (7 months)	Pivots (rotates) [10 months]
Crawling	Does not lift head	On elbow (3 months)	On outstretched hand (4 to 5 months)	Crawls flat on the abdomen (8 months)	On hands and knees (10 months)
Standing	Does not support weight	Supports weight (4 to 5 months)	Stands with support (8 months)	Stands unaided (12 months)	
Walking	No walking	Bouncing (6 months)	Cruising (holding on) [11 months]	Walks independently (15 months)	

Analyses

- HINE Section 2 motor milestones by category over time (including at 15, 18 and 24 months of age).

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- Total score of HINE Section 2 motor milestones over time (including at 15, 18, 24 months of age) and change from baseline over time.
- Mean (-/+ SE) plots of total score and change from baseline over time.
- Summary of HINE Section 2 motor milestone improvement at last assessment compared to baseline.
- Spaghetti plot of total score by age for individual participants.
- List of total score by visit for individual participants.

The above analyses will be performed using the interim evaluable sets for interim analyses and ITT set for final analyses as defined in Section 3.6. Supplementary analysis may be performed by using the Per-Protocol set for summary of HINE-2 total score over time and change from baseline in total score over time.

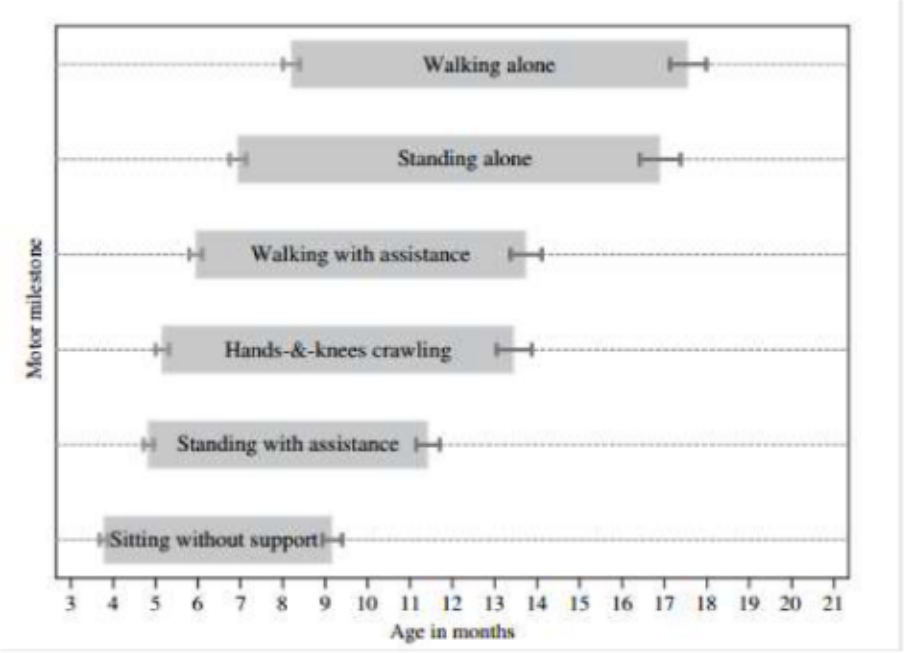
5.6.3. Secondary Efficacy Endpoints

Depending on the number of participants evaluated on each scale, summary statistics or individual patient data may be presented.

WHO Motor Milestones

The WHO motor milestones are a set of six milestones in motor development, all of which would be expected to be attained by 24 months of age in healthy children. The individual milestones are: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone and walking alone. The WHO reported [WHO Motor Development Study] that in about 90% of cases the order of attainment followed a fixed sequence for five of the milestones (namely, sitting without support, standing with assistance, walking with assistance, standing alone and walking alone) with only hands and knees crawling shifting between the earlier milestones. The following figure shows the age in months at which motor milestones are attained and the bounds of the 1st and 99th percentiles reported by the WHO.

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WHO motor milestones will be assessed using the WHO motor milestones criteria [WHO Multicentre Growth Reference Study Group 2006; Wijnhoven 2004]. The WHO motor milestones are assessed in all participants up to the end of the study and when participants are aged at 15, 18 and 24 months in addition to regular assessment schedule. As part of the assessment, the examiner records an overall rating of the subject's emotional state and then for each milestone one of the following four classifications:

- No (inability) – Child tried but failed to perform the milestone.
- No (refusal) – Child refused to perform despite being calm and alert.
- Yes – Child was able to perform the milestone.
- Unable to test – Could not be tested because of irritability, drowsiness or sickness.

Missing WHO motor milestone test items will not be imputed, and only available data will be used for analysis as described below.

Analyses

- Summary of WHO motor milestone achievement over time (including at 15, 18, 24 months of age).
- Summary of WHO motor milestone improvement comparing to baseline over time and at last assessment.
- Swim lane plot to show achievements of WHO motor milestones for each subject incorporating milestone achievements of SMA history.
- List of WHO motor milestone achievements by visit for individual subjects.

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CHOP INTEND

The CHOP INTEND test was specifically designed to evaluate the motor skills of infants with significant motor weakness, including infants with SMA [Glanzman 2010]. The CHOP INTEND test captures neck, trunk, and proximal and distal limb strength in 14 elicited and 2 observational items. CHOP INTEND has been established as a safe and reliable infant motor measure in infantile-onset SMA and has been validated [Glanzman 2011].

The CHOP INTEND infant motor function scale is comprised of 16 test items, nine of which are scored 0, 1, 2, 3, or 4 with greater scores indicating greater muscle strength, five are scored as 0, 2, or 4, one is scored as 0, 1, 2, or 4, and one as 0, 2, 3, or 4. This can result in a worst possible total score of 0 to a best possible total score of 64. Thirteen of the items are tested on both the right and left side and the item score will be calculated as the maximum of either side, or if one side is missing set to be the non-missing side. Summing these items can result in a worst possible score of 0 to a best possible score of 64.

CHOP INTEND is used to assess spontaneous movement in the upper extremities, spontaneous movement in the lower extremities, hand grip, head in midline with visual stimulation, hip adductors, rolling elicited from the legs, rolling elicited from the arms, shoulder and elbow flexion and horizontal abduction, shoulder flexion and elbow flexion, knee extension, hip flexion and foot dorsiflexion, head control, elbow flexion, neck flexion, head/neck extension, and spinal incurvation.

CHOP INTEND is to be evaluated during the study for participants < 2 years of age at the time of informed consent and for participants 2 to ≤ 3 years of age at the time of informed consent if they did not achieve independent sitting prior to Screening. Participants may discontinue CHOP INTEND assessments after Day 421 once they have demonstrated a maximum score of 64 at one visit. Other than at regular assessment schedule, CHOP INTEND are also assessed when participants are 18 months of age.

Missing values

If not all items for CHOP-INTEND were performed at a visit, the approach described below will be used for the handling of missing data. Missing data will be imputed on an individual CHOP INTEND test item level. Age-based visits will be pooled together with regular visits for imputation.

If a subject has baseline defined at Day 1 but has a missing item, then an imputation will be performed using the screening value. If the screening item is missing then the missing item will be imputed as the median of the non-missing values of the group to which the subject belongs: SMA onset status at onasemnogene abeparvovec administration (pre-symptomatic, symptomatic onset <= 6 months, symptomatic onset > 6 months) by age at nusinersen dose (<= 12 months, > 12 months). If for the subject with missing CHOP INTEND test items at a particular visit, the corresponding visit is flanked by visits with non-missing test items, then the missing value for those test items will be imputed using linear interpolation with the result rounded to the nearest integer score. Otherwise, if the imputation is the last visit, the missing value will be imputed as the last observed value

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carried forward (LOCF) for the subject. In the specific situation where the missing test is at the age-based visit and the subject has another regular scheduled visit at the same date, then the imputed values (from the regular scheduled visit) will be utilised for the age-based visit to maintain consistency.

Of note, only observed data will be utilized for imputation purposes. Missing CHOP INTEND items will be imputed first prior to any analysis.

Analyses

- Summary of CHOP INTEND total score over time (including at 18 months of age) and change from baseline over time.
- Mean (-/+ SE) plots of total score and change from baseline over time.
- Proportion of subjects achieving ≥ 40, 50, 60 by visit.
- Spaghetti plots of total score by age for individual subjects.
- Summary of CHOP INTEND total score and change from baseline over time for participants who did not achieve sitting without support at screening per SMA history.
- List of total score by visit for individual subjects.

Hammersmith Functional Motor Scale – Expanded (HFMSE)

The HFMSE is a reliable and validated tool used to assess motor function in children with SMA. The scale was originally developed with 20 scored activities and was devised for use in children with Type 2 and Type 3 SMA with limited ambulation to give objective information on motor ability and clinical progression [Main 2003]. The expanded scale includes an additional module of 13 items developed to allow for evaluation of ambulatory patients with SMA [O'Hagen 2007]. Each item is scored 0 (unable), 1(performs with modification or adaptation) or 2 (able) and the total score is calculated by summing the 33 items and ranges from 0 to 66 with higher scores indicating greater motor function.

The HFMSE will be assessed in participants who have reached ≥ 2 years of age during the study period. The baseline for HFMSE is defined as the first assessment at which it is administered where 6 or fewer items are missing. If 6 or fewer items are missing, then these items will be imputed to be 0 when summing all 33 items.

Post baseline, if greater than 6 items are missing but at least one item is not missing, then the total score will be imputed by interpolating total scores between the previous and subsequent visit or, if there is no subsequent visit, by using the score from the previous visit.

Analyses

- Summary of HFMSE total scores by visit.
- Spaghetti plot of HFMSE total score by age for individual subjects.
- Summary of HFMSE total score and change from baseline over time for subjects with evaluable baseline at or prior to Day 1.

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- List of HFMSE total score by visit for individual subjects.

Revised Upper Limb Module (RULM)

The RULM is an outcome measure developed to assess upper limb functional abilities in patients with SMA, including young children, and patients with severe contractures in the lower limbs in whom the possibility to detect functional changes, such as rolling or long sitting, is limited. This test consists of upper limb performance items that are reflective of activities of daily living (i.e., raise a can to mouth as if drinking, take a coin and place it in a box, remove the lid of a container). The RULM 19 item test is quickly administered and has been evaluated in patients with SMA 2 to 52 years of age [Mazzone 2016].

The RULM will be assessed in participants who have reached ≥ 2 years of age during the study period. The baseline for RULM is defined as the first assessment at which it is administered where 3 or fewer items are missing. A derived total score will be calculated by summing the scores from these individual items. If, for an individual item, a response is recorded for both the left and right side the highest score will be used in calculating the total. For the 19-item test, if 3 or fewer items are missing then these items will be imputed to be 0 when summing all items. Otherwise, if more than 3 items are missing and at least 1 item is non-missing then the total score will be imputed by interpolating total scores between the previous and subsequent visit or, if there is no subsequent visit, by using the total score from the previous visit.

Analyses

- Summary of RULM total score and entry item A (as collected on CRF) by visit.
- Spaghetti plot of RULM total score by age for individual subjects.
- Summary of RULM total score and change from baseline over time for subjects with evaluable baseline at or prior to Day 1.
- List of RULM total score by visit for individual subjects.

Time to Event

An event of permanent ventilation will be defined as tracheostomy or ≥ 16 hours ventilation/day continuously for > 21 days in the absence of an acute reversible event. The Investigator will determine the date at which a participant is considered to have met the endpoint and enter this date in the CRF.

A participant who does not meet the endpoint definition will be censored for:

- time to death: at the last occasion the participant is seen and confirmed alive (either in-person visit or by telephone contact)
- time to permanent ventilation: at the last date the participant has a diary entry for ventilation. For subjects who moved over to have diary collection less frequently, the last occasion the subject was seen and confirmed alive will be used.

The reference date for calculation of time to event will be date of the first nusinersen dose.

A Kaplan-Meier survival curve of the time to death or permanent ventilation will be presented and used to estimate the median time to death or permanent ventilation and corresponding 95% CI.

[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted].

[redacted]

[redacted]

Ventilator Use

The available records of ventilator use status for each subject during the study will be listed.

[redacted]

[redacted]

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5.7. Safety Endpoints

The following clinical assessments will be performed to evaluate the safety profile of nusinersen:

- AE and SAE recording.
- Medical history, SMA history, onasemnogene abeparvovec dosing history, primary reason for participation in the study (as indicated by the caregiver), and steroid use history.
- Vital sign measurements.
- ECGs.
- Growth parameters.
- Neurological examinations.
- Laboratory safety test results.
- SNAP amplitudes.

Analyses of safety data will be based on the ITT Set. For analyses of Safety endpoints, displays similar to those for efficacy endpoints will be used. Baseline is defined as the last non-missing result prior to the first dose of nusinersen.

5.7.1. Adverse Event

AEs will be coded using the Medical Dictionary for Regulatory Activities.

All AEs will be analyzed based on the principle of treatment emergence. An AE will be regarded as treatment-emergent if it was present prior to receiving the first dose of nusinersen and subsequently worsened in severity or was not present prior to receiving the first dose of nusinersen but subsequently appeared. Details of identifying treatment emergence for events with missing start and stop dates may be found in Section 3.4. Furthermore, if the start date of an AE is missing or partially missing, the imputation algorithm described in Section 5.1 will be used to identify treatment emergent adverse events.

In the situation where change in severity (but no change in seriousness) occurs for an adverse event, study sites are instructed to enter an end date and start a new record for the adverse event. In the new record, the changed severity is to be recorded and the start date will be set to be the end date of the previous record. These records will be programmatically linked by preferred term and start/end date. Consider three scenarios:

- The first AE record occurs prior to the first dose, the second AE record occurs on or after the first dose, and the severity increases: Only the second record will be counted as treatment-emergent.
- The first AE record occurs prior to the first dose, the second AE record occurs on or after the first dose, and the severity decreases: Neither record will be counted as treatment-emergent.
- Both records occur on or after the first dose: If the AE severity on the second record is worse than the severity on the first record, then count both records as treatment-

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emergent. But, if the severity improves, then only count the first record as treatment-emergent.

Of note, when counting the total number of treatment-emergent events, events linked through change in severity will still be counted as separate events.

Adverse events will be coded using the MedDRA dictionary version 28.0 or later. This coding system provides more than five levels to classify adverse events. In general, adverse events will be presented by system organ class and preferred terms but other classifications may be used if warranted.

The incidence and frequency (event count) of treatment-emergent AEs will be summarized overall, by severity, and by relationship to nusinersen. A participant having the same AE more than once will be counted only once in the incidence for that event; multiple occurrences of the same adverse event for the same subject will all be counted in the frequency for that adverse event. The summary tables will include incidence estimates for overall system organ class as well as for preferred terms within each system organ class. Incidence will be presented by decreasing order by system organ class and by decreasing order by preferred term within each system organ class. The most common adverse events, i.e., those that occurred in at least 5% of the subjects, will be presented. Upon examination of the actual data, different cut-offs may be used if it is deemed more appropriate. The occurrence of the AE with the greatest severity will be used in the calculation of incidence by severity; the occurrence of the AE with the strongest relationship to nusinersen will be used in the calculation of incidence by relationship to nusinersen.

Adverse Events by Severity

The Investigator is to record the severity of each adverse event as mild, moderate, or severe. If a subject experienced the same adverse event multiple times, the event with the worst severity will be counted for incidence summaries. The incidence within each category may be presented.

Adverse Events related to Study Treatment and/or Lumbar Puncture Procedure

The Investigator is to record the degree to which each adverse event is related to Study Drug and Lumbar Puncture (related/not related). The incidence of adverse events related to study drug and those related to lumbar puncture will be summarized.

Serious Adverse Events (SAE)

The incidence of serious adverse events will be summarized by system organ class and preferred term. Incidence of serious adverse events will also be summarized by relationship to study drug. All SAEs will be listed as well.

Adverse Events that Led to Discontinuation from Treatment and/or Withdrawal from Study

The incidence of adverse events that led to discontinuation of study treatment and those that led to withdrawal from the study will be presented. All adverse events that led to discontinuation of study treatment and those that led to withdrawal from the study will be listed.

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Deaths

The incidence of death will be summarized. All deaths will be listed including cause of death. The incidence of events that led to death will be presented.

5.7.2. Growth Parameters

Growth parameters of body length or height (for all subjects), head circumference (for subjects up to 36 months of age), chest circumference (for subjects up to 36 months of age), and arm circumference (for subjects up to 36 months of age) will be measured. In participants with scoliosis, arm span may be measured in lieu of body length or height. Arm span is defined as the distance from the fingertip in one hand to that in the opposite hand and should be measured with the arms outstretched laterally away from the body. If arm span cannot be measured due to contractures, the Investigator may measure ulnar length between the point of the elbow and the midpoint of the prominent bone of the wrist. Additional parameters of weight-for-age, weight-for-length/height, and head-to-chest circumference ratio will be calculated.

Growth parameters at baseline and at each visit will be presented. The change from baseline to each visit will be summarized using descriptive statistics. Plots for mean change from baseline to each analysis visit will be generated for weight for age percentile and weight for length/height percentile. The frequency and percentage for weight-for-age, weight-for-length/height and length/height-for-age will also be presented for each of in the following categories: ≤ 1st, ≤ 3rd, ≤5th, ≤15th, ≤25th, ≤50th and > 50th percentile.

5.7.3. Laboratory Safety Assessments

The following laboratory tests will be performed to assess the safety profile of nusinersen:

- Hematology: complete blood count with differential and platelet count
- Coagulation parameters (by local laboratory): activated partial thromboplastin time, prothrombin time, and international normalized ratio
- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, bilirubin (direct and indirect), alkaline phosphatase, ALT, AST, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, potassium, cystatin C, creatine phosphokinase and/or creatine kinase
- Urinalysis: urine total protein (by local laboratory); specific gravity, pH, protein, glucose, ketones, bilirubin, blood, red blood cells, WBCs, epithelial cells, bacteria, casts, and crystals

A complete list of laboratory analytes is provided in Appendix B.

For a parameter if the local and central result are available with the same date and time then only the central analysis result will be considered for presentations by visit.

Laboratory data will be examined using an analysis of "shifts" and all available data will be considered for these irrespective if collected centrally or locally. Each subject's

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laboratory values will be classified according to whether the test result is "low" (i.e., below the lower limit of normal [LLN]), "normal" (within the normal range), or "high" (i.e., above the upper limit of normal [ULN]). If a subject is missing a baseline value but had a post-baseline value, then the baseline assessment is labeled as "unknown". Likewise, if a subject had a baseline value but had no post-baseline values, then the minimum and maximum post-baseline are labeled as "unknown". Post-baseline laboratory results are defined as any assessment taken after the first dose, including data collected from local laboratories. The shifts (relative to the normal range) from baseline to low and high will be calculated. If a subject's value shifts, it can change from normal to either low or high, from low to normal or high, from high to normal or low, or from unknown to low, normal, or high. For each parameter, the incidence of shift to low will be summarized using the minimum post-baseline values. Shift to low includes subjects with a normal, high, or unknown baseline value and at least one post-baseline value of the given test. Similarly, the incidence of shift to high will be summarized using the maximum post-baseline values. Shift to high includes subjects with a low, normal, or unknown baseline value and at least one post-baseline value.

Urinary protein results (+1, +2, +3 or >0.2g/L considered positive) will be summarized. For liver function tests, the additional categories will be defined to present the baseline and post-baseline values as within the upper limit of normal: $> 1 - \leq 2 \times$ ULN, $> 2 - \leq 3 \times$ ULN, $> 3 - \leq 5 \times$ ULN, $> 5 - \leq 10 \times$ ULN, $> 10 - \leq 20 \times$ ULN, $> 20 \times$ ULN for ALT/AST, $> 1 - \leq 2 \times$ ULN, $> 2 \times$ ULN for total bilirubin, and $> 1 - \leq 1.5 \times$ ULN and $> 1.5 \times$ ULN for alkaline phosphatase. Elevations in AST or ALT ($> 3 \times$ ULN) accompanied by concurrently elevated total bilirubin defined as $> 1.5 - \leq 2 \times$ ULN and $> 2 \times$ ULN will be also summarized. Scatter plot of highest ALT/AST and highest bilirubin at post-baseline will be presented where the data points will be color labeled by time between onasemnogene abeparvovec administration and first nusinersen dose (2-3 months versus >=3 months).

5.7.4. ECG

The number and percentage of subjects with shifts from normal to each of the categorical values denoting an abnormal scan (abnormal not AE, abnormal AE) as determined by the investigator will be summarized. A listing of subjects with abnormal status in ECG will be presented.

5.7.5. Neurological examinations

HINE Sections 1 and 3 will be administered to participants ≤ 24 months of age at the time of informed consent, and a standard neurological examination will be performed in participants > 24 months of age at the time of informed consent and for participants who reach > 24 months of age during their study participation. On dosing visits, neurological examination will be performed at 2 timepoints: pre-dose and at approximately 1 hour post-dose (or when sedation has worn off, if it was used).

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HINE

Sections 1 (neurological items) and 3 (behavior) of the HINE serve as the basis for neurological examinations.

The neurological items comprise cranial nerve function (facial appearance, eye appearance, auditory response, visual response, sucking/swallowing), posture (head in sitting position, trunk in sitting position, arms at rest, hands, legs in sitting position, legs in supine and standing positions, feet in supine and standing positions), movements (quantity, quality), tone (scarf sign, passive shoulder elevation, pronation/supination, adductors, popliteal angle, ankle dorsiflexion, pulled to sit, ventral suspension), and reflexes and reactions (tendon reflexes, arm protection, vertical suspension, lateral tilting, forward parachute). Behavior is comprised of state of consciousness, emotional state, and social orientation. A higher score is indicative of a better, or normal result. For some items, both the left and right sides are assessed however, this granularity is not captured in the CRF and the sites have been instructed to record the mean, resulting in reported values between the expected scores.

For each item, for each subject, the worst post-baseline and the best post-baseline outcomes will be determined and 'shift' tables showing the shifts from baseline to the worst and from baseline to the best post-baseline value will be presented. In this analysis, all assessments post the first dose at baseline will be considering post baseline visits. For any item where the investigators have entered scores outside the set of expected values the scores will be mapped prior to determining shifts as follows: for baseline values, to the next highest expected value and for post-baseline values to the next lowest expected value.

Subject profile plots and listings will also be presented.

In addition, a summary of change in HINE Section 1 suck/swallow from baseline to Day 302 in patients without the use of gastrointestinal tube at baseline will also be presented.

Standard Neurological Examination

Neurological examinations include assessment of mental status, level of consciousness, cranial nerves, reflexes, motor system, coordination/cerebellar function and sensation – temperature and vibration. The result collected for the majority of the tests is 'normal' or 'abnormal', however the assessment of sensations is reported as 'present' or 'absent' and the assessment of reflexes is captured on an ordinal scale. For each test it is recorded if secondary to SMA.

Subject profile plots and listings will be presented.

5.7.6. Vital signs

Vital signs will include temperature, heart rate, systolic and diastolic blood pressure, pulse oximetry, and respiratory rate. Vital signs will be taken at every onsite visit throughout the

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study. At treatment visits, vital signs will be taken at 2 timepoints: predose and at 1 hour postdose (± 30 minutes).

The number and percentage of subjects meeting selected criteria post-baseline will be summarized.

The criteria are:

- Systolic blood pressure increments or decrements of 20 and 40 mmHg
- Diastolic blood pressure increments or decrements of 10 and 20 mmHg
- Pulse rate increments or decrements of 15 and 30 bpm
- Body temperature >38 centigrade

Vital sign data for individual patients will also be listed.

5.7.7. SNAP amplitudes

Sensory nerve conduction studies will be performed to assess the function of sensory nerves/neurons. SNAP will be assessed in the sural and radial nerves unilaterally, in which the amplitude (onset to peak) of the response will be measured at the clinic by the Investigator or designee.

SNAP will be assessed at Screening and on Days 302 and 778 (End of Study)/Early Termination Visit.

Actual values and changes from baseline to each visit in SNAP amplitude for radial and sural will be presented using descriptive statistics.

5.8. Immunogenicity data

Immunogenicity (IM) testing (anti-nusinersen antibody positivity), using designated plasma samples collected from each study subject, is planned to be conducted and reported. Immunogenicity plasma samples are to be collected pre-dosing on Days 1, 64, 183, 302, 421, 540, 659, and follow-up Day 778/ET. Plasma samples collected at other time points for nusinersen concentration determinations may also be evaluated for IM testing if of further interest and deemed warranted by the pharmacokineticist. An individual sample result will be designated 'antibody positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed 'antibody negative'. The validated 1% false positive rate for the confirmatory assay will be used for the analysis.

For immunogenicity, the baseline value is defined as the immunogenicity data collected prior to first dose in the study. If no baseline immunogenicity data are collected, the value is missing and will be shown as 'Unknown' for immunogenicity analyses.

A study subject will be given 'antibody positive' status if they have at least one confirmed positive sample result at any time during the treatment or post-treatment evaluation periods. A study subject will be given 'antibody negative' status if all evaluated IM sample results are antibody negative and they have at least one evaluable IM result from Day 64 or later during

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the treatment and post-treatment evaluation periods. Otherwise, a study subject will be given 'antibody inconclusive' status.

Study participants with at least one confirmed post-treatment positive result will be considered positive for treatment-emergent anti-nusinersen antibodies if their baseline result is negative. Study participants that are confirmed positive at baseline and have at least one post-baseline sample with a > 2-fold increase in titer will be considered to have treatment-emergent anti-nusinersen antibodies. Study participants that are confirmed positive at baseline, with subsequent post-baseline samples titers that are ≤ 2-fold from baseline will be considered to not have treatment-emergent anti-nusinersen antibodies. In the event the baseline titer is missing then positive results post-baseline will be considered treatment emergent. For participants with unknown status at baseline the post baseline status will be defined as positive if any results are positive, and negative if all results are negative.

Antibody positivity will also be categorized (when possible) as being either 'persistent' or 'transient'.

Persistent is defined as having one positive test followed by another one more than 100 days after the first positive test. In addition, "persistent" is also defined as having one or more positive samples and no sample more than 100 days after the first positive sample. Transient is defined as having one or more positive results and not confirmed to be persistent.

The main analysis for immunogenicity will be presenting subjects with baseline prior to first dose of nusinersen based on three classified baseline antibody status:

- For subjects who are positive at baseline, for post-baseline status the number and percentage with treatment emergent positive, negative and no evaluable post-baseline result will be presented.
- For subjects who are negative at baseline, for post-baseline status the number and percentage with treatment emergent positive, negative and no evaluable post-baseline result will be presented.
- For subjects who are unknown at baseline, the number and percentage of subjects with positive results post baseline (it is not possible to confirm treatment emergent status), negative and no evaluable post-baseline result will be presented.

In addition, the number and percentage of participants who have positive persistent, positive transient and negative status will be presented. This will be presented using all dosed participants as the denominator and in addition, using all dosed participants with negative or positive status at baseline and at least one evaluable sample post baseline as the denominator.

Summaries will be presented for the ITT Set.

In addition, in antibody positive study subjects, antibody titers of any antibody positive samples will be reported (listed) and appropriately summarized across subjects and by treatment (e.g., at each evaluated time point, or by observed peak titer values, etc.) at the discretion of the designated study pharmacokineticist and/or statistician.

The incidence of AEs selected by anaphylactic reaction SMQ, angioedema SMQ, and hypersensitivity SMQ will be presented for subjects by Antibody status post-baseline in the following categories:

- Treatment emergent positive
  - Persistent
  - Transient
- Negative post-baseline
- No evaluable sample post baseline

[redacted]

[redacted]

5.10. Pharmacodynamic Endpoints

The pharmacodynamic (PD) properties of nusinersen will be assessed using the following:

[redacted]

CSF sample collected at pre-dose on Days 1, 15, 29, 64, 183, 302, 421, 540 and 659 will be tested for neurofilament concentration. Plasma samples collected at pre-dose on Days 1, 64, 183,302, 421, 540, 659 and 778/ET will be tested for neurofilaments concentration in addition to age-based visits at month 15, 18 and 24 for participants <300 days of age.

Baseline is defined as the most recent non-missing measurement collected prior to the first dose or Day 1. If any measurement is non-missing prior to the first dose, the value closest to and prior to the first dose is used as baseline value. If no measurement is available prior to the first dose but a value on Day 1 is available, then this would be utilized as the baseline value.

Analyses

- Summary tables will be presented for Plasma and CSF levels of NF-L, change and percentage change from baseline by visit.
- The plot of mean change from baseline and mean percentage change from baseline over time for Plasma and CSF levels of NF-L will be presented on the original scale.
- Plots of geometric mean (±95% CI) over time will be presented for Plasma and CSF levels of NF-L on the linear and semi-logarithmic scale.
- A plot of geometric mean ratio (±95% CI) for change to baseline over time will be presented for Plasma and CSF levels of NF-L on the linear scale.

- Spaghetti plots of Plasma and CSF NF-L concentrations over actual study days, age at sample collection (months), and the time from onasemnogene abeparvovec dosing to sample collection (months) will also be presented.

6. Changes from Protocol-Specified Analyses

Although Protocol V4.0 of the study defines the Safety Set for non-efficacy analysis and Evaluable Set for efficacy analysis, the ITT Set, with same definition as Safety Set will be used in this SAP and reporting.

[redacted]

7. Summary of Changes from the Previous Version of the SAP

- Study objectives and endpoints were updated per protocol V4.0 (NF-L analysis was added as a secondary endpoint).
- Study design was updated per protocol V4.0 (The total number of participants planned for enrollment and the minimum number of participants in Subgroups A and B were

updated. Additionally, the age for inclusion in Subgroups A or B was changed from ≤ 9 months to < 300 days).

- In Section 3.6, Analysis set "Safety Set" was changed to "ITT Set" (with the same definition) which will be used for all clinical endpoints, and a new analysis set "Per-Protocol Set" was defined to be used for supplementary analysis on selected analyses on the primary efficacy endpoint (HINE-2). Additionally, definitions of [redacted], PD population and Immunogenicity set were also added to be used for [redacted], PD, and Immunogenicity analysis. The main displays to be used in the reporting were also updated.
- In Section 5.1, details of visit windowing for unscheduled and early termination visits were added.
- In Section 5.6.2 and 5.6.3, the item-level imputation rules were updated for HINE-2 and CHOP INTEND, and the item-level imputation rule for WHO motor milestones was removed as it is no longer applicable.
- Analyses for efficacy and safety endpoints were adjusted.
- Description and analyses for Immunogenicity, [redacted] and PD (NF-L) endpoints were adjusted.

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APPENDIX A. PERMANENT VENTILATION DEFINITION CRITERIA: ACUTE REVERSIBLE EVENT

Purpose: Acute, intercurrent events may result in transient utilization of increased respiratory support for participants with SMA in this study. Such events may not reflect irreversible SMA disease progression and may complicate the ability to detect the effects of nusinersen on SMA disease progression.

One of the secondary endpoints is defined as 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**).

The purpose of this appendix is to define an acute reversible event and to indicate how this prespecified definition will be used in this study.

Any one of the following that occur between **7 days before and 7 days after** the onset of threshold-level respiratory support (≥ 16 hours/day) meets the definition of an acute reversible event:

1. Fever ≥ 102°F/38.9°C (tympanic, rectal, axillary, skin, sublingual)

Infection

Blood, sputum, throat, or CSF culture positive × 2 for virus, bacteria, or fungus

Blood, throat, sputum, or CSF viral polymerase chain reaction positive

Blood, throat, sputum, or CSF for infectious antigen diagnostic (e.g., streptococcus+ or HBsAg)

Blood, throat, sputum, or CSF positive for direct microscopic visualization (e.g., bronchoalveolar lavage or Gram stain revealing the presence of bacteria by tissue biopsy)

Surgical procedure

Operation (i.e., gastrostomy/jejunostomy tube or an orthopedic procedure)

Any procedure in which regional or general anesthesia is administered

If any of the above is verified by appropriate source documents (e.g., emergency room visit summary, outpatient clinic note, inpatient hospital summary, operative report), the endpoint is **NOT** met until the participant requires threshold-level ventilation (≥ 16 hours/day) continuously for > 21 days beginning 14 days after the acute reversible event. The rationale is that, in the context of an acute reversible event, the SMA participant is given a "grace period" of 14 days to clear the event or recover from surgery/anesthesia. Once the grace period has expired, if the participant requires threshold-level ventilation for > 21 consecutive days, this respiratory dependence is likely to be due to SMA disease progression, and the endpoint is met.

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APPENDIX B. LABORATORY ANALYTES

Clinical Safety Assessments (Minimum Requirements)		Other Assessments
<u>Blood Chemistry</u> Sodium Potassium Chloride Total protein Albumin Calcium Phosphorus Bicarbonate Glucose Blood urea nitrogen Creatinine Creatine phosphokinase and/or Creatine kinase Cystatin C Total serum bilirubin (direct and indirect) Alkaline phosphatase AST ALT GGT	<u>Urinalysis</u> Specific gravity pH Protein Glucose Ketones Bilirubin Blood RBC WBC Epithelial cells Bacteria Casts Crystals <u>Hematology</u> Red blood cells Hemoglobin Hematocrit Platelets WBCs WBC differential (% and absolute) • Neutrophils • Eosinophils • Basophils • Lymphocytes • Monocytes	[redacted] <u>Immunogenicity Evaluation</u> Plasma anti-nusinersen antibodies **The following are to be assessed by local laboratory only:** Urine total protein (quantitative) Coagulation (activated partial thromboplastin time, prothrombin time, and international normalized ratio)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; [redacted]; [redacted]; GGT = gamma glutamyl transferase; [redacted]; [redacted]; RBC = red blood cell; [redacted]; WBC = white blood cell.

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Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

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