Official Title:	An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443
NCT Number:	NCT02594124
Document Date:	06-September-2023

Biogen

Statistical Analysis Plan

Version No.: 5.0

An Open-Label Extension Study for Patients With Spinal Muscular Atrophy Who Previously Participated in Investigational Studies of ISIS 396443

Analysis of CS11, integrating CS11 with CS1, CS2, CS10, CS12, CS3A, CS3B, CS4 and 232SM202 (CS7)

Name of Study Treatment: ISIS 396443

Protocol No.: Version 6, 20 October 2021

Study Phase: Phase 3

APPROVAL

Approved By:

DocuSigned by:
[redacted]

08-Sep-2023

[redacted], SMT Statistician — Date

DocuSigned by:
[redacted]

08-Sep-2023

[redacted], Program Statistician — Date

DocuSigned by:
[redacted]

08-Sep-2023

[redacted], Medical Director — Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	18-July-2017	Not applicable
2.0	09-January-2019	• Introduced MMDR visits. • Updated windowing for analysis visit to allow for efficacy analyses every 8 months. • Updated integrated safety presentation for infantile SMA onset subjects by display according to age at screening when subjects receive ISIS 396443. • Incorporated changes in protocol amendments version 2 and 3.
3.0	27-September-2019	• [redacted] • [redacted] • In section 4.2 Efficacy displays, for the re-evaluated subjects, corrected a typo from '=54' to '<=54' for HFMSE.

SAP Version	Date	Primary Reasons for Amendment
		• Additional efficacy analyses utilizing MMDR Day 1
4.0	15-December-2020	• Incorporated changes in Statistical analysis of assessments as part of Protocol Amendment Versions 4 and 5, eg. MMDR visit schedules for motor functions, PedsQL, X-ray etc. • Updated imputation methods for CHOP INTEND from MMDR Day 1. • Removed CGI from this SAP due to difficulty in reliable interpretation. • [redacted] • Updated Appendix A windowing for efficacy based on updated MMDR schedule. • [redacted].
5.0	06-September-2023	• To fulfill final analysis purpose and perform analyses for all data. • To add presentations of age at first nusinersen dose for CS3B subjects and CS4 subjects.

TABLE OF CONTENTS

Contents

ABBREVIATIONS

ACEND	Assessment of Caregiver Experience with Neuromuscular Disease
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
AST/SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
ATC	Anatomical Therapeutic Class
AUC	area under the curve
[redacted]	[redacted]
BLQ	below the lower limit of quantification
BUN	blood urea nitrogen
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP	Compound Muscle Action Potential
C_{max}	maximum observed drug concentration
[redacted]	[redacted]
CRF	case report form
[redacted]	[redacted]
[redacted]	[redacted]
CV	coefficient of variation
CI	confidence interval
[redacted]	[redacted]
DSMB	Data Safety Monitoring Board
EAC	Event Adjudication Committee
ECG	Electrocardiogram
EDC	Electronic data collection
EODBP	End of Double Blind Period
HFMSE	Hammersmith Functional Motor Scale - Expanded
HINE	Hammersmith Infant Neurological Examination
IM	immunogenicity
IT	intrathecal
ITT	intent-to-treat
LLN	lower limit of normal
LLOQ	lower limit of quantification
LP	lumbar-puncture
MedDRA	Medical Dictionary for Regulatory Activities
MMDR	Modified Maintenance Dosing Regimen
PCR	polymerase chain reaction
PedsQL	pediatric Quality of Life Inventory
[redacted]	[redacted]
[redacted]	[redacted]
PT	Preferred term

[redacted]	[redacted]
RBC	red blood cell
RULM	Revised upper limb module
SD	standard deviation
6MWT	6-Minute Walk Test
SE	standard error
SMA	Spinal Muscular Atrophy
SOC	System Organ Class
Tmax	time at which Cmax occurs
ULM	upper limb module
ULN	upper limit of normal
[redacted]	[redacted]
[redacted]	[redacted]
WBC	white blood cell
WHODrug	World Health Organization drug dictionary

1.0 INTRODUCTION

The first planned interim analysis for the CS11 study was conducted with a cutoff date of 30June2017 and was detailed in two separate interim statistical analysis plans:

- CS11 only [18 Jul 2017]
- Integration of CS11 and index studies.

This statistical analysis plan (SAP) combines both integrated and CS11 only reporting.

CS11 is an open-label extension study in subjects with SMA who previously participated in investigational studies of nusinersen. The primary purpose of this study is to gather additional information on the long-term safety, tolerability, and efficacy of repeated doses of nusinersen (12 mg) administered as IT injections by lumbar puncture (LP).

Subjects will enter CS11 from five different studies, two of these were randomized, double-blind, sham-procedure controlled studies (CS3B and CS4) and three were open-label studies (CS3A, CS12 and 232SM202 Part 2). The populations participating in these studies are infantile (CS3A and CS3B), later onset SMA (CS12 and CS4) and infantile and later onset (232SM202).

1.1 A Brief Description of the Index Studies Follows:

1.1.1 Overview of Infantile Onset SMA Studies

CS3A was a Phase 2, multicenter, open-label, multiple-dose, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of nusinersen administered intrathecally to subjects with onset of SMA symptoms at <= 6 months of age and aged ≤ 7 months at screening. Two 'loading' dose levels, 6 or 12 mg (scaled equivalent) were evaluated sequentially. The initial dose level of 6 mg was studied in a cohort of 4 subjects, and the 12 mg dose level in 16 subjects. Loading doses were administered on Days 1, 15, and 85. Thereafter, all subjects received maintenance doses of 12 mg equivalent nusinersen on Days 253, 379, 505, 631, 757, 883, 1009, 1135 and 1261. Subjects were followed until Day 1352 (45 months). The study was terminated early.

CS3B was a Phase 3, multicenter, randomized, double-blind, parallel-group, sham-procedure-controlled study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of nusinersen administered to subjects with 2 SMN2 copies who had onset of clinical signs and symptoms of SMA at ≤ 6 months of age. 121 subjects were randomized 2:1 to receive a scaled equivalent 12 mg dose of nusinersen or underwent a sham procedure as control, respectively. Nusinersen was administered using a loading regimen (dosing on Study Days 1, 15, 29, and 64) followed by maintenance dosing once every 4 months (dosing on Days 183 and 302). Subjects randomized to the sham-procedure control group underwent a sham-procedure on Study Days 1, 15, 29, 64, 183, and 302. The total duration for treatment and follow-up was to be 13 months. As this study showed significant efficacy of nusinersen compared to sham at the pre-specified interim analysis, the study was terminated early.

Study no. / study type	Design	Sample size	Doses and duration

CS3A/ Phase 2, safety and efficacy	Multicenter, open-label, multiple-dose, dose-escalation	20 total: Cohort 1: 4 Cohort 2: 16	6 mg (scaled equivalent) on Days 1,15, and 85 followed by 12 mg (scaled equivalent) on Days 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261 12 mg (scaled equivalent) on Days 1, 15, 85, 253, 379, 505, 631, 757, 883, 1009, 1135, and 1261. Total duration: 1352 days (45 months)
CS3B/ Phase 3, efficacy and safety	Multicenter, randomized, double-blind, parallel-group, sham-procedure-controlled	121 total: 80 ISIS 396443* 41 Sham	12 mg (scaled equivalent) on Days 1, 15, 29, 64, 183, and 302. Total duration: 442 days (14 ½ months)

*One subject in CS3B randomized to receive nusinersen did not receive any medication within CS3B but is dosed within CS11

1.1.2 Overview of Later-onset SMA Studies

A brief description of CS12 and the other 3 studies that preceded it (CS1, CS2 and CS10) is given below:

CS1 was a Phase 1, multicenter, open-label, single-dose, dose-escalation study to evaluate the safety, tolerability, and pharmacokinetics of nusinersen in subjects with SMA. A single dose of nusinersen was administered to subjects with SMA who were 2 to 14 years of age. Four doses, 1, 3, 6, and 9 mg, were evaluated sequentially. Each dose was studied in a cohort of 6 or 10 subjects, where all subjects received study treatment. Subjects in Cohorts 1 and 2 were followed until Day 29 (1 month), and subjects in Cohorts 3 and 4, until Day 85 (3 months).

CS2 was a Phase 1/2, open-label, multiple-dose, dose-escalation study designed to assess the safety, tolerability, and pharmacokinetics of nusinersen in 2- to 15-year-old subjects with SMA. Four dose levels (3, 6, 9, and 12 mg) were evaluated sequentially. Doses were administered on Days 1, 29, and 85 at the 3, 6, and 12 mg dose groups and on Days 1 and 85 for the 9 mg dose group. Subjects in Cohort 1 of CS1, who had received a single dose of 1 mg, were eligible to participate as were untreated subjects who satisfied the inclusion/exclusion criteria. Subjects were followed until Day 253 (8 months).

CS10 was a Phase 1, open-label, single-dose study to assess the safety, tolerability, and pharmacokinetics of nusinersen in subjects with SMA who had previously participated in Cohorts 2, 3, and 4 (3, 6, and 9 mg, respectively) of CS1. Single doses of 6 or 9 mg of nusinersen were evaluated sequentially. Subjects were followed until Day 169 (5½ months).

CS12 was a Phase 1, open-label, multiple-dose study to assess the safety and tolerability of a 12 mg nusinersen dose in subjects with SMA who previously participated in either CS2 or CS10. Doses were administered on Days 1, 169, 351, and 533. The study was terminated early.
Data from these studies will be combined longitudinally.

CS4 was a Phase 3, multicenter, double-blind, randomized, sham-procedure-controlled study of nusinersen administered intrathecally over 15 months to patients, from age between 2 to 12 years at screening, with later-onset SMA. 126 subjects were randomized 2:1 to receive a 12 mg dose of nusinersen or undergo a sham procedure as control, respectively. Randomization was stratified based on the subject's age at screening: <6 years versus >6 years. Nusinersen was administered using a loading regimen (dosing on Study Days 1, 29, and 85) followed by a maintenance dosing 6 months thereafter (Day 274). Subjects randomized to the sham-procedure control group underwent a sham-procedure on Study Days 1, 29, 85, and 274. The study consisted of screening, treatment, and post-treatment follow-up-periods. The total duration of participation in the study was approximately 16 months. As this study demonstrated significant efficacy of nusinersen compared to sham, at the pre-specified interim analysis, the study was terminated early.

Study no. / study type	Design	Sample size	Doses and duration
Completed studies			
CS1/ Phase 1, safety	Multicenter, open-label, single-dose, dose-escalation	34 total: Cohort 1: 6 Cohort 2: 6 Cohort 3: 6 Cohort 4: 10	 Cohort 1: 1 mg Cohort 2: 3 mg Cohort 3: 6 mg Cohort 4: 9 mg Single dose on Day 1 Total duration: 29 days (1 month) for Cohorts 1 and 2, 85 days (3 months) for Cohorts 3 and 4
CS10/ Phase 1, safety	Multicenter, open-label, single-dose, extension to CS1.	18 total: Cohort 1: 4 Cohort 2: 14	 Cohort 1: 6 mg Cohort 2: 9 mg Single dose on Day 1 Total duration: 169 days (5½ months)
CS2/ Phase 1/2, safety and efficacy	Multicenter, open-label, multiple-dose, dose-escalation	34 total: Cohort 1: 8 Cohort 2: 8 Cohort 3: 9 Cohort 4: 9	 Cohort 1: 3 mg on Days 1, 29, 85 Cohort 2: 6 mg on Days 1, 29, 85 Cohort 3: 9 mg on Days 1, 29, 85 Cohort 4: 12 mg on Days 1, 29, 85 Total duration: 253 days (8 months)
CS12/ Phase 1, safety	Multicenter, open-label, multiple-dose extension to CS1, CS10, CS2	42 total	12 mg on Days 1, 169, 351, 533 Total duration: 542 days (18 months)
CS4/ Phase 3, efficacy and safety	Multicenter, randomized, double-blind, parallel-group, sham-procedure-controlled	126 total: 84 ISIS 396443 42 Sham	12 mg on Days 1, 29, 85, and 274. Total duration: 482 days (16 months)

1.1.3 Overview of Infantile and Later-onset SMA Study (232SM202)

232SM202 was a Phase 2 multicenter study conducted in 2 parts. Part 1 was originally designed as a randomized, double-blind, sham-procedure controlled study to assess the safety and tolerability and explore the efficacy of intrathecally administered nusinersen over a period of approximately 14 months (from the first dose until the End of Part 1 Evaluation). 21 subjects were randomized in a ratio of 2:1 to receive nusinersen by intrathecal lumbar puncture (LP) injection or a sham-procedure control. Randomization was stratified based on age at onset of clinical signs and symptoms consistent with SMA: >6 months versus <=6 months. Part 1 of the study was stopped early due to the efficacy results seen in the CS3B study.

Part 2 study procedures was determined based on the treatment assignment in Part 1. For subjects who were randomized to receive nusinersen in Part 1, Part 2 Day 1 occurred following the End of Part 1 Evaluation or approximately 4 months following the last injection of nusinersen in Part 1. On Part 2 Day 1 subjects received their first dose of nusinersen for Part 2 and returned to the study site on Days 120, 239, 358, 477, 596, and 715 for follow-up evaluations and subsequent maintenance dose injections. For subjects who were receiving sham procedure in Part 1, Part 2 Day 1 occurred following the End of Part 1 Evaluation or as soon as possible following the End of Part 1 Evaluation. At Day 1, subjects received their first dose of nusinersen (first loading dose). Subjects returned to the study site on Days 15, 29, 64, 183, 302, 421, 540, 659, and 778 for follow-up evaluations and subsequent injections. The study was terminated early.

Study no. / study type	Design	Sample size	Doses and duration
232SM202 Part 1/ Phase2, safety	Multicenter, randomized, double-blind, parallel-group, sham-procedure-controlled	21 total: 14 ISIS 396443 7 Sham	12 mg (scaled equivalent) on Days 1, 15, 29, 64, 183, and 302. Total duration: 385 days (13 months)
232SM202 Part 2	Multicenter, open-label, multiple dose	20 total: 14 previous ISIS 396443 6 previous Sham	12 mg (scaled equivalent) on Days 120, 239, 358, 477, 596, and 715 Days 15, 29, 64, 183, 302, 421, 540, 659, and 778 Total duration: 659 days (22 months)

1.1.4 Overview of CS11 (SHINE)

Since the start of CS11 study, there have been protocol amendments that have allowed for subjects from other studies to enter this long extension study (for example, CS3A and 232SM202). The aim of each of the protocol amendments was also to modify and unify the visit structures, assessments and regimens. The main changes were:

- The dose regimen was changed to be every 120 days for the subjects from later onset studies. Visit names were changed to be modified maintenance dosing regimen (i.e. MMDR Day 1, MMDR Day 120 etc.)
- New assessments (i.e. HFMSE, RULM and others for infantile onset studies) were introduced and harmonized, such that all studies had the same assessments
- The MMDR dosing schedule consists of MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, 960, 1080 1200, 1320, 1440, 1560, and 1680 (±14 days) until the EOS Evaluation/Early Termination (ET) Visit. The study will last 5 years from MMDR Day 1
- For Protocol Version 4, the Clinical Global Impression of Change (CGIC) was removed, although data was analyzed for CGIC scores collected while the previous protocol versions applied. For Protocol Version 5, the Pediatric Voice Handicap index (pVHI) was added
- In Protocol Version 6, a limit was set for the number of subjects who are receiving nusinersen concomitantly with other SMA therapies to 20% (n = 58) of the total population. The follow-up visits for subjects who discontinued study treatment were removed. For various efficacy and safety assessments, if an assessment is not performed at a visit, attempts were made to perform the assessments at the subsequent dosing visit(s) until completed.

Enrollment: 292 patients (from CS3B, CS4. CS12, CS3A studies and 232SM202).

Study no. / study type	**Design**	**Sample size**	**Doses**
CS11 Phase 3 safety and efficacy	Multicenter, open-label, multiple-dose extension	292 totals:	
		Group 1A (sham procedure in CS3B to nusinersen in CS11): 24 Group 1B (nusinersen in CS3B to nusinersen in CS11): 65	12 mg on Days 1, 15, 29, 64, followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule 12 mg of nusinersen on Days 29 and 3 sham procedures on Days 1, 15, and 64 followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule.

		Group 2A (sham procedure in CS4 to nusinersen in CS11): 42	12 mg on Days 1, 29, 85, followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule
		Group 2B (nusinersen in CS4 to nusinersen in CS11): 83	12 mg of nusinersen on Days 1 and 85 and 1 sham procedure on Day 29 followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule
		Group 3 (nusinersen in CS12 to nusinersen in CS11): 45	12 mg on MMDR Days 1, followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule
		Group 4 (nusinersen in CS3A to nusinersen in CS11): 13	12 mg on MMDR Days 1, followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule
		Group 5 (nusinersen in 232SM202 to nusinersen in CS11): 20	12 mg on MMDR Days 1, followed by maintenance doses of nusinersen approximately every 4 months according to the MMDR dosing schedule

2.0 DESCRIPTION OF OBJECTIVES AND ENDPOINTS

The objective of the CS11 protocol is to gather additional information on the long term safety, tolerability, and efficacy of repeated 12-mg doses of nusinersen (also known as BIIB058 and ISIS 396443) administered as intrathecal (IT) injections by lumbar puncture (LP) in subjects with spinal muscular atrophy (SMA).

Primary objective

To evaluate the long-term safety and tolerability of nusinersen administered by IT injection to subjects with SMA who previously participated in investigational studies of ISIS 396443

Secondary objective

To examine the long-term efficacy of nusinersen administered by IT injection to subjects with

SMA who previously participated in investigational studies of ISIS 396443

[redacted]

[redacted]

This statistical analysis plan describes the analyses to be performed, which will pool the data from the index studies with the CS11 data.

The endpoints which will be integrated and analyzed are listed below.

2.1 Safety and Tolerability Endpoints

- AEs and SAEs
- Vital signs and weight.
- Neurological examinations
- Clinical laboratory tests (serum chemistry, hematology, urinalysis, and urine total protein)
- Coagulation parameters (aPTT, and INR)
- ECGs
- Use of concomitant medications

2.2 Efficacy Endpoints

- Achievement of motor milestones (WHO motor milestones and/or Section 2 of HINE)
- Time to death or permanent ventilation (tracheostomy **or** ≥16 hours ventilation/day continuously for >21 days in the absence of an acute reversible event). The definition of an acute reversible event is provided in the SHINE Ventilation Endpoint Guidance.
- Percentage of subjects not requiring permanent ventilation
- Change from baseline in applicable motor function assessments: CHOP INTEND, HFMSE, RULM, 6MWT, and contracture assessment
- Change from baseline in CMAP
- Growth parameters
- Proportion of CMAP responders
- Number of motor milestones (WHO or HINE-2) achieved per subject
- Proportion of subjects who achieved standing alone
- Proportion of subjects who achieved walking with assistance
- Number of serious respiratory events
- Number and length of hospitalizations
- Change from baseline in Cobb-Angle on X-ray of the thoracolumbar spine
- Changes in quality of life assessments: PedsQL, and/or ACEND

- Disease-related hospitalizations and AEs
- Survival rate

[redacted]

3.0 INTERIM ANALYSES

The first interim analysis was conducted using a cut-off date of 30 June 2017. Further interim analyses have been/may be conducted with alternative cut off dates determined by examining the progress of subjects in order to support regulatory submissions, nusinersen drug development planning, and business activities. It may be that only certain subjects and only a pre-defined list of assessments is cleaned and locked for a particular interim analysis.

For the interim analyses for efficacy endpoints, efficacy sets at each visit will be defined as the

subset of subjects in the Safety set who have the opportunity to be assessed at that visit.

4.0 GENERAL CONSIDERATIONS

In this Statistical Analysis Plan, the terms "control" and "previous control" refer to the set of subjects who were randomized to undergo the sham procedure during the index study CS3B (group 1A) and CS4 (group 2A) and 232SM202 (group 5).

In order to distinguish nominal visit names from duration defined in terms of days, visit names will be referred as "Day 15", "Day 29," etc., and "15 days" or "29 days," etc., and will be used to define time intervals.

Safety set: safety presentations will utilize the safety populations as defined in the index studies which was based on subjects who received at least one dose of nusinersen or sham procedure. A second Safety set will be defined as all subjects who are enrolled and received at least 1 dose of nusinersen or underwent sham procedure during CS11. Both Safety sets will be used for safety and efficacy analyses.

The MMDR Safety set will be defined as the subset of subjects that had received an MMDR day 1 dose.

One CS3B subject was randomized to nusinersen but withdrew from the study prior to receiving any dose due to an adverse event. This subject went on to be dosed with nusinersen in the CS11 study. For integrated safety analysis, baseline for this subject will be based on the first nusinersen dose in CS11. For the main efficacy analysis considering all patients from the start of CS3B, since this subject wasn't dosed in CS3B, the date of randomization will be considered as baseline and CS11 efficacy visits will be windowed to the planned analysis visits accordingly. In efficacy analyses where the patients are grouped based on age at first dose, the baseline will be the first dose in CS11 and this subject will be included in the >=10 month to <23 month group.

[redacted]

New endpoints were introduced as part of CS11 and during CS11 as part of protocol amendments compared to those used in the index studies. In order to allow presentation of results longitudinally, analyses will be presented from the following baselines, based on the timepoints that endpoints were introduced:

- First dose of nusinersen in index studies
- First dose of nusinersen in CS11
- Dose of MMDR Day 1 in CS11

Presentations of immunogenicity data will be based on all dosed subjects.

Summary statistics will be presented throughout. For continuous endpoints, the summary statistics will generally include number of subjects with data, mean, standard deviation, median, minimum and maximum. For categorical endpoints, the summary statistics will generally include: number of subjects dosed, number of subjects with data, and the percentage of those with data in each category. Frequency distributions will be presented as appropriate.

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

4.1 Safety Displays

4.1.1 Integrated Displays

For integrated analyses, the following groupings will be used. Infantile onset is defined as age at symptom onset <=6 months and later onset is defined as age at symptom onset > 6 months. Screening age in these displays is the age at screening in the first study at which they are dosed with ISIS 396443.

1) *Infantile-onset*:

- Controlled study (CS3B): this will include only the index study data
  - Control
  - ISIS 396443
- Controlled and uncontrolled studies including extensions (which include all the infantile onset subjects treated with ISIS 396443 in CS3B, CS3A and 232SM202) by age at screening (the age at screening here refers to the screening visit prior to starting ISIS 396443; for example, for a subject who was in the CS3B previous control group, it will be the screening visit for CS11)
  - Screened <= 7 months of age (previous ISIS 396443 data from CS3B and CS3A to CS11 inclusive)
  - Screened >7 months of age (previous control data from CS3B to CS11 inclusive only and 232SM202 infantile onset, which includes previous ISIS 396443 data from Part 1/Part 2 and previous control subjects from Part 1 data to CS11 inclusive)
  - Total (sum of the Screened <= 7 and >7 months columns)

2) *Later-onset:*

- Controlled study (CS4) this will include only the index study data
  - Control
  - ISIS 396443
- Controlled and uncontrolled studies including extensions (this will include all the later onset SMA subjects treated with ISIS 396443)

- Subjects first dosed with ISIS 396443 in either CS4 or 232SM202 Part 1, plus any follow-up in CS11 or 232SM202 Part 2.
- Subjects first dosed in CS1 or CS2 and follow-up in CS10, CS12, CS11
- Subjects who received sham in CS4 or 232SM202 Part 1 from the first dose of ISIS 396443 in CS11 or 232SM202 Part 2, plus any follow-up in CS11

3) *All SMA subjects treated with ISIS 396643*

- Infantile onset
  - Screened <= 7 months of age (previous ISIS 396443 data from CS3B and CS3A to CS11 inclusive)
  - Screened >7 months of age (previous control data from CS3B only and 232SM202 infantile onset, which includes previous ISIS 396443 data from Part 1/Part 2 and previous control subjects from Part 1 data to CS11 inclusive)
- Later onset
- All treated subjects

4.1.2 CS11 Only Displays

For analyses of CS11 only data the following groupings will be used. It should be noted that screened <=7 and > 7 months of age will be as described in the integrated analysis (i.e. using the screening date of the study in which the subject first received ISIS 396443 treatment).

- Infantile onset
  - Screened <= 7 months of age (previous ISIS 396443 in CS3B and CS3A)
  - Screened >7 months of age (previous control in CS3B and 232SM202)
- Later onset CS11 data from subjects originating from CS4, CS1, CS2, 232SM202
- Total (infantile and later onset)

4.2 Efficacy Displays

4.2.1 Age at First Nusinersen Dose

Since age is an important covariate in SMA, for the CS4 and CS3B studies analyses will be performed categorized by age at first nusinersen dose group for both safety and efficacy analyses. The following depicts the age groups:

- For CS3B subjects (previous ISIS 396443 data from CS3B to CS11 inclusive)
  - Age < 6 months
  - Age >=6 to < 10 months
- For CS3B subjects (previous control) dosed in CS11: Age >=10 to < 23 months

- For CS4 subjects (previous ISIS 396443 data from CS3B to CS11 inclusive)
  - Age >=2 to <3.5 years
  - Age >=3.5 to <5 years
- For CS4 subjects (previous control) dosed in CS11: Age >=5 to <9.5 years

4.2.2 Other Displays

In addition, displays will be presented where the approach is to preserve the index study groupings so for infantile onset studies:

- CS3A from their first nusinersen dose in CS3A
- CS3B previous control from their first sham procedure in CS3B including all efficacy in CS3B only
- CS3B previous control from their first nusinersen dose in CS11
- CS3B previous control from their first sham procedure in CS3B and including all efficacy in both CS3B and CS11
- CS3B previous ISIS 396443 from their first nusinersen dose in CS3B

And the later onset studies:

- Type 2 subjects who received their first ever nusinersen dose in CS2/CS12
- Type 3 subjects who received their first ever nusinersen dose in CS2/CS12
- CS4 previous control from their first sham procedure in CS4 including all efficacy in CS4 only
- CS4 previous control from their first nusinersen dose in CS11
- CS4 previous control from their first sham procedure in CS4 and including all efficacy in both CS4 and CS11
- CS4 previous ISIS 396443 from their first nusinersen dose in CS4

Efficacy analysis from MMDR Day 1:

From MMDR Day 1, the sites will attempt to perform the same set of efficacy assessments on all subjects. In longitudinal summaries for these measures, subjects will be pooled using the same groupings as planned for safety presentations by infantile or later onset SMA. In addition, summaries from MMDR Day 1 will be produced using the original study groups, such as 'Previous ISIS 396443' or 'Previous control' for subjects originally dosed in CS4 and CS3B or CS12 patients split by SMA type.

For outcomes started at MMDR day 1 in patients in CS3B or CS4 we will plot the age at visit date the horizontal axis vs change on the vertical axis. Each patient will be represented by a line (spaghetti plot). A mean line will be fitted to the outcomes with its corresponding confidence intervals.

5.0 STUDY SUBJECTS

5.1 Subject Accountability

The number of subjects who were dosed, completed the index study and did not enter CS11, and completed CS11, along with reasons for discontinuing treatment and withdrawing from the index or CS11 studies will be summarized. Listings of those subjects who discontinued treatment and/or withdrew from the index or CS11 studies and the reasons for discontinuation/withdrawal will be presented. Subjects who died during the index or CS11 studies will also be listed separately.

5.2 Demographic and Baseline Disease Characteristics

For all the subjects who received nusinersen in the index studies, baseline will be the index study baseline. For subjects on sham procedure in the index studies or in Part 1 for 232SM202, a second baseline will be defined prior to their first dose of ISIS 396443 in CS11 or 232SM202 Part 2, respectively. In the summaries based on MMDR Day 1, the MMDR Day 1 dosing date will be considered the starting point and demographics and disease characteristics will be summarized at this time point.

Baseline data for demography, medical history, SMA history, and baseline disease characteristics may be taken from the index studies data.

Demography includes age, sex, ethnicity, and race. Medical history will be coded in MedDRA and the number and percentage of subjects with each medical history presented by preferred term. SMA history, depending on the data collected on the index studies (example gestational age, birth weight, age at symptom onset, age at SMA diagnosis, and the number of copies of the SMN2 gene.).

Race and ethnicity are not available for all subjects in CS11 since certain countries do not permit collection. If race was not permitted to be collected in CS11 then for these subjects it will be presented as 'Not reported' in any summary table. This approach will be followed even if race or ethnicity is available from an index study.

Demographic and baseline disease characteristics will be presented for the Safety set and Efficacy set as appropriate.

5.3 Extent of Exposure

The number of doses received and the number of sham procedures performed will be displayed using frequency distributions. The amount of nusinersen received will be presented using summary statistics. Number of doses and overall time on therapy will be presented for age at first dose display.

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 or first sham procedure) + 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. The date of first dose or first sham procedure is the first date in the index study.

Time on study will be categorized into intervals and summarized by treatment group and overall. Given the long half-life of nusinersen, subjects are considered to be exposed to Study Drug from the time the first dose was administered to the last day of follow-up. Essentially, exposure is equivalent to time on study.

The number of doses of drug received and time on study up to MMDR Day 1 and from MMDR Day 1 to the last day on study will be presented.

5.4 Concomitant Therapy

Throughout the study, concomitant medications or treatments deemed necessary for management of adverse events or to provide adequate supportive care may be prescribed. A concomitant medication is any non-protocol specified drug or substance including over-the-counter medications, herbal medications and vitamin supplements. As per Protocol Version 5, study subjects are allowed to take concomitant Food and Drug Administration-approved and/or country-specific approved therapies and experimental therapies for SMA (e.g., risdiplam at the investigator's discretion and per local protocol). In addition, a mild sedative (e.g., midazolam) and a local anesthetic (e.g., lidocaine) may be used for the LP procedures (per institutional guidance).

All concomitant medications will be coded using the World Health Organization drug dictionary (WHODrug).

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, myringotomy, and placement of tympanostomy tubes) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between screening and last visit. All ancillary procedures will be coded using MedDRA.

For the purposes of analysis, a concomitant therapy (including medication or ancillary procedure) is defined as any therapy that was taken on or after the first injection of nusinersen or first sham procedure. This includes therapies which were started prior to the initiation of injection of nusinersin or sham procedure if their use continued on. In order to define concomitant therapies with missing start or stop dates, the following additional criteria will be used:

- if both the start and stop dates of a particular therapy were missing, that therapy is considered concomitant;
- if the start date of a therapy was 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 was prior to the date of dosing and the stop date of that therapy was missing and the therapy was listed as continuing, that therapy is considered concomitant;
- if the start date of a therapy was prior to the date of dosing and the stop date of that therapy was missing and the therapy was listed as *not* continuing, that therapy is considered concomitant, or
- if the start/stop date of a therapy is partial then where 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 study treatment/sham procedure start date 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.

The number and percentage of subjects taking each type of concomitant medication at Baseline and during the study will be presented by preferred name. The number and percentage of subjects who underwent each type of ancillary procedure during the study will be presented.

5.5 Protocol Deviation

Major protocol deviations will be summarized, and all protocol deviations will be provided as a listing.

5.6 Gap between Index Studies and CS11

A summary will be presented for the gap (days) between index studies (CS3A, CS3B, CS12, CS4 and 232SM202) and first dose in CS11.

6.0 EFFICACY DATA

6.1 Imputation of Missing Data

6.1.1 Imputation for Integrated Displays

Imputing and windowing sequence of events:

- First step is to consider all the visits (scheduled and unscheduled), where at least one item has been assessed, missing items will be imputed using the rules below.
- Second step is to window as described in Section 6.2.

For subjects randomized to nusinersen in the index studies (or 232SM202 Part 1), the index studies (example CS3B or 232SM202 Part 1 and 2) and CS11 will be considered as one period (nusinersen period) and all data available will be used for imputation. For subjects who were randomized to

receive Sham in the index studies or 232SM202 Part 1, the two periods – i.e. the sham period (index study/ 232SM202 Part 1) and nusinersen period (CS11 /232SM202 Part 2 +CS11) – will be considered completely separated and no imputation will be allowed (i.e., no interpolation) between the 2 periods. The exception is for the combined analysis where sham and nusinersen are presented as one treatment arm.

The imputation for HFMSE and upper limb will be based on the total score, while the imputation for WHO, CHOP INTEND and HINE will be based on item level/ motor milestone level. The imputation of missing data will follow these rules:

1) Any missing baseline will be imputed using median within stratum (defined at the end of this Section) considering non-missing baseline records.
    - For WHO and HINE motor milestones, if the calculated median is not an integer number, then it will be rounded to be an integer (i.e. a median of 0.5 will be rounded to 1.)
2) For post baseline visits, flanked by non-missing visits, missing values will be imputed using linear interpolation. For the linear interpolation if baseline is missing then the imputed baseline will be used (see step 1). Only actual visits with a non-missing date will be imputed for each subject.
    - For HFMSE, if 6 or more item scores are missing, then impute the total score as if all the 33 items were missing.
    - For RULM, if 3 or more items are missing, then impute the total score as if all the 19 items were missing.
    - For ULM, if more than 2 items are missing, then impute the total score as if all the 9 items were missing.
    - For WHO motor milestones, if for a milestone either 'No (refusal)' or 'Unable to test' are observed at a visit, then the result will be first set to missing.

3) If it was the last assessment and date was present and at least one item was non-missing the following approaches will be followed:
    - For the HFMSE and RULM/ULM, the value will be imputed using the last observed total score.
    - For the other assessments, the lowest observed value for item assigned to the analysis visit within the stratum will be used for the imputation. For example, for missing CHOP INTEND at the last visit, CHOP INTEND at the last visit was imputed using the minimum of the stratum. For example, if the last three visits have the same item missing, then the minimum of the stratum will be used for all these visits.

The stratum for the imputation of baseline and last assessment, mentioned in point 1 and 3 are as follows:

- Type 2 (first nusinersen dose on CS1/CS2).
- Type 3 (first nusinersen dose on CS1/CS2).
- Previous control (first sham procedure on CS3B/CS4/ 232SM202 Part 1).
- Previous control in CS11/Part 2 (first nusinersen dose on CS11/ 232SM202 Part 2).
- Previous ISIS 396443 (first nusinersen dose in CS3B, CS4, CS3A and 232SM202 Part 2)

The median value calculated for imputing missing baseline will be within a stratum defined by:

1. For 232SM202 age of SMA onset (<=6 months, >6 months)
2. For all the other studies the median disease duration at first dose (ie. '<= median value' and '> median value') will be utilized.

Disease duration at first dose = age at first dose or sham procedure - age of SMA onset

6.1.2 Imputation for Displays from MMDR Day 1

Imputing and windowing sequence of events:

The efficacy assessment at MMDR Day 1 (corresponding to baseline) will be the assessment at MMDR Day 1 (or any other visit within 60 days prior to MMDR Day 1 dosing date). If this assessment is missing at MMDR Day 1, then it will be imputed per the following rules:

- For HFMSE, RULM and WHO, the same methodology for imputation will be used as described in section 6.1.1 and this will be within the index study arm i.e. CS3B previous control
- For CHOP INTEND, use linear interpolation between visits that occurred prior to MMDR Day 1 and post MMDR Day 1 (e.g. if item 1 of CHOP is missing but is present at visit Day 183 and MMDR Day 240, then linear interpolation will be used to impute CHOP item 1).

For efficacy visits post MMDR Day 1:

- From MMDR Day 1, any unscheduled or end of study visits will be mapped to the scheduled MMDR visit using a window of +/-60 days each side of the target day. If >=2 assessments are assigned to the same window then the closest assessment to the target day will be selected. In a situation where two assessments are equidistance to the target day, then the latest one will be selected. No other windowing will be applied for these analyses.
- For subjects with an available baseline (either imputed or observed), missing data on study will be imputed using a consistent approach to that defined in the integrated analysis section. If linear interpolation is used, then all the observed data will be used including unscheduled visits.

Note that after the above imputations, extra steps will be taken for subjects who took risdiplam to distinguish visits up to risdiplam taken (ie pre-risdiplam visits or Spinraza only visits) and visits post risdiplam. This will allow analyses to be performed where the result from an analysis visit after initation of risdiplam can be excluded. All the records within an analysis visit will be evaluated against risdiplam start date to flag the assessments accordingly. For those results being imputed as average or linear interpolation, if all the records from which the imputed results are calculated all occurred prior to risdiplam, averaged or linear interpolated results will be clearly noted as such. Otherwise, only results which occurred prior to risdiplam will be used for analyses where risdiplam use is excluded.

6.2 Windowing

Assessments were windowed to analysis visits to account for the following reasons:

- early closure of index studies
- gap between index studies and CS11
- different visit schedule within index studies and CS11 and the introduction of a new schedule within CS11

The proposed windows are detailed in Appendix A. For integrated display, if >=2 assessments are assigned to the same window, average is taken for HFMSE, RULM and CHOP INTEND. For WHO/HINE MM, the closest assessment to the target day will be selected. In a situation where two assessments are equal distance to the target day, then the latest one will be selected.

6.3 Responder Analysis

Responder analysis by visit will be performed based on CHOP INTEND assessment and WHO milestones for CS3B and CS4 populations, respectively.

At interim analyses, in order to account for the denominator across the analysis visits, an Efficacy set for each windowed analysis visit (Day X) will be defined as: a subset of subjects in the Safety set who have the opportunity to be assessed at the Day X visit, where the lower bound for the windowed analysis visit are denoted: L= lower. Specifically, it will include all subjects with a time difference of at least L days between the date of first dose and the end of study (or specific data cuts date). A subject who has died or withdrawn will be included provided that there is a difference of at least L days between the date of first dose and the end of study (or specific data cuts date). If a subject was known to have withdrawn from the study at a date, within the window, due to rolling over to commercial nusinersen drug, then they will be excluded from the corresponding Efficacy set and subsequent analysis visits' Efficacy sets.

An evaluable set will be defined for each analysis visit as the subset of subjects in the Efficacy set at the analysis visit who meet the following criteria:

- Value assigned from the windowing
- Subject who died or discontinued from the study – no imputation of efficacy data will be performed for such subjects and they will be considered non-responders.
- No value assigned from windowing, but ongoing in study with a subsequent assessment assigned to a later analysis visit. In this situation, a value will be imputed as the last observed earlier assessment where all assessments made within the window at the previous analysis visit are considered and the last assessment is picked, rather than only considering analysis visits.

At the final analysis, due to the varying duration of index studies and the introduction of different visit schedules through protocol amendments it means that subjects have varying lengths of follow-up. This is attributable to the early termination of index studies at interim analyses for efficacy and when the CS11 amendment with MMDR visits was introduced at sites. This means that for subjects

who discontinued or died it is not possible to determine how long they would have been followed if they had completed CS11. In order to allow responder analyses to be presented the following approach will be implemented for the groups of subjects below.

CHOP INTEND:

- CS3B previous control from their first nusinersen dose in CS11
- CS3B previous control from their first sham procedure in CS3B and including all efficacy in both CS3B and CS11
- CS3B previous ISIS 396443 from their first nusinersen dose in CS3B

WHO motor milestones:

- CS4 previous control from their first nusinersen dose in CS11
- CS4 previous control from their first sham procedure in CS4 and including all efficacy in both CS4 and CS11
- CS4 previous ISIS 396443 from their first nusinersen dose in CS4

Below is an example of the approach for CS3B previous ISIS subjects and the same approach applies to the other groups of subjects.

For a group of patients, ie CS3B previous ISIS, the patients who completed SHINE will be considered and the shortest follow-up time will be identified as M. The windowing scheme applied to this group will be cross checked with M and the interval which is prior to the one containing M will be identified as the maximum visit at which a responder analysis will be presented.

For example with M = 1420 and the following interval and target days:

- Study days >1178 to <= 1418 will be labeled Day 1298
- Study days >1418 to <= 1658 will be labeled Day 1538

Since M falls in the Day 1538 interval it means that Day 1298 will be the maximum visit up to which a responder analysis is presented.

Additional considerations are described as below:

- The denominators for responder analysis across visits will be fixed as for the safety set, however, subjects who withdraw to take commercial therapy or complete the index study and don't enroll in the CS11 study will only be included in the denominator up to the point they withdraw and otherwise will be removed from the denominator at subsequent visits. If the assessment is available at the withdrawal, the result will be evaluated against responder criteria and counted as a responder if criteria is met.
- For subjects who died or discontinued from the study within the interval (with the exception of subjects described in previous bullet point)– no imputation of efficacy data will be

performed and they will be considered as non-responders at visits from when they died or withdraw.

- For subjects, with a value assigned to an interval and who don't meet the previous two bullet points, then the responder status will be assessed based on the result.
- For subjects with no value assigned from windowing, but known to be still in study at a subsequent analysis visit. In this situation, a value will be imputed as the last observed earlier assessment where all assessments made within the window at the previous analysis visit are considered and the last assessment is picked, rather than only considering analysis visits.
- In a situation for CHOP INTEND where no subsequent assessments are available and at the last visit a score of 64 was achieved then the last observed value will be used as subsequent assessments until subjects died or discontinued.

Responder analysis will also be presented for CMAP at last visit for the following groups of subjects and the denominators will be as for safety population:

- CS3B subjects: from baseline of CS3B study
- CS3A subjects: from baseline of CS3A study
- CS2/CS12 subjects: from baseline of CS12 study
- Infantile SMA onset subjects in CS11 from MMDR Day 1
- Later SMA onset subjects in CS11 from MMDR Day 1

6.4 Analysis Methods for the Efficacy Endpoints

Motor function assessments will be performed at Screening and/or predose at MMDR Day 1, every 8 months until MMDR Day 720 and every 12 months thereafter. If motor function assessments have already been performed at Day 960 for a participant prior to approval of Protocol Amendment Version 4.0 at a site, motor function assessments (i.e., CHOP INTEND, HFMSE, RULM, 6MWT, and contracture assessment) will still need to be assessed at Days 1080, 1440, and 1800.

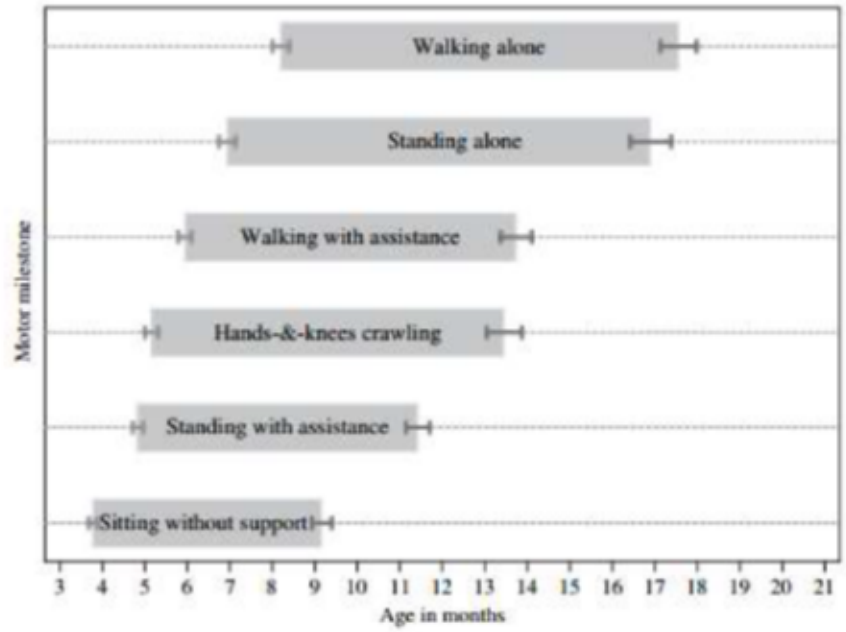
6.4.1 Motor Milestones

From Protocol Amendment Version 4, motor milestones will be assessed using the World Health Organization (WHO) Motor Milestones criteria [WHO Multicentre Growth Reference Study Group 2006; Wijnhoven 2004]. For subjects <2 years of age who have not yet achieved independent walking, motor milestones will also be assessed using Section 2 of the HINE.

6.4.1.1 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, standing with assistance, hands and knees crawling, 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.



Windows of milestone achievement: WHO motor development study

As part of the motor milestones 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

Analyses

- Summary of motor milestones at baseline

- Any new motor milestones by visit for the index study CS4 population only. A subject will be considered a responder if at the visit under consideration they can still demonstrate the same milestones they could achieve at baseline, but in addition they need to have achieved at least one new milestone.

For the following groups and baselines i) index study for CS4, ii) CS11 baseline for later-onset patients and iii) from MMDR Day 1 for all patients, two types of display will be produced as follows:

- Number of new motor milestones achieved per subject by visit, depending on the group presented this will be from when WHO was collected.
- Proportion of subjects achieving milestones will be presented with shift tables showing baseline status and then status at last visit (see additional detail below). Unimputed results will be used for shift tables.

Summary of shifts in motor milestones

For each milestone, the proportion of subjects who have the following status will be presented by baseline status as follows:

- Achieved at baseline
  - Maintained achievement – if the subject achieved the milestone at baseline and all subsequent assessments
  - Achieved at last visit (not maintained from baseline)
  - Inability at last visit
  - Died
  - Withdrawn for reasons other than death

- Inability at baseline
  - Achieved on treatment
    - inability at last visit
    - Achieve at last visit and demonstrated at all subsequent visits following first achievement
    - Achieved at last visit
  - Inability at last visit
  - Died
  - Withdrawn for reasons other than death

Subjects with unknown status at baseline will be summarized using the same categories as for inability at baseline. Subjects who discontinue due to moving to commercial treatment will be counted based on the last observed WHO result.

6.4.1.2 HINE Motor Milestones

Motor milestones will be assessed using Section 2 of the HINE in subjects <2 years of age who have not yet achieved independent walking. HINE motor milestones assessment 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 will be tested during each assessment. A subject who results after testing all appear in the first column (no grasp, no kicking, unable to maintain head upright, and so on) 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).

Motor milestone	Milestone Progression ----------→				
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 (4-5 months)	Touches toes (5-6 months)
Head control	Unable to maintain upright (normal < 3 mo)	Wobbles (4 months)	All the time upright (5 months)		
Rolling	No rolling	Rolling to side (4 months)	Prone to supine (6 months)	Supine to prone	
Sitting	Cannot sit	Sit with support at 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 (4-5 months)	Crawling flat on abdomen (8 months)	On hands and knees (10 months)
Standing	Does not support weight	Supports weight (4-5 months)	Stands with support (8 months)	Stands unaided (12 months)	
Walking	No walking	Bouncing (6 months)	Cruising (walks holding on) (11 months)	Walking independently (15 months)	

The age restriction (<2 years of age) described above was introduced as part of Protocol Amendment Version 2. The majority of subjects will stop the HINE motor milestone assessment by MMDR Day 1 (because they will be >2 years of age before or around this visit).

Analyses

HINE MM analysis will be done for CS3B subjects.

- Summary of total motor milestones at baseline.

- The change in total motor milestones from baseline over time.
- Summary of highest motor milestones item achieved at last analysis visit.

The subjects that enter the study from 232SM202 will be under Protocol Amendment Version 3. Since they are expected to be greater than two years of age, we do not expect any more HINE-2 assessments performed in CS11.

The HINE-2 motor milestone responder analysis defined in the protocol will not be presented since there are different durations of follow-up for subjects depending when the amendment was implemented. HINE-2 data will be combined with WHO data as described in the following Section.

6.4.1.3 HINE and WHO Motor Milestones

For CS3A and CS3B the HINE-2 and WHO milestone results will be combined to allow assessment of achievement during the entire treatment period from first dose in the index study. The following definitions will be utilized:

Milestones	HINE-2	WHO
Sitting	Stable sit or Pivots rotates	Sitting without support
Crawling	On hands and knees	Hands and Knees Crawling
Standing with assistance	Stands with support or stands unaided	Standing with assistane.
Standing alone	Stands unaided	Standing alone
Walking with assistance	Crusing (walks holding on) or Walking independently	Walking with assistance
Walking alone	Walking independently	Walking Alone

The first instance that patient achieves a milestone based on these definitions will be determined. Due to the presence of death the Fine and Gray model (Fine et al 1999) will be implemented to include death as a competing risk. Plots of the cumulative incidence for each milestone by study day will be presented and the cumulative incidence at 1, 1.5, 2, 3, 4 and 5 years with corresponding confidence intervals presented.

6.4.2 Time to Event Endpoints

Event of permanent ventilation or death

In CS3B and 232SM202, permanent ventilation was defined as tracheostomy or >=16 hours of ventilator support per day continuously for >21 days in the absence of an acute reversible event. A guidance document containing details on how an acute reversible event was defined including the concept of a grace period, was provided to sites. The grace period of an acute reversible event was defined as 14 days after the event, the starting point the threshold of permanent ventilation (≥ 16 hours per day) for > 21 consecutive days starts to count. The rationale is that in the context of an

acute reversible event, the SMA subject 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 subject 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.

The original definition of permanent ventilation in CS3A was >= 16 hours of ventilation per day continuously for at least 14 days in the absence of an acute reversible illness. In the CS11 Protocol Amendment Version 2, CS3A endpoint was updated to match the CS3B definition (>= 16 hours of ventilation per day continuously for at least 21 days in the absence of an acute reversible illness). Examination of the ventilation data collected in CS3A before entry to CS11 revealed that it would be impossible to reassess CS3A subjects under the CS3B definition. CS3A subjects that have not yet reached the endpoint in the index study, will be assessed in CS11 using the CS3B definition for endpoint.

Ventilation use during the study will be collected via the ventilation diary for all the subjects. The methodology of recording the ventilation data within the eCRF has changed over the course of the study. Originally every day was entered which followed the approach in the CS3B study, but this was changed to be only from when ventilation had increased to ≥16 hours/day and then entered for a minimum of 30 days. In addition, the investigator was asked to assess the ventilation endpoint and record the date of the 22nd day of consecutive ventilator use at of >= 16 hours and note the presence of an acute reversible event. The CRF page of ventilation endpoint will be confirmed by the sites regardless whether a subject has met permanent ventilation criteria or not.

All the above information, alongside adverse events, ancillary procedures and hospitalization data from the eCRF will be taken in account in verifying if any subjects have met the endpoint as collected from ventilation endpoint CRF page. This verification will be performed by the Biogen medical director and statistician.

If necessary, missing daily ventilator use, in the original part of the study where ventilation was collected daily and imputation will be performed using the greater of the days that flank the missing day(s). Should the daily ventilation use be reported as a range, e.g., 6 to 12 hours, the maximum will be used. Following Protocol Amendment Version 2, ventilation data was not collected daily by the sites, and imputations will not be performed.

Analyses

The Kaplan-Meier method will be used for estimating the time from first dose in CS3A, CS3B and 232SM202 for the following endpoints:

- to death
- to permanent ventilation
- to death or permanent ventilation or tracheostomy
- Plots of KM curves will be presented

For CS3B subjects in CS11, the estimated time to death from the first dose / sham procedure in CS11 will also be presented using Kaplan-Meier method.

Subjects who do not meet the endpoint definition will be censored for:

- time to death at the last occasion the subject was seen and confirmed alive (either in-person visit or by telephone contact)
- time to permanent ventilation at the last date a subject had a diary entry for ventilation where subject withdrew prior to moving onto Protocol Amendment Version 2. For subjects who moved over to have diary collection less frequently the last occasion the subject was seen and confirmed alive will be used. Subjects who died prior to the event will be censored.

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

In addition, the proportions of subjects who died or met permanent ventilation will be summarized for subjects in CS11.

6.4.3 CHOP INTEND

Subjects who are ≥2 years will be continued to be assessed until a CHOP INTEND maximum score of 64 is achieved and after they will stop this assessment.

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. 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 each item, a score will be collected on the left and right side.

Definition of Responder

A subject is defined as a CHOP INTEND responder if the change from baseline in CHOP INTEND total score is greater or equal to 4 points. Additional detail regarding handling of this are described in Section 6.3.

In order to examine if the response is consistent with a range of thresholds, the proportion of subjects achieving: worsening of >=6, >=5, >=4, >=3, >=2, >=1 points, no change (=0 points), and improvement of >=1, >=2, >=3, >=4 (endpoint for main analysis), >=5, >=6 points will be presented.

Analyses

- Summary at baseline.
- The change from baseline over time
- Thresholds of change from baseline by visit.

- Plots of both total score and change from baseline.
- Percentages of patients who achieve particular thresholds (e.g. ≥40, ≥50).
- For CS3B subjects (index study + CS11 integrated) and age at first dose display, spaghetti plots of total score vs. age at visit will be presented with fitted lines displayed.

6.4.4 CMAP

CMAP (Compound Muscle Action Potential) is an electrophysiological measure used to determine the approximate number of motor neurons in a muscle or group of muscles. CMAP amplitude and CMAP area will be evaluated at two sites, right side ulnar nerve and right side peroneal nerve. CMAP was collected from Screening in CS11 for all subjects except those previously dosed in CS4. Following the implementation of version 2.0 of the protocol, from the MMDR Day 1 visit, all subjects will have CMAP administered.

The analyses of CMAP will be based on observed values. The change and percentage change from baseline CMAP amplitude and CMAP area at each site will be presented by windowed analysis visit. A plot of the mean change from baseline over time and the actual score over time will be presented and similarly a plot of the percentage change will be provided.

The proportion of subjects with: i) a worsening from baseline in CMAP amplitude of >=0.3 mV, >=0.5mV, >=1mV, >=2mV and >=3 mV and ii) an improvement from baseline in CMAP amplitude of >=0.3 mV, >=0.5mV, >=1mV, >=2mV and >=3 mV and iii) no change as a change of between -0.3 and 0.3 mV (-0.3<CMAP amplitude<0.3) will be presented for each site by visit.

The analyses will be performed for the infantile onset (CS3A, CS3B) and later onset (CS2/CS12) studies where CMAP was captured in the index study or collected from the initiation of CS11. Additionally, CMAP will be summarized for all subjects from MMDR Day 1.

Responder analysis

A subject is defined as a responder if (s)he had a peroneal amplitude >=1 mV at last visit (including the amplitude >=1 mV at baseline and also demonstrated as such at last visit). The proportion of responders will be summarized. The responder analyses will be presented for the following groups of subjects:

- CS3B subjects: baseline from CS3B study through CS11
- CS3A subjects: baseline from CS3A study through CS11
- CS2/CS12 subjects: baseline from CS12 study through CS11
- Infantile SMA onset subjects in CS11 from MMDR Day 1
- Later SMA onset subjects in CS11 from MMDR Day 1

6.4.5 HFMSE

The Hammersmith Functional Motor Scale – Expanded (HFMSE) is a 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. The expanded scale includes an additional module of 13 items developed to allow evaluation of ambulatory SMA patients.

Each item is scored 0, 1 or 2 and the total score is calculated by summing the 33 items and ranges from 0 to 66 with higher scores indicating greater motor function. 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, then the total score will be imputed by interpolating scores between the previous and subsequent visit or, if there is no subsequent visit, by using the score from the previous visit.

The proportion of subjects achieving a response over time will be presented as follows:
The proportion of subjects achieving: worsening of >=10, >= 5, >= 3, >=2, >=1 points, any worsening, no change (=0 points), any improvement, >=1, >=2, >=3,>=5, >=10 points improvement will be presented.

Analyses

- HFMSE at baseline
- Change from baseline
- Thresholds of change from baseline by visit
- Thresholds of change from baseline to last available assessment
- Total score by visit (Windowed visits up to Day 350, Last assessment prior to MMDR Day 1 and by MMDR visit)
- Plots of both total score and change from baseline and individual scores over time.
  For CS4 subjects (index study + CS11 integrated) and age at first dose display, a mixed model of repeated measurements (MMRM) will be used to analyze change from baseline by visits with age group, visit and their interaction as main factors, and baseline HFMSE and age at first-dose as covariates. Baseline HFMSE by visit interactions will also be included in model. Unstructured covariance matrix will be used. Least square (LS) means and 95% confidence intervals (CI) will be estimated. Model convergence will be checked and if non-convergence exists, it will be investigated by statistician and appropriate adjustments may be implemented.
- The same MMRM model will be used but excluding data following initiation of risdiplam treatment.
- For CS3B or CS4 subjects (index study + CS11 integrated) and age at first dose display, spaghetti plots of total score vs. age at visit will be presented with fitted lines displayed.

As all subjects are eligible to have HFMSE assessed from Protocol Version 2 and the MMDR Day 1 visit the following will be presented:

- Summary of total score from MMDR Day 1 by visit

Summary statistics will be displayed for both the score and change from baseline over windowed analysis time. The mean score and mean change from baseline over time will be presented graphically with error bars to denote the standard error of measurement. In this display the number of subjects at each windowed analysis visit will be displayed below the x-axis.

The analyses will be performed for the later onset studies where HFMSE was captured in the index study or collected from the initiation of CS11. Additionally, HFMSE will be summarized for all subjects from MMDR Day 1.

6.4.6 Upper Limb Module (ULM) and Revised Upper Limb Module (RULM) Tests

The Upper Limb Module Test (ULM) is an outcome measure specifically 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. Two versions of the test were administered to CS11 participants with subjects previously enrolled in CS12 who were non-ambulatory performing the 9 item test (ULM) (Mazzone et al. 2011) and subjects enrolled in CS4 previously, performing the revised 19 item test (RULM: Revised Upper Limb Module) test (Mazzone et al. 2016). As part of the protocol version 2 amendment the revised 19 item test will be administered to all non-ambulatory subjects.

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. For the 9 items test if 1 item is missing then this will be imputed to be 0 when summing all 9 items.

A number of presentations will be made to explore the upper limb score over time and presentations will be made using the 19 items and 9 items scale separately. In order to allow the CS2 subjects to be followed over time as they transition between scale an [redacted] analysis will be performed where total RULM score is mapped to be on the ULM scale (Revised upper limb module for spinal muscular atrophy: Development of a new module, Mazzone et al 2017).

In order to further explore the response as measured by upper limb score a number of thresholds will be evaluated: The proportion of subjects achieving: worsening of >=10, >= 5, >= 3, >=2, >=1 points, any worsening, no change, any improvement, >=1, >=2, >=3,>=5, >=10 points improvement will be presented.

Analyses

- RULM at baseline
- ULM/RULM Change from baseline and actual score by visit
- RULM Thresholds of change from baseline by visit
- Plots of RULM total score and change from baseline.
- For CS4 subjects (index study + SHINE integrated), a mix model of repeated measurements (MMRM) will be used to analyze change from baseline by visits with age group, visit and their interaction as main factors, and baseline RULM and age at first-dose as covariates. Baseline HFMSE by visit interactions will also be included in model. Unstructured covariance matrix will be used. Least square (LS) means and 95% confidence intervals (CI) will be estimated. Model convergence will be checked and if non-convergence exists, it will be investigated by statistician and appropriate adjustments may be implemented.
- The same MMRM model will be used but excluding data following initiation of risdiplam.

- For CS3B or CS4 subjects (index study + CS11 integrated) and age at first dose display, spaghetti plots of total score vs. age at visit will be presented with fitted lines displayed.

The analyses will be performed for the infantile and later onset studies where available in the index study or collected from the initiation of CS11. Additionally, RULM will be summarized for all subjects who have received a dose at MMDR Day 1, from MMDR Day 1.

6.4.7 6 Minute-Walk Test

The 6 Minute-Walk Test (6MWT) is an objective evaluation of functional exercise capability which measures the distance a person can walk quickly in 6 minutes. The 6MWT can be performed safely in ambulatory patients with SMA and correlates with standard SMA outcome measures, including timed walking tests (Montes et al. 2010). In SMA, the 6MWT may be more sensitive to clinically meaningful changes in patients with Type 3 SMA as it is a direct measure of their functional mobility. The 6MWT has also been used as a primary outcome measure in several clinical trials in neuromuscular disease including Duchenne Muscular Dystrophy (McDonald et al. 2010) and late-onset Pompe disease (van der Ploeg et al. 2010).

As part of the nusinersen clinical development program, this test was only administered to ambulatory subjects and only collected in CS2 and CS12 and then introduced for CS4 subjects in CS11. In CS1/2 and CS4, a subject was considered ambulatory if he/she was able to walk 15 feet independently (without support or braces). In CS11, ambulatory is defined as any subject who has achieved independent walking as defined by the WHO Motor Milestones criteria (Test Item #6 – Walking Alone). If a subject was considered to be non-ambulatory at baseline and provided a 6MWT result post-baseline then baseline will be imputed as 0.

The distance walked in the first and sixth minute will be used to calculate *Percentage Fatigue* as:

% Fatigue=100*(distance walked in 1st minute – distance walked in 6th minute)/ distance walked in the 1st minute

If the distance walked is recorded for the 1st minute and the 6th minute is missing then % Fatigue will be set to 100.

In the context of one single test, a positive value indicates an increase in fatigue over the 6 minutes.

The following will be presented:

- Summary of percentage of fatigue and change from baseline over time
- Summary of total distance and change from baseline over time
- The proportion of subjects who increase walking distance >=30 meters from baseline over time
- Plot of both total distance and change from baseline over time
- Median change from baseline over time for fatigue and distance

The focus with these analyses will be for the subjects in CS2/CS1 who were able to walk at baseline or achieved walking during the CS2/CS1 or CS12 study. For subjects who entered from other studies the data will be listed.

6.4.8 Performance Limiting Contracture Assessment

Motor performance in SMA is defined as a demonstrated ability to perform a skill under certain test conditions. This performance changes with disease progression and/or intervention (including surgery) and is based on the observed response on the day of the assessment. Motor performance will be affected by muscle strength, cognitive ability, contractures, and maturational development (puberty). All subjects will be evaluated for contractures from version 3 of the protocol.

A summary of the number of subjects experiencing performance limiting contractures by location, degree of contracture impact on the performance of motor assessment (no, minimal, moderate or severe) and visit will be presented.

6.4.9 Change in Growth Parameters

Growth parameters comprise length for age, weight for age, weight for length, head circumference for age, chest circumference, head to chest circumference ratio, and arm circumference are to be assessed through the study.

The WHO child growth standards (WHO Child Growth Standards, 2006) will be used to determine the percentiles for each parameter for subjects <5 years old. In parallel the 2000 CDC Growth Charts (ages 0 to <20 years) will be used to assess the growth change for older subjects (>5 years old.) It must be noted that these scales are designed for healthy children. Patients with SMA have lower muscle mass and are therefore expected to have lower weight for height and age. The WHO provides a SAS macro (SAS igrowup package) which can be downloaded from a website [WHO Anthro] and this will be utilized to calculate the percentiles for each child. The CDC chart and SAS macro can be downloaded from a web site [CDC]. The two scales were developed using different methods and populations, for this reason the weight percentile should not be mixed using both scales. The CDC chart will be used only to calculate the weight percentiles.

The change from baseline to each windowed analysis visit (using the Safety windows) will be summarized using descriptive statistics for the following growth parameters: weight for age percentile (using WHO and CDC scales), weight for length/height, head circumference, chest circumference, head to chest circumference ration and arm circumference. Presentations will be made for all studies.

Analyses

- Growth parameters at baseline
- Change from baseline

The growth parameters at MMDR day 1 and the change from MMDR day 1 will be summarized for all subjects who have received a dose at MMDR Day 1.

6.4.10 PedsQL

Subjects in CS11 will be evaluated using the Pediatric Quality of Life Inventory (PedsQL™) Measurement 4.0 Generic Core Scales and 3.0 Neuromuscular Module (Varni et al. 1999) at Screening and/or predose (within 7 days of dosing) at MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, 1080, and 1440), and at the EOS Evaluation/ET Visit.

The questionnaires are specific to the age of the subject, and sites are instructed to get both subjects and caregivers to complete the same age specific questionnaire as was collected at baseline irrespective of whether or not the subjects cross an age boundary at a subsequent visit. From Protocol Amendment Version 2, this guidance was changed and the sites were instructed to use the PedsQL version according to the age of the subject at the visit.

The PedsQL parent questionnaire is collected for children and teenagers in the following age categories: 2-4, 5-7, 8-12 and 13-18. Four dimensions are collected: Physical, Emotional, Social and School functioning and each item is scored on a 5 point ordinal scale (0= Never, 1 = Almost Never, 2= Sometimes, 3 = Often, 4 = Almost Always).

In the neuromuscular module, one parent questionnaire is collected for all subjects irrespective of age with three dimensions: 'About my child's neuromuscular disease', Communication' and 'Family resources'. The same 5-point ordinal scale is collected for each question.

A psychosocial health summary score, constructed from three dimensions, will be calculated as the sum of items over the number of items answered in the emotional, social and school functioning scales. A total score will be calculated as the sum of all the items over the number of items answered on all the scales. If greater than 50 percent of the items are missing, then the summary score or total score will be set to be missing.

For the neuromuscular module, a score for each dimension and then total score will be calculated in the same manner, no health summary scores are evaluated.

Due to the age specific nature of these questionnaires, subjects aged 2-4 years would not be expected to complete the self-evaluation.

Analysis

- Total change and percentage change from baseline score (each total score and parent/subject evaluation separately) to each visit will be presented
- Total change and percentage change from MMDR day 1 will be summarized for all subjects who have received a dose at MMDR Day 1.

6.4.11 ACEND

Parents of subjects will complete the Assessment of Caregiver Experience with Neuromuscular Disease (ACEND) questionnaire at specific visits. This assessment instrument has been designed to quantify the caregiver impact experienced by parents of children affected with severe neuromuscular diseases, including children with SMA (Matsumoto et al. 2011). Subjects should not complete quality of life questionnaires intended for completion by a caregiver.

The ACEND includes a total of seven domains assessing physical impact (including feeding/grooming/dressing, sitting/play, transfers, and mobility) and general caregiver impact (including time, emotion, and finance) and each domain comprises several items. The total score for

a domain with n items, each item assessed on ordinal scale from 1 to *z*, is derived as follows: 100 multiplied by (Mean of the n items in the domain -1) divided by (*z*-1). This total score will be on a scale of 0 to 100 with a higher score indicating a greater impact on the caregiver. At least two items for the time domain and one item for the remaining domains need to be non-missing for a domain total to be calculated; else the total score will be set to be missing.

Analyses:

- Total scores in each domain at baseline
- Total scores by domain and visit
- Change from baseline in total score by domain and visit

For subjects who start this from MMDR Day 1 the following analysis will be performed:

- Summary of total score by domain from MMDR Day 1 by visit

[redacted]

6.4.13 X-Ray of Spine

Subjects currently ≥2 years of age or upon turning 2 years of age (with the exception of subjects treated at German sites) will have an X-ray of the thoracolumbar spine on Screening and/or predose (within 7 days of visit) at MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, 1080, and 1440), and at the EOS Evaluation/ET Visit. The X-rays will be used to determine the severity of scoliosis by measuring the Cobb angle. The spine X-ray was performed at screening of CS4 index study and from the beginning of CS11, and the image acquisition guidelines will remain consistent between the CS4 and the current extension study.

With Protocol Amendment Version 1, the X-ray was introduced only for the subjects in CS4, and with Version 2, X-ray was introduced to all the rest of the subjects entering CS11 from other index studies.

Analyses for group CS4 subjects:

- Mean cobb angle by visit
- Mean change from baseline by visit
- Plots of mean and mean change from baseline by visit
- Proportion of subjects who have procedures for growing rods or scoliosis fixation (spinal fusion and spinal correction surgeries) as identified by study Medical Director, will be presented using Kaplan-Meier product-limit method for the subjects with cobb angle data.

For subjects who start this assessment after Protocol Amendment Version 2, the following analysis will be performed:

- Summary of Cobb angle and change from MMDR Day 1 by visit.
- Proportion of subjects who have procedures for growing rods or scoliosis fixation (spinal fusion and spinal correction surgeries) as identified by study Medical Director, will be presented using Kaplan-Meier product-limit method for patients with cobb angle data.

6.4.14 Number and Length of Hospitalizations

Details on hospitalizations are collected in the eCRF hospitalization form. This form was collected as part of the CS3B and 232SM202 study and for these subjects continued to be used in CS11.

In the CS4, CS3A and CS12 studies, no hospitalization form was collected.

An updated eCRF following Protocol Amendment Version 2 included a hospitalization form for all subjects and therefore a summary of hospitalizations data will be starting from MMDR Day 1.

Based on starting point of data availability, the following analyses will be presented.

Number and annualized rate of hospitalizations due to serious adverse events (SAE) over 360-day interval

The proportion of subjects with number of hospitalizations 0, 1, 2, 3, 4, >=5 will be presented.

Annualized rate for the period will be calculated as total number of hospitalizations divided by total number of subject-years followed in the 360-day period for each cohort of subjects which are listed below.

- CS3B or CS4 index study plus CS11: previous control or nusinersen display.
- CS3B or CS4 index study plus CS11: age at first nusinersen dose display.
- From baseline of CS11, infantile, later SMA onset and all SMA subjects displays.

The number of hospitalizations was determined by counting the number of SAEs which required hospitalization. If multiple SAEs which occurred on the same date and led to hospitalization, it will be counted as one hospitalization.

Duration and time of hospitalization by 360-day interval

For each subject the proportion of time in hospital will be determined, for a given 360-day interval. The numerator will be the total number of days in hospital and the denominator will be the time the subject was followed in the interval. The following will be presented:

- 0% of time in hospital
- > 0% to < 10% of time in hospital
- >=10% to <20% of time in hospital
- >=20% to <30% of time in hospital
- >=30% to <40% of time in hospital
- >=40% to <50% of time in
- >=50% to <60% of time in hospital
- >=60% of time in hospital

Summary statistics for each interval will be presented.

The analyses will be presented for all subjects from MMDR Day 1 and CS3B subjects from the start of CS11.

If a subject enters hospitalization in one 360-day interval and leaves hospital in the next 360-day interval then the days in hospital will be counted in the first interval.

6.4.15 Number of Hospitalizations Due to Serious Respiratory Adverse Event

The number and annualized rate of serious respiratory events (ie events coded into the SOC of respiratory, thoracic, and mediastinal disorders) will be summarized as described in Section 6.4.14.

6.4.16 Disease-related (SMA) Hospitalizations and AEs

Many AEs can possibly be related to either SMA or to normal childhood illness, further context would be required to differentiate the precipitating factors. With reference to the 2017 Standards of Care publications [Finkel 2017, Mercuri 2017], the Study Medical Director created a list of preferred terms that relate to specific events that are highly likely to be resultant from SMA. These are listed in Appendix B. The incidence of disease related adverse events will be summarized from the start of CS11. Similarly, the subset of disease related SAEs leading to hospitalization will also be presented.

6.4.17 Signs and Symptoms of Dysphagia

The Parent Assessment of Swallowing Ability (PASA) questionnaire was developed by a Biogen team in order to assess the signs and symptoms of dysphagia and collected from the initiation of Protocol Amendment Version 3. This questionnaire consists of 33 items across 4 domains covering: general feeding, drinking liquids, eating solid foods and assessment of swallowing concerns. The first three of these domains are generally assessed with 5 levels of response: Never, Rarely, Sometimes, Often and Always, although two items are assessed with a simple 'Yes'/'No', answer. In the final domain the assessment of swallowing concerns has 4 levels of response: Strongly agree,

Agree, Disagree and Strongly disagree. In answering each item, the parent is directed to consider the previous 7 days.

The number and percentage of subjects scoring each category in the PASA in each domain will be presented by visit. For all subjects, mean scores of items by domain over time for domains of general feeding, drinking liquids and eating solid foods will be presented from MMDR Day 1 by SMA onset, with item score defined as 4=Never, 3=Rarely, 2=Sometimes, 1=Often and 0 = Always. Similarly, the mean score will be presented for the domain of assessment of swallowing concerns (3=Strongly disagree, 2=Disagree, 1=Agree and 0 =Strongly agree) will be presented from MMDR Day 1. Spaghetti plots of item score versus MMDR visit will be generated by domains.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
	[redacted]	
	[redacted]	[redacted]
	[redacted]	
	[redacted]	
[redacted]	[redacted]	[redacted]
	[redacted]	
	[redacted]	

[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	
	[redacted]	
[redacted]	[redacted]	[redacted]
	[redacted]	
	[redacted]	[redacted]
	[redacted]	
	[redacted]	[redacted]
	[redacted]	
	[redacted]	

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Baseline concentrations will be summarized overall, by age of onset using descriptive statistics.

Summary tables will be presented for mean concentration, geometric mean concentration, geometric mean ratio by visit. A plot of mean over time will be presented for concentration on the semi-logarithmic scale. The geometric mean ratio will be presented on the original scale.

For the later onset population, they are receiving doses every 4 months from MMDR Day 1. In order to explore the transition from 6 monthly to 4 monthly dosing, summaries of MMDR Day 1 to subsequent MMDR visits will be presented for subjects who received 12 mg loading doses (i.e. CS4 and some CS2 subjects).

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

6.4.22 Subgroup Analyses

Subgroup analyses by age are already covered for the CS3B and CS4 groups of patients based on the planned displays.

7.0 SAFETY DATA

Analyses of safety data will include adverse events and serious adverse events, laboratory data, ECGs, vital signs, and neurological examinations. Worsening or new findings noted from the physical or neurological examinations will be reported as AEs as appropriate.

7.1 Adverse Events

All adverse events (AEs) will be analyzed based on the principle of treatment emergence. An adverse event will be regarded as treatment-emergent if it was present prior to receiving the first dose of nusinersen or first sham procedure in the index study and subsequently worsened in severity, or was not present prior to receiving the first dose of nusinersen or first sham procedure in the index study but subsequently appeared. For subjects receiving the sham procedure in the index study, an additional treatment emergent definition will be used to define if the adverse event is treatment emergent to the first dose of nusinersen in CS11.

Of note, events that are duplicated in both index and CS11 the data for that AE will be taken from CS11. These duplicates will be defined based on the coded terms and start dates. Other variables will be used as needed.

For events with missing start or stop dates, the following criteria will be used for the purpose of identifying treatment-emergent adverse events (TEAEs):

- if both the start and stop dates for a particular event are missing, then the event is considered to have occurred on or after the first dose or sham procedure;
- if the start date for a particular event is missing and the stop date/time falls after the first dose or first sham procedure date/time, then the event is considered to have occurred on or after the first dose or sham procedure;
- if the start time is missing and the start date is same as the first dosing or first sham procedure date, then the event is considered to have occurred on or after the first dose or sham procedure;
- 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.

Specifically, let AESTDT denote the start date of an adverse event and TRTSTDT be the start date of treatment/sham procedure. For the purpose of identifying treatment emergent adverse events, the following algorithm will be used for the imputation of missing or partial date:

- If AESTDT is completely missing or the year is missing, then impute AESTDT to TRTSTDT.
- If, in AESTDT, year is present and month/day are missing and year is equal to the year portion of TRTSTDT, then impute the month/day portion of AESTDT to the month/day portion of TRTSTDT.
- If, in AESTDT, year is present and month/day are missing and year is not equal to the year portion of TRTSTDT, then impute the month/day portion of AESTDT to January 01.
- Consider the situation in AESTDT where year and month are present with only day missing. If the year and month are the same as those for TRTSTDT, then impute day in AESTDT with day in TRTSTDT. Otherwise, impute the day in AESTDT with the first day of the month.

It is important to emphasize that the imputed date will not be used for calculations such as onset and duration of an adverse event.

Due to the long half-life of nusinersen, analyses of treatment-emergent adverse events will include all events reported during the study.

In order to allow safety to be presented in a similar manner to the efficacy displays from MMDR Day 1, the date and time of the MMDR Day 1 dose will be used to define events which are considered treatment emergent to MMDR Day 1.

Adverse events will be coded using the MedDRA dictionary. 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 or frequency (event count) of treatment-emergent adverse events will be summarized by infantile and later onset groups and overall. A subject having the same adverse event more than once will be counted only once in the incidence for that adverse 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 or frequency 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 subjects in either group, will be presented. Upon examination of the actual data, different cut-offs may be used if it is deemed more appropriate.

7.1.1 Adverse Events Following Dosing

Adverse events following dosing will be presented. For identifying adverse events following dosing (ie TEAEs), the algorithm in Section 7.1 for the imputation of missing or partial start dates will be used. If time is missing and the event occurs on the same day as the day for dosing/sham procedure, the time for the dosing/sham procedure will be used as the imputed time.

7.1.2 Adverse Events Potentially Related to Lumbar Puncture

The incidence of AEs potentially related to LP will be presented by SOC and PT terms. The Safety medics will identify potential LP related AEs based on all AEs provided by Programming Lead as it was done in previous interim analyses.

[redacted]

7.1.4 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. For each group, the incidence within each severity category will be presented. The incidence of severe events will be summarized by group and overall.

7.1.5 Adverse Events by Relationship to Study Treatment

The Investigator is to record the degree to which each adverse event is related to Study Drug (not related, unlikely or remotely related, possibly related, and related). If a subject experienced the same adverse event multiple times, only the event with the strongest relationship to Study Drug will be counted. For each group, the incidence within each relationship category will be presented. The incidence of drug-related events (those categorized as possibly related or related) will be summarized by group and overall.

7.1.6 Serious Adverse Events

The incidence and frequency of treatment-emergent serious adverse events will be summarized by group and overall, and by time of onset by 360-day time intervals. All serious adverse events will be listed including any that occurred prior to commencement of study treatment.

7.1.7 Adverse Events that Led to Discontinuation from Treatment

The incidence of adverse events that led to discontinuation of study treatment will be presented. All adverse events that led to discontinuation of study treatment will be listed.

7.1.8 Deaths

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

7.1.9 Presentations

The following presentations will be shown for treatment emergent adverse events (TEAEs):

- An overall summary showing, for each group, the number and percentage of subjects with an adverse event, a moderate or severe event, a severe event, a possibly or related event, a related event, a potential LP related event, an event that led to death, a serious event (including fatalities), a related serious event, an event that led to discontinuation of Study Drug, and an event that led to withdrawal from the study
- Incidence by system organ class and preferred term
- Incidence, by preferred term, in at least 5% of subjects in either group
- Incidence of mild, moderate and severe events by system organ class and preferred term
- Incidence of severe events by system organ class and preferred term
- Incidence of not related, unlikely to be related, possibly related, and related events by system organ class and preferred term
- Incidence of drug-related events by system organ class and preferred term
- Incidence and frequency of serious adverse events by system organ class and preferred term and a listing of serious adverse events
- Incidence of drug-related serious adverse events by system organ class and preferred term and a listing of serious adverse events
- Incidence of death and a listing of each death
- Incidence of events that led to death
- Incidence and frequency of events leading to discontinuation of Study Drug by system organ class and preferred term and a listing of such events
- Incidence of events leading to withdrawal from the study by system organ class and preferred term and a listing of such events
- Incidence and frequency of adverse events over time by system organ class and preferred term and a listing of such events.
- Incidence of potentially LP related events following dosing/sham procedure.

- Incidence of adverse events antibody status by system organ class and preferred term and a listing of such events.

Some of the above displays will be repeated from MMDR Day 1.

To avoid the potential for misleading interpretation of analysis of adverse events, no statistical testing will be performed.

7.2 Clinical Laboratory Data

The following clinical laboratory parameters are to be assessed:

- Hematology: hemoglobin, hematocrit, red blood cell count, WBC count with differential both as absolute values and as a percentage (neutrophils, eosinophils, basophils, lymphocytes, and monocytes), and platelet count
- Blood chemistry: liver function (total bilirubin (direct and indirect), alkaline phosphatase, ALT/SGPT, AST/SGOT), kidney function and electrolytes (BUN, creatinine, cystatin C, sodium, potassium, chloride), total protein, albumin, calcium, phosphorous, glucose, and CPK
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, blood, RBC, WBC, epithelial cells, bacteria, casts, crystals and urine total protein
- Coagulation: aPTT, INR

Coagulation and urine total protein testing was collected at every visit from the introduction of Protocol Amendment Version 2 at sites.

For a parameter, if the local and central results are available with the same date and time, then only the central analysis result will be considered for presentations by visit. In a situation where two or more central lab results have the same date and time then the earliest LBREFID will be selected.

Laboratory tests, including chemistry panel and complete blood count with differential, will be summarized by study visit. At the time of development of this document, it has been found that a few extreme lab results are erroneous due to incorrect lab unit which is impossible to resolve prior to data base lock due to closed sites etc. These results will be excluded from the summaries. The justification of the exclusions will be documented in a note to file provided by Study Medical Director and reviewed by members of SMT.

Each subject's 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". 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 the minimum and maximum post-baseline

classified values (ie normal, low or high) will be presented. If a subject had a baseline value but had no post-baseline values, then the minimum and maximum are labeled as "unknown". Should a treatment affect a laboratory parameter, that parameter could be affected at different times for different subjects. Therefore, these analyses present the most extreme values for each subject. For many laboratory parameters, the effect could be in either direction, (i.e., an increase or a decrease), so both the maximum and minimum values have been analyzed. In addition, 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. All blood and urine samples will be used in the shift analyses.

Based on the protocol, coagulation lab tests (aPPT and INR) and urin total protein are assessed by local laboratories. Local laboratories have historical issues, such as no normal range established or not providing normal ranges. To alleviate the issues for these protocol-defined local lab tests, text-book reference ranges for INR and urin total protein will be provided by clinical development medical director. Their shift tables will be presented by incorporating text-book normal ranges.

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 x ULN, >3 x ULN, > 5x ULN, >10 x ULN, and >20x ULN for ALT/AST, >1x ULN, >1.5 x ULN, and >2 x ULN for total bilirubin (including direct and indirect bilirubin), and >1x ULN and >1.5 x ULN for alkaline phosphatase. In addition, incidence of post baseline ALT or AST increase (>=3x ULN) will be summarized by concurrent elevation in bilirubin (maximum post-baseline bilirubin >1.5 x ULT, >2 x ULN).

Median, minimum and maximum lab results vs. visit for certain lab tests will be presented graphically.

7.3 ECGs

ECGs are to be recorded at Screening during the index studies, screening in CS11 and/or predose (within 7 days of dosing) at MMDR Day 1, approximately annually thereafter, (i.e., MMDR Days 360, 720, 1080, 1440), and at the EOS Evaluation/ET Visit. After the ECG is completed, an initial local read of the ECG should occur before the ECG is sent for a central read (all ECGs will be centrally read). The various possible readings (normal, abnormal, clinically significant) will also be summarized.

Additional ECGs may be performed per the judgment of the Investigator, as deemed clinically necessary.

ECGs will be analyzed using two approaches.

7.3.1 Qualitative Analysis

Incidence tables will summarize both the number and percentage of subjects with abnormal but not clinically-significant and clinically-relevant worsening, defined as a post-baseline ECG interpreted as abnormal and clinically-significant, with a comparison with baseline value of normal, deteriorated, not available, not required, or missing. The incidence of clinically-significant worsening will be summarized at any time post-baseline.

7.3.2 ECG Outliers

Outlier analyses will be performed for the corrected Fridericia QT interval (QTcF). This will include summaries of the number and percentage of subjects with a post-baseline corrected QTcF interval greater than certain threshold values (e.g., > 450 msec, > 480 msec, and > 500 msec) and the number and percentage of subjects with an increase from baseline in corrected QT interval in various categories (e.g., > 30 msec and > 60 msec). These summaries will be performed on an overall basis, as well as separately for subjects whose baseline corrected QTcF intervals are normal (≤ 450 msec) and elevated (> 450 msec). QTcF is defined as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR\ Interval}}$$

If RR interval is not captured, then this will be calculated as follows:

$$\text{RR interval} = 60/VR$$

Where VR is the ventricular rate.

7.4 Vital Signs

Vital signs are to be measured at Screening, pre-dosing and at various time points post- dosing on dosing days. At each of these times, temperature, heart rate, respiratory rate, systolic and diastolic blood pressure, and pulse oximetry awake will be measured.

Vital signs will be summarized by study visit.

The number and percentage of subjects meeting selected criteria post-baseline and outliers 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

outliers are:

- Systolic blood pressure <90 mmHg, >140 mmHg and >160 mmHg

- Diastolic blood pressure <50 mmHg, >90 mmHg and >100 mmHg
- Pulse rate <60 and >100
- Body temperature <36 and >38
- Respiratory rate <12 breaths/min and >20 breaths/min

7.5 Neurological Examinations

7.5.1 HINE Sections 1 and 3

Sections 1 and 3 of the HINE will be conducted on all subjects ≤24 months of age. This standard examination (developed by [Dubowitz and Dubowitz 1981]) is a quantitative scorable method for assessing the neurological development of infants between 2 and 24 months of age. The examination includes assessment of cranial nerve functions, posture, movements, tone, and reflexes.

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.

For each item and 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 after the first dose at baseline will be considering post baseline visits.

7.5.2 Neurological and Focused Neurological Examinations

Starting Protocol Amendment 5, focused neurological examinations were implemented to replace standard neurological examinations. Focused neurological examinations have less items than standard neurological examinations.

For all subjects >24 months of age, focused neurological examinations, which include assessments of mental status, level of consciousness, sensory function, motor function, cranial nerve function, coordination and cerebellar function, plantar response and reflexes, will be conducted. These assessments will be done pre-dose and 1 hour post-dose at every onsite visit throughout the study.

The following table summarizes the results from each assessment section/test (Note: *italics* represents focused neurological examinations).

Sections	Tests	Outcomes of result
Coordination and cerebellar function	Finger to nose, *Gait, Tremor*	Normal, abnormal

Cranial Nerves	*Eye movement*, Facial motion, Gag reflex, Hearing, Jaw movement and facial sensation, (SCM, Trapezius), Tongue, *Vision*	
General	Appearance/Facial/Motor Expression, *Mental status*, Speech/language,	Normal, abnormal
	Level of Consciousness	0 – No response 1 – Responds after painful stimuli 2 – Responds after prodding 3 – Responds after name called 4 – Lethargic response 5 – Responds readily
	Mood	1 - Happy 2 - Neutral 3 - Irritable
Motor	Muscle tone	Normal, abnormal
	Chg in Muscle Tone from Pre Exam	N or Y
Plantar response	Reflex (left toe, right toe)	Normal, abnormal
Reflexes	*Reflex (left/right ankle, left/right biceps, left/right brachioradialis, left/right knee, left/right tricep)*	0 - Unable to elicit reflex 1 – Hyporeflexia 2 - Normal 3 – Hyperreflexia 4 - Hyperreflexia with clonus
Sensation	*Temperature (left/right finger tip, left/right lower toe); Vibration (left/right finger tip, left/right lower toe)*	Present, absent

For each abnormal test result, it is recorded whether or not it is secondary to SMA.

A worsening shift will be summarized for focused neurological exams:

- The number and proportion of subjects who moved from 'Normal' baseline to 'Abnormal' postbaseline at any time will be presented.
- For sensory function tests, the number and proportion of subjects who move from 'Present' to 'Absent' at any time will be presented.

- For level of consciousness and mood assessments, the number and proportion of subjects whose scores decrease or increase from baseline will be presented, respectively.

In addition, for reflexes and level of consciousness, the mean scores versus analysis visit will be presented.

Only changes not deemed secondary to SMA will be presented.

An updated eCRF following the Protocol Amendment Version 2 included neurological exam assessment for all subjects and therefore a summary will be possible from MMDR Day 1.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

11.0 SAMPLE SIZE CONSIDERATIONS

The sample size is based solely on the number of subjects enrolled in the CS3A, CS3B, CS4, CS12 and 232SM202 studies.

12.0 CHANGE TO PREVIOUS VERSIONS OF THE SAP

For the interim analysis conducted on data with a cut-off date of 30June2017, this interim statistical analysis plan was prepared. In this SAP, the changes included as Protocol Amendment Version 5 are incorporated.

Key changes are as follows:

From SAP Version 1:

- Windowing for the integrated efficacy analysis was altered to allow for efficacy assessments every 8 months.
- Presentation of safety data will follow the same approach to that utilized for integrated safety where the infantile onset subjects are presented separately based upon the age at screening in the study in which they receive nusinersen.
- Statistical analysis of assessments as part of Protocol Amendment Versions 2, 3, 4, and 5 included.

From SAP Version 2:

- [redacted]
- [redacted]

[redacted]

- In section 4.2 Efficacy displays, for the re-evaluated subjects equality added to be '<=54' for HFMSE
- New efficacy analyses added utilizing MMDR Day 1
- Section 7.1 in the previous SAP, described an approach to link adverse event terms where the severity had lessened at a subsequent time point and to only count the first instance of these in summaries of the number of events. Now the text has been removed in order to simplify the reporting of the adverse events and to use a consistent approach to that utilized in previous integrated safety analyses.

From SAP Version 3:

- Abbreviations have been updated.
- MMDR dosing schedule has been updated to MMDR Days 1, 120, 240, 360, 480, 600, 720, 840, 960, 1080 1200, 1320, 1440, 1560, and 1680 (±14 days) until the EOS Evaluation/Early Termination (ET) Visit.
- Contracture assessments have been added to motor function assessments.
- Disallowed concomitant medication were removed.
- Additional examples have been provided for concomitant procedures.
- Updates to imputation methods for CHOP INTEND from MMDR Day 1.
- Efficacy assessment for motor functions occur at screening and/or predose at MMDR Day 1, every 8 months until MMDR Day 720, inclusive (i.e., MMDR Days 240, 480, 720), and every 12 months thereafter (i.e. predose at MMDR Days 1080 and 1440), and at the EOS Evaluation (MMDR Day 1800 [±14 days)/ET Visit.
- PedsQL schedule updated to Screening and/or predose (within 7 days of dosing) at MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, 1080, and 1440), and at the EOS Evaluation/ET Visit.
- CGI has been removed from this SAP due to difficulty in reliable interpretation.
- X-ray of the spine schedule updated to Screening and/or predose (within 7 days of dosing) at MMDR Day 1, approximately annually thereafter (i.e., MMDR Days 360, 720, 1080, and 1440), and at the EOS Evaluation/ET Visit.
- [redacted]
- Updates to Appendix A windowing for efficacy based on updated MMDR schedule
- Language was updated on Neurological Examinations to ensure consistency with Protocol Version 5.
- Section on analyses to assess the impact of COVID-19 was added.

From SAP Version 4

- Summary of gap between end of index studies and first dose in CS11 is added.
- Age at First Nusinersen Dose Display is added.
- Denominator determination for CHOP INTEND and WHO MM responder analyses are updated.

- Analysis for WHO MM are updated, majorly added responder analysis and shift presentations and removed some for better presentation of data.
- HINE/WHO MM combined analyses on time to achive first milestone are added.
- Growth failure analyses are removed.
- Cobb angle analysis is simplified to present mean or change over time and a summary to present proportion of subjects with growing rod or scoliosis fixation procedures occurred over time using Kaplan-Meier method.
- Number and length of hospitalization is updated to be more specific on analyses to be done.
- Serious respiratory event, serious disease (SMA)-related AEs leading hospitalization and disease (SMA)-related AEs are added.
- [redacted]
- [redacted]
- [redacted]
- Safety laboratory is updated to add analyses using text-book normal range. In addition, summary of lab results over visit per protocol are added.
- Vital sign is updated to add summary over time per protocol.
- [redacted]
- [redacted]

Appendix A

The end of study day will follow the maximum window in protocol amendment Version 6.0 as MMDR Day 1800 + 14 days. Depending on when last assessments are actually finished for the study, the following windowing maybe extended beyond the protocol-define EOS day.

Description of the windowing for efficacy (Integrated display):

Subjects originating in index study CS4:

- Study days > 1 to <=50 will be labelled Day 25
- Study days >50 to <=131 will be labelled Day 92
- Study days >131 to <= 211 will be labelled Day 169
- Study days >211 to <=302 will be labelled Day 253
- Study days >302 to <=400 will be labelled Day 350
- Study days >400 to <=570 will be labelled Day 450
- Study days >570 to <=810 will be labelled Day 690
- Study days >810 to <=1050 will be labelled Day 930
- Study days >1050 to <= 1290 will be labelled Day 1170
- Study days > 1290 to <= 1530 will be labelled Day 1410
- Study days > 1530 to <= 1890 will be labelled Day 1710

For study days > X-180 to <= X+-180 will be labelled Day X where X begins at 2070 and increases by 360 until the EOS Evaluation/ET Visit. For CS4 subjects who were randomized to sham procedure in CS4 then this windowing scheme will also be applied from the start of CS11. Study day will be recalculated the date of first dose in CS11.

Subjects originating in index study CS1 or CS2:

- Study days >50 to <=131 will be labelled Day 92
- Study days >131 to <= 211 will be labelled Day 169
- Study days >211 to <=302 will be labelled Day 253
- Study days >302 to <=400 will be labelled Day 350
- Study days >400 to <=500 will be labelled Day 450
- Study days >500 to <=600 will be labelled Day 550
- Study days >600 to <=700 will be labelled Day 650
- Study days >700 to <=800 will be labelled Day 750
- Study days >800 to <=900 will be labelled Day 850
- Study days >900 to <=1000 will be labelled Day 950
- Study days >1000 to <=1170 will be labelled Day 1050

Then for study days > X-120 to <= X+120 will be labelled Day X where X begins at 1290 and increases by 240 until Day 2010. For study days > Y-180 to <= Y-180 will be labelled Day Y where Y begins at 2310 and increases by 360 until the EOS Evaluation/ET Visit.

Subjects originating in index study CS3B and CS3A

- Study days >1 to <= 22 will be labeled Day 15
- Study days >22 to <=47 will be labeled Day 29
- Study days >47 to <= 123 will be labeled Day 64
- Study days >123 to <=242 will be labeled Day 183
- Study days >242 to <=348 will be labeled Day 302
- Study days >348 to <=486 will be labeled Day 394
- Study days >486 to <= 698 will be labeled Day 578
- Study days >698 to <= 938 will be labeled Day 818
- Study days >938 to <= 1178 will be labeled Day 1058
- Study days >1178 to <= 1418 will be labeled Day 1298
- Study days >1418 to <= 1658 will be labeled Day 1538
- Study days >1658 to <= 2018 will be labeled Day 1838

For study days > Y-180 to <= Y+180 will be labelled Day Y where Y begins at 2198 and increases by 360 until the EOS Evaluation/ET Visit.

For CS3B subjects who were randomized to sham procedure in CS3B then the same windowing scheme will also be applied from the start of CS11. Study day will be recalculated from the date of first dose in CS11.

Subjects originating in index study 232SM202 Part 1 and 2

- Study days <=1 will be labelled Baseline
- Study days >1 to <= 22 will be labelled Day 15
- Study days >22 to <=47 will be labelled Day 29
- Study days >47 to <= 123 will be labelled Day 64
- Study days >123 to <=242 will be labelled Day 183
- Study days >242 to <=362 will be labelled Day 302
- Study days >362 to <=482 will be labelled Day 422
- Study days >482 to <= 600 will be labelled Day 540
- Study days >600 to <= 719 will be labelled Day 659
- Study days >719 to <= 838 will be labelled Day 778

Then for study days > X-120 to <=X+120 will be labelled Day X where X begins at 958 and increases by 240 days until Day 1678. For study days > Y-180 to <= Y-180 will be labelled Day Y where Y begins at 1978 and increases by 360 until the EOS Evaluation/ET Visit.

Description of the windowing for efficacy (since MMDR Day 1):

Windowing will be applied to unscheduled MMDR visits for efficacies (except for cognitive assessments). The analysis windowing will be defined as:

Baseline - MMDR Day 1:

Non-missing assessment at MMDR Day 1 or any other visit within 60 days prior to MMDR Day 1 dosing date

MMDR Day 120: 60 < study days <= 180
MMDR Day 240: 180 < study days <= 300
MMDR Day X: X-60 < study days <= X+60, where X begins at 360 and increases by 120 till early termination or EOS (MMDR Day 1800). Ideally, the last windowing will be MMDR Day 1800: 1740 < study days <= 1860, and it can go beyond that if data exist. The windowing can go beyond.

[redacted]

Study days calculated as (assessment date – MMDR Day 1 dosing date) + 1 for post MMDR Day 1 assessments.

Description of the windowing for safety:

For safety assessments for subjects originating in CS1, CS2, CS4 and 232SM202 (later onset) the following windowing will be used:

- Study days >1 to <= 16 will be labeled Day 1
- Study days >16 to <=57 will be labeled Day 29
- Study days >57 to <= 127 will be labeled Day 85
- Study days >127 to <=211 will be labeled Day 169
- Study days >211 to <=302 will be labeled Day 253
- Study days >302 to <=400 will be labeled Day 350
- Study days >400 to <= 540 will be labeled Day 450
- Study days >540 to <= 690 will be labeled Day 630
- Study days >690 to <= 810 will be labeled Day 750

Then for study days > X-60 to <=X+60 will be labelled Day X where X begins at 870 and increases by 120 days.

For safety assessments for subjects originating in CS3B, CS3A and 232SM202 (infantile onset) the following windowing will be used:

- Study days >1 to <= 22 will be labeled Day 15
- Study days >22 to <=47 will be labeled Day 29
- Study days >47 to <= 123 will be labeled Day 64
- Study days >123 to <=243 will be labeled Day 183
- Study days >243 to <=362 will be labeled Day 302

Then for study days > X-60 to <=X+60 will be labelled Day X where X begins at 422 and increases by 120 days.

Appendix B

The following table lists adverse events which are most likely SMA-disease related events at the time of this document development. The events are subject to update after database lock and a final selected events will be used for presentations.

Body System or Organ Class	Dictionary-Derived Term
Congenital, familial and genetic disorders	Developmental hip dysplasia
	Spinal muscular atrophy
	Talipes
Gastrointestinal disorders	Constipation
General disorders and administration site conditions	Gait disturbance
Musculoskeletal and connective tissue disorders	Bone deformity
	Joint contracture
	Joint range of motion decreased
	Joint stiffness
	Kyphoscoliosis
	Kyphosis
	Limb asymmetry
	Limb discomfort
	Muscle atrophy
	Muscle contracture
	Muscle spasms
	Muscle tightness
	Muscle twitching
	Muscular weakness
	Neuromuscular scoliosis
	Osteoporosis
	Osteoporotic fracture
	Rib deformity
Nervous system disorders	Motor developmental delay
Nervous system disorders	Motor dysfunction
	[redacted]
Psychiatric disorders	Encopresis
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome
	Acute respiratory failure
	Atelectasis
	Respiratory muscle weakness

REFERENCES

CDC

Dubowitz L, Dubowitz V. The neurological assessment of the preterm and full-term newborn infant. London (UK): William Heinemann Medical books Ltd; 1981.

Fine, J. P., and Gray, R. J. (1999). "A Proportional Hazards Model for the Subdistribution of a Competing Risk." Journal of the American Statistical Association 94:496–509.

[redacted]

Mazzone ES, Mayhew A, Montes J, et al. Revised upper limb module for spinal muscular atrophy: Development of a new module. Muscle Nerve. 2016 Epub 2016/10/04.

Mazzone ES1, Mayhew A2, Montes J3, Ramsey D4, Fanelli L1, Young SD3, Salazar R3, De Sanctis R1, Pasternak A5, Glanzman A6, Coratti G1, Civitello M7, Forcina N1, Gee R8, Duong T8, Pane M1, Scoto M4, Pera MC1, Messina S9, Tennekoon G6, Day JW8, Darras BT5, De Vivo DC3, Finkel R7, Muntoni F4, Mercuri E1. Muscle Nerve. 2017 Jun;55(6):869-874. Epub 2017 Feb 6.

Montes J, McDermott MP, Martens WB, et al. Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. Neurology. 2010;74(10):833-8.

Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Qian Y, Sejersen T; SMA Care group. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscul Disord. 2018 Mar;28(3):197-207. doi: 10.1016/j.nmd.2017.11.004. Epub 2017 Nov 23. PMID: 29305137.

Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, Mazzone ES, Vitale M, Snyder B, Quijano-Roy S, Bertini E, Davis RH, Meyer OH, Simonds AK, Schroth MK, Graham RJ, Kirschner J, Iannaccone ST, Crawford TO, Woods S, Qian Y, Sejersen T; SMA Care Group. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscul Disord. 2018 Feb;28(2):103-115. doi: 10.1016/j.nmd.2017.11.005. Epub 2017 Nov 23. PMID: 29290580.

WHO Anthro: http://www.who.int/childgrowth/software/en/

WHO Motor Development Study: Windows of achievement for six gross motor development milestones, Acta Pædiatrica, 2006; Suppl 450: 86/95

Sproule DM, Hasnain R, Koeniqsberger D, et al. Age at disease onset predicts likelihood and rapidity of growth failure among infants and young children with spinal muscular atrophy types 1 and 2. J Child Neurol 2012 Jul; 27(7): 845-851.

Van der Ploeg AT, Clemens PR, Corzo D, et al. A Randomized Study of Alglucosidase Alfa in Late-Onset Pompe's Disease. New England Journal of Medicine. 2010;362(15):1396-1406

DocuSign

Certificate Of Completion

Envelope Id: A044771025C34EC9800D745CBCCB1C3B
Status: Completed
Subject: Complete with DocuSign: CS11 CSR SAP_v5.0_Final.pdf
Vendor Name:
Source Envelope:
Document Pages: 74
Signatures: 3
Envelope Originator:
Certificate Pages: 2
Initials: 0
[redacted]
AutoNav: Enabled
225 Binney St
EnvelopeId Stamping: Enabled
Cambridge, MA 02142
Time Zone: (UTC-05:00) Eastern Time (US & Canada)
[redacted]
IP Address: [redacted]

Record Tracking

Status: Original
9/7/2023 1:02:55 PM
Holder: [redacted]
[redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] [redacted] 7042079 Biogen Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 9/7/2023 1:08:03 PM Viewed: 9/8/2023 3:11:25 AM Signed: 9/8/2023 3:11:47 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] EMPLOYED BY Cytel-Senior Biostatistician Biogen Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 9/7/2023 1:08:03 PM Viewed: 9/8/2023 9:11:17 AM Signed: 9/8/2023 9:11:54 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
[redacted] [redacted] [redacted] Biogen Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 9/7/2023 1:08:04 PM Viewed: 9/8/2023 6:06:30 AM Signed: 9/8/2023 6:07:23 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	9/7/2023 1:08:04 PM
Certified Delivered	Security Checked	9/8/2023 6:06:30 AM
Signing Complete	Security Checked	9/8/2023 6:07:23 AM
Completed	Security Checked	9/8/2023 9:11:54 AM

Payment Events	Status	Timestamps