COVER PAGE

Official Title:	An Open-Label Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Subjects With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy
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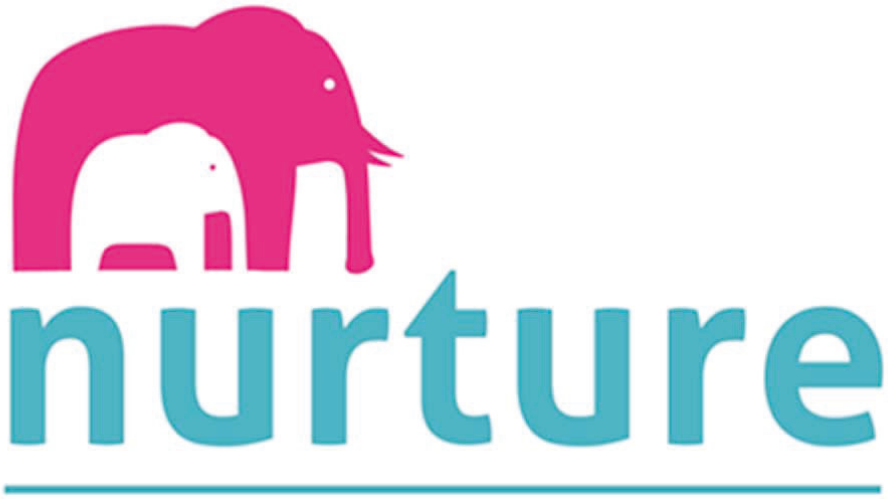

Statistical Analysis Plan

STATISTICAL ANALYSIS PLAN

Product Studied: ISIS 396443

Protocol Number: 232SM201

An Open-label Study to Assess the Efficacy, Safety, Tolerability, and Pharmacokinetics of Multiple Doses of ISIS 396443 Delivered Intrathecally to Subjects With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy

Date of Protocol: 17 Oct 2021, Version 9

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LIST OF ABBREVIATIONS

[redacted]	[redacted]
ALT/SGPT	alanine aminotransferase/serum glutamic pyruvic transaminase
AST/SGOT	aspartate aminotransferase/serum glutamic-oxaloacetic transaminase
ATC	Anatomical Therapeutic Class
BLQ	below the lower limit of quantification
BUN	blood urea nitrogen
CHOP INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
[redacted]	[redacted]
CPK	creatine phosphokinase
CRF	case report form
CSF	cerebrospinal fluid
CV	coefficient of variation
[redacted]	[redacted]
DSMB	Data Safety Monitoring Board
HINE	Hammersmith Infant Neurological Examination
HFMSE	Hammersmith Functional Motor Scale - Expanded
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
[redacted]	[redacted]
PK	pharmacokinetics
[redacted]	[redacted]
PPS	Per-protocol set
PT	Preferred term
[redacted]	[redacted]
RBC	red blood cell
[redacted]	[redacted]
SD	standard deviation
SMA	Spinal Muscular Atrophy
[redacted]	[redacted]
SOC	System Organ Class
ULN	upper limit of normal

WBC	white blood cell
WHO	World Health Organization
WHODrug	World Health Organization drug dictionary

1. Description of Objectives and Endpoints

1.1. Primary objective, primary endpoint

The primary objective of the study is to examine the efficacy of multiple doses of nusinersen administered intrathecally in preventing or delaying the need for respiratory intervention or death in infants with genetically diagnosed and presymptomatic SMA.

The primary endpoint is the time to death or respiratory intervention (invasive or non-invasive ventilation for ≥ 6 hours/day continuously for 7 or more days OR tracheostomy).

1.2. Secondary objectives, secondary endpoints

The secondary objectives of the study are to examine the effects of ISIS 396443 in infants with genetically diagnosed and presymptomatic SMA on the following:

- Development of clinically manifested SMA as determined by a composite of clinical features seen in subjects with SMA
- Growth and function
- Safety, tolerability and PK

The secondary efficacy endpoints of this study are as follows:

- Proportion of subjects alive
- Attainment of motor milestones as assessed by World Health Organization (WHO) criteria
- Attainment of motor milestones assessed as part of the Hammersmith Infant Neurologic Examination (HINE, Section 2) at 13 and 24 months of age
- Change from baseline in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale
- Change from baseline in Hammersmith Functional Motor Scale Expanded (HFMSE)
- Change from baseline in the growth parameters: weight for age/length, head circumference, chest circumference, head to chest circumference ratio, and arm circumference
- Proportion of subjects developing clinically manifested SMA as defined by any of the following (all assessed at approximately 13 and 24 months of age unless otherwise noted, Motor milestones assessed by WHO criteria):
    - Age-adjusted weight <5th percentile or decrease of ≥2 major weight growth curve percentiles (3rd, 5th, 10th, 25th, or 50th) or a percutaneous gastric tube placement for nutritional support
    - Failure to achieve the ability to sit without support
    - Failure to achieve standing with assistance
    - Failure to achieve hands-and-knees crawling
    - Failure to achieve walking with assistance by 24 months of age
    - Failure to achieve standing alone by 24 months of age

- Failure to achieve walking alone by 24 months of age

In Protocol Version 6, the first two secondary endpoints of survival and WHO motor milestones were specified at 13 and 24 months of age. The 13 and 24-month timepoints are still key ages but since Nurture was extended through 8 years of age, the status at 3, 4,5, 6, 7 and 8 years of age are included.

The secondary safety endpoints of this study are as follows:

- Incidence of AEs and /or SAEs
- Change from baseline in clinical laboratory parameters, electrocardiograms (ECGs), and vital signs.
- Neurological examinations

The secondary Pharmacokinetics (PK) endpoint of this study are CSF and plasma ISIS 396443 concentration.

[redacted]

2. Study Design

This is a Phase 2, open-label, multicenter, multinational, single-arm study to assess the efficacy, safety, tolerability, and PK of multiple doses of ISIS 396443 in subjects with genetically diagnosed and presymptomatic SMA. Up to 25 subjects are planned to be treated in the study. All subjects will receive ISIS 396443. One dose level will be evaluated, and all subjects will be dosed with 12 mg (5 mL) regardless of age. In versions of the protocol prior to version 6 the volume of the injection, and thus the dose, was adjusted based on the subject's age on the day of dosing, such that each subject received a 12-mg scaled equivalent dose based on CSF volume scaling. ISIS 396443 will be administered using a loading regimen (dosing on Study Days 1, 15, 29 and 64) followed by maintenance dosing once every 4 months beginning on Day 183.

Safety data will be reviewed on an ongoing basis by the Sponsor and the Medical Monitor. Safety data were reviewed on an ongoing basis by an independent Data Safety Monitoring Board (DSMB) until the final DSMB meeting held on 28 Apr 2017. An interim analysis was conducted when 10 subjects had the opportunity to attend a Day 64 assessment, using a cut-off date of 21st January 2016. Further interim analyses were conducted. The cut off dates utilized for these analyses were determined by assessing the current progress of subjects in the study and the number of subjects who had an opportunity to attend a given study visit.

The study will consist of screening, treatment and post-treatment follow-up periods. The total duration of participation in the study is approximately 8 years.

2.1. Screening

After informed consent is obtained, subjects will undergo a Screening evaluation no greater than 21 days prior to administration in order to determine eligibility for the study. If a subject fails any of the screening criteria, they will be allowed to be rescreened 1 time during the Screening period at the discretion of the Investigator.

2.2. Treatment

Subjects who meet the eligibility criteria will be admitted to the study center on Day 1, undergo pre-dose evaluations and receive an LP injection of study treatment. After injection on Day 1, subjects will remain at the study center for at least 24 hours post–procedure for safety monitoring.

Subjects will return to the study center on Days 15, 29, 64, 183, 302, 421, 540, 659 and 778 for follow-up evaluations and subsequent injections. Following injections received on Day 15 and subsequent visits, subjects will remain at the study center for at least 6 hours post-procedure for safety monitoring. An overnight stay is required for the first injection but is otherwise optional and at the discretion of the investigator. Safety monitoring visits will occur the day after injections. At the time of implementation of Protocol Version 7, onsite safety assessments are no longer required per protocol on the day following injection of study treatment; however, a postdose follow-up email or phone call evaluation will be required within 1 to 7 days after the dosing visits on Days 64, 183, 302, 421, 540, 659, and 778. In addition, the study center will monitor the subject's condition through telephone contact on a monthly basis starting on Day 94

and continuing to Day 897. Two additional study visits will be required on Days 365 and 700 in order to collect information for the 13 and 24-month of age assessments; a study treatment injection will not occur at these visits.

Subjects will return to the study site on Days 897, 1016, 1135, 1254, 1373, 1492, 1611, 1730, 1849, 1968, 2087, 2206, 2325, 2444, 2563, 2682, and 2801 (±14 days for all days) for subsequent injections of nusinersen and follow-up evaluations (±14 days) over a dosing period of approximately 5.5 years. Subjects will remain at the study site for at least 1-hour postdose for safety monitoring and can be discharged at the discretion of the Site Investigator and in compliance with the institutional requirements once the subjects have adequately recovered from the dosing procedure. From Day 897 through Day 2801, overnight stays are optional for all injections at the discretion of the Investigator. Study assessments can be performed over multiple days if needed. Starting from Day 897, follow-up safety monitoring telephone calls will occur 1 to 14 days postdose and every other month for the duration of the study, except for the months when in-clinic visits occur. During these calls, changes in concomitant medications, AEs, and ventilator use/SMA disease status that have occurred since the last phone call or study visit will be recorded.

A CSF sample will be taken pre-dose on each injection day.

2.3. Follow-Up

Subjects are to return to the study site for a follow-up evaluation (Final Study Visit on Day 2891) approximately 3 months after the last dose of study treatment. Subjects who prematurely withdraw from the study are to complete the early termination study procedures and observations at the time of withdrawal.

2.4. Schedule of events

The schedule of events is presented in Appendix 1.

3. Statistical Methods: General Considerations

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

The Intent-to-treat (ITT) will be used for all efficacy analyses. The primary analyses for efficacy will be performed on the subjects with SMN2 copy number of 2 in the ITT.

The ITT is defined as all subjects who receive at least 1 dose of ISIS 396443. It should be noted, that in the protocol the ITT was labelled as the Full Analysis Set but the definition has not changed. The Per Protocol Set (PPS) is defined as the subset of the ITT who complete the initial 4 doses of the drug, have a baseline and at least the Day 183 efficacy assessments, and have no significant protocol deviations which would be expected to affect the efficacy assessments. Significant protocol deviations will be determined prior to database lock but will include subjects who were greater than 6 weeks of age at first dosing, subjects who had SMN2 copy number other than 2 or 3, subjects with clinical signs or symptoms of SMA at screening or prior to dosing. The analysis of the primary endpoint will be repeated using the PPS.

The analysis of safety will be performed on the ITT.

The analysis of PK, PD, biomarkers and immunogenicity will be conducted on subjects with available data.

Determination of SMN2 copy number will be conducted by a central laboratory for subjects with unknown SMN2 copy number at screening. For subjects with genetic documentation of SMN2 copy number at screening this will be sufficient for enrollment but whilst on study they will be tested by the central laboratory. In the case of any discrepancy with the enrolled result the central laboratory result will be utilized. In summaries of study subjects and efficacy, described in this SAP presentations will be made by SMN2 copy number and overall.

Summary statistics will be presented throughout. For continuous endpoints, summary statistics will generally include number of subjects with data, mean, standard deviation, median, minimum and maximum. For categorical endpoints, 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 9.4 or above, will be used for all summaries and statistical analyses.

4. Study Subjects

4.1. Subject Accountability

The number of subjects who were screened, who were enrolled, who were dosed, who completed treatment and who completed the study, along with the reasons for discontinuing treatment and withdrawing from the study, will be presented. A subject is considered enrolled if the investigator has obtained informed consent, verified eligibility criteria and prompted the IXRS system to allocate a dose of ISIS 396443.

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

4.2. Demography and Baseline Disease Characteristics

Baseline data (demography, medical history, birth characteristics and SMN history, and baseline characteristics) will be summarized.

Demography includes age at first dose, sex, ethnicity, and race. Medical history will be coded in MedDRA and the number and percentage of subjects with each history presented. Birth characteristics and SMN history includes gestational age, birth weight, twin birth (Y/N) and the number of copies of the SMN2 gene.

Baseline disease characteristics will be assessed by CHOP INTEND total score, HINE motor milestones, [redacted] and growth parameters – these assessments are further described in Section 5.1. Baseline will generally be defined as the closest measurement before the first dose.

Demographic and baseline disease characteristics will be presented for the ITT Set and the PPS.

4.3. Extent of Exposure

The number of doses received will be summarized using frequency distributions. The amount of ISIS 396443 received will be summarized using summary statistics.

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) +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 subject.

Time on study will be categorized into intervals and summarized by SMN2 copy number and overall.

Given the long half-life of ISIS 396443, 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.

In order to explore the instances of failed dosing. A listing will be provided, detailing for all subjects the following: for each day at which an LP was performed or attempted, how many attempts, the use of guidance and the successful LP. The number of subjects and the frequency of LP days with a failure (ie number of attempts > 1) and frequency of attempts will be presented, whilst on study and additionally, considering the period during the loading regimen of doses up to and including Day 64.

4.4. Concomitant therapy

Throughout the study concomitant medications or procedures deemed necessary for 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. Prior to Protocol Amendment 8, subjects were prohibited from receiving other experimental agents during the study including marketed agents at experimental doses that are being tested for the treatment of SMA (e.g., valproate, riluzole, creatinine, sodium phenylbutyrate, hydroxyurea, oral salbutamol). The use of approved SMN replacement therapy is permitted. All concomitant medications will be coded using the World Health Organization drug dictionary (WHO Drug).

Procedures are any therapeutic intervention (e.g., surgery/biopsy including tracheostomy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed and these will be collected on the ancillary procedure page of the eCRF and will be coded using MedDRA.

For the purposes of analysis, a concomitant therapy (including medication or procedure) is defined as any therapy that was taken or administered on or after the first injection of ISIS 396443. This includes therapies that were started prior to the initiation of injection of ISIS 396443 if their use continued on or after the first injection of ISIS 396443. 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 start date as TRTSDT. The medication is classified concomitant provided any of the following is NOT true:

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

The number and percentage of subjects who were taking each type of concomitant medication at baseline and during the study will be presented. The number and percentage of subjects taking each type of ancillary procedure will be presented by preferred term. The number and percentage of other therapies for treatment of SMA will also be presented.

4.5. Protocol deviations

Protocol deviations identified during site monitoring will be captured in a protocol deviation log and categorized as major or minor deviations. These deviations will be listed. Major protocol deviations will be summarized including those that lead to exclusion from the Per-Protocol Set.

5. Efficacy, Pharmacokinetic and Immunogenicity data

A number of the endpoints are age-specific and, therefore, over the course of the study as subjects get older, different scales will be utilized. Baseline or first assessment can differ from endpoint to endpoint or from subject to subject, and baseline definition or analysis for each endpoint will be defined/described for each endpoint in subsequent sections as appropriate.

For HFMSE, the records at baseline and all following analysis visits will be used to fit a random effect mixed model and assess the pattern, where applicable. In these models, the total scores at the analysis visits will be assessed versus the subjects' age at corresponding visits to allow understanding of the response to the treatment.

Summary of imputation rules

	HFMSE	WHO	CHOP INTEND/ HINE
Level imputations performed	Total	Milestone	Milestone or item
Baseline missing	Not applicable	If necessary, impute missing baseline using median within SMN2 copy number stratum considering non-missing baseline records	
Post baseline missing	Linear interpolation	Worst of flanking visits	Linear interpolation
If last visit has missing items	Use score from previous visit.	If missing, impute with the lowest value within SMN2 copy number stratum at visit	

Detailed descriptions are included for each endpoint.

5.1. Description of efficacy and biomarker data

5.1.1. Ventilation data

Ventilator use during the study will be tracked at study visits, via prompts in the CRF with detail collected using a ventilation diary. The subjects are pre-symptomatic at entry and completion of the diary by caregivers will not commence until a subject first requires ventilation – the diary will then

need to be completed every day until the end of the study. For each day, the number of hours of ventilation and the type of ventilation – invasive/non-invasive – will be captured. Ventilator use will be considered as zero hours prior to the first use of ventilation in the tracker. For days on which ventilator use was not recorded, the number of hours of use will be imputed using the greater of the days that flank the missing day (s).

5.1.2. Growth parameters

Growth parameters comprise length, weight, length for age, weight for age, weight for length, head circumference, chest circumference, head to chest circumference ratio, and arm circumference and are to be assessed during screening, and at study visits. The windowing scheme is provided in Appendix 4.

The WHO child growth standards for subjects aged up to 10 years will be used to determine the percentiles for each parameter. The WHO provide 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 given weights/lengths of each child.

5.1.3. Motor milestones

The assessments that are performed at a given visit will depend on the subject's age at that visit and current motor abilities. For the purposes of this protocol, ambulatory will be defined as any subject who has achieved independent walking as defined by the WHO Motor Milestones criteria of Walking Alone.

Motor milestones are assessed during screening and at study visits (where dosing is performed, the assessment of milestones is performed pre-dose). Assessments are made using HINE, Section 2 (up to Day 778) and WHO motor milestones, and each are described in further detail below. From Day 897 until Day 1849, the assessment of WHO motor milestones will occur at alternating dosing visits. From Day 1849, the assessment of WHO motor milestones will occur annually.

HINE motor milestones

Up to Day 778, subjects will have motor milestones assessed using Section 2 of the Hammersmith Infant Neurological Examination (HINE). HINE Section 2 is comprised of eight tests: head control, sitting, voluntary grasp, ability to kick in supine position, rolling, crawling, standing, and walking.

There are 26 possible motor milestones that can be achieved using this schema (presented below). A subject whose results after testing all appear in the first column (unable to maintain head upright, cannot sit, no grasp, etc) has not achieved any motor milestone. A subject whose results all appear in the second column (head wobbles, sits with support at hips, uses the whole hand for a voluntary grasp, etc.) has achieved 8 motor milestones. A subject whose results all appear in the third column (head maintained upright all the time, props when sitting, index finger and thumb but immature grasp, etc.) has achieved 16 motor milestones.

Missing values

If not all motor milestones test items were performed at a visit, the approach described below will be used for the handling of missing data. Missing data will be imputed on an individual milestone level. If a subject has baseline defined at Day 1 but has a missing value, then an imputation will be performed using the screening value. If the screening value is missing then it will be imputed as the

median of all subjects with non-missing values with the same SMN2 copy number, rounded up if necessary to the closest integer score. If for the subject with a missing value at a particular post-baseline visit the corresponding visit is flanked by visits with non-missing milestones, the missing value will be imputed by linear interpolation, using the flanking post-baseline visits or the baseline item score if the missing visits are next to baseline. Thus, the imputation could be performed for several consecutive missing visits providing these visits are flanked on both sides by a non-missing value. In the interpolation, the time in days of the actual assessments will be used and the baseline assessment will be set to be Day 1, the score will be rounded to the nearest integer. Otherwise, if the imputation is the last visit, the missing motor milestone value will be imputed as the lowest value observed across all subjects with the same SMN2 copy number at that visit. Of note, only observed data will be utilized for imputation purposes. Missing motor milestone items will be imputed first prior to any analysis.

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	Stands with support	Stands unaided	

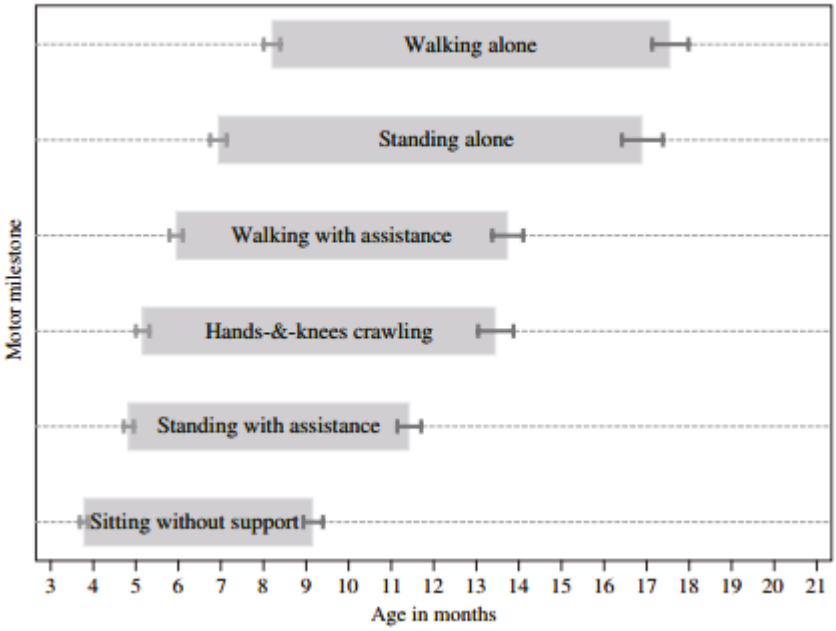
		(4-5 months)	(8 months)	(12 months)
Walking	No walking	Bouncing (6 months)	Cruising (walks holding on) (11 months)	Walking independently (15 months)

Note: the age presented in parentheses is what is considered normal age of achievement (Haataja 1999). The full table from the publication is in the appendix.

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

The motor milestones will be assessed using the WHO motor milestone criteria [WHO Multicentre Growth Reference Study Group 2006]. As part of the assessment, the examiner records an overall rating of the subject's emotional state and then for each milestone one of the following four classifications:

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

If not all WHO motor milestones test items were performed at a visit, then the approach described below will be used for the handling of missing data.

Missing values

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. If at least one milestone is assessed as 'No, inability' or 'Yes', yet the remainder are missing then an imputation will be performed considering each milestone, separately as follows. If a subject has baseline defined at Day 1 but has a missing milestone, then an imputation will be performed using the screening value. If the screening value is missing, then the missing milestone will be imputed as the median of the non-missing baseline values. In the event that the median at baseline is 0.5 then the missing value will be imputed as 1. If for the subject with a missing value at a particular visit the corresponding visit is flanked by visits with non-missing milestones, the missing value will be imputed by, using the worst result from the flanking visits. Otherwise, if the imputation is the last visit, the missing value will be imputed as the lowest value observed across all subjects with the same SMN2 copy number at that visit. Of note, only observed data will be utilized for imputation purposes. Missing motor milestone items will be imputed first prior to any analysis.

In an effort try and attach greater precision to the dates of first achievement of milestones, the caregivers are recording the first date they observe the child achieving each milestone and this is additionally captured in the CRF.

5.1.4. CHOP INTEND

Up to Version 5 of the protocol CHOP INTEND was assessed up to day 778. Under Version 6 of the protocol the CHOP INTEND will be assessed in subjects until they have a maximum score of 64. Once a score of 64 is achieved, CHOP INTEND will no longer be assessed.

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

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

CHOP INTEND is to be evaluated during the screening period, and at each visit on study from Day 64 until a maximum score of 64 is reached. For each item assessed an assessment is also made of the behavior by classifying into the following states:

State 1	Deep Sleep
State 2	Light Sleep
State 3	Drowsy or semi-dozing
State 4	Alert, with bright mood
State 5	Eyes open, considerable activity
State 6	Crying

Baseline

The baseline for CHOP INTEND is defined as the closest assessment at or prior to first dose of ISIS 396443.

Missing values

If not all items for CHOP-INTEND were performed at a visit, the approach described below will be used for the handling of missing data. Missing data will be imputed on an individual CHOP INTEND test item level. If a subject has baseline defined at Day 1 but has a missing item, then an imputation will be performed using the screening value. If the screening item is missing, then the missing item will be imputed as the median of all subjects with non-missing values with the same SMN2 copy number. If for the subject with missing CHOP INTEND test items at a particular visit, the corresponding visit is flanked by visits with non-missing test items, then the missing value for those test items will be imputed using linear interpolation with the result rounded to the nearest integer score. Otherwise, if the imputation is the last visit, the missing value will be imputed as the lowest value observed across all subjects with the same SMN2 copy number at that visit. Of note, only observed data will be utilized for imputation purposes. Missing CHOP INTEND items will be imputed first prior to any analysis. Since it is possible that a number of subjects will have reached the maximum CHOP INTEND value and stopped performing the test the appropriateness of these imputations will be assessed across visits and if the number of subjects contributing a value at a visit is < 5 it may not be valid to utilize these imputation rules and another approach may be implemented such as last observed visit.

Sensitivity analysis

A sensitivity analysis will be performed where the behavioral state is taken into account. As a first step, for any items where the behavioral state is 1, 2, 3 or 6 the score will be set to be missing. For a given subject, any such scores set to missing will be imputed using the closest available earlier result which has a behavior state of 4 or 5. If it happens that scores with behavioral states of 1, 2, 3 or 6 are at baseline, then set them missing. Following this step the imputation of any missing items to create a total score will follow a consistent approach with the rules in the missing values section above, including baseline imputation.

5.1.5. Hammersmith Functional Motor Scale – Expanded

All subjects ≥2 years of age will be evaluated using the HFMSE for the duration of the study. Subjects who are ≥2 years of age but have not yet achieved the maximum score of 64 with CHOP INTEND will be assessed with both until a CHOP INTEND maximum score of 64 is achieved. The HFMSE should be performed after the CHOP INTEND with an approximately 15-minute rest period in between to allow the subject to be fully engaged with both assessments.
The HFMSE is a reliable and validated tool used to assess motor function in children with SMA. The scale was originally developed with 20 scored activities and was devised for use in children with Type II and Type III 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 for evaluation of ambulatory patients with SMA.

Each item is scored 0 (unable), 1(performs with modification or adaptation) or 2 (able) and the total score is calculated by summing the 33 items and ranges from 0 to 66 with higher scores indicating greater motor function.

Baseline

The baseline for HFMSE is defined as the first assessment at which it is administered on or after Day 778 where 6 or fewer items are missing.

Missing values

If 6 or fewer items are missing, then these items will be imputed to be 0 when summing all 33 items. If greater than 6 items are missing, then the total score will be set to be missing. Post baseline, if greater than 6 items are missing, then the total score will be imputed by interpolating total scores between the previous and subsequent visit or, if there is no subsequent visit, by using the score from the previous visit.

The analysis visits are defined based on a windowing scheme described in Appendix 4.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.2. Visit windowing

The study visit schedule was designed to facilitate assessment of motor function at 13 and 24 months of age and then to follow them up to 8 years of age. Since subjects are dosed at less than ≤ 6 weeks of age the intention was that the Day 365 visit would be used for the assessment of the 13-month milestones and the Day 700 visit for assessment of the 24-month milestones.

Many of the planned analyses of efficacy data rely on summarizing results from similarly aged subjects at each study visit. Since subjects are enrolled from such a young age, departures from the planned visit schedule could result in a wide age range of subjects within a given visit. No windowing is planned for the efficacy visits and the presentation of data will be made using the study visits as collected in the CRF but compliance with the protocol windows have been monitored and if necessary a windowing scheme can be proposed. In order to present summaries of change from baseline for endpoints introduced during the study it may be necessary to assign baseline as the first visit at which the endpoint is assessed. Depending on the planned interval between assessments for a given endpoint and at which visit a majority of subjects have available values it may also make sense to define baseline at a later assessment in order to allow summaries by visit. In this situation, the age of subjects at the baseline assessment will be reported.

5.3. Analysis methods for the Primary endpoint

The primary endpoint is time to respiratory intervention or death where age of the subject at the time of event or censoring is presented. An event of respiratory intervention is defined as either invasive or non-invasive ventilation for 6 hours/day continuously for 7 or more consecutive days OR tracheostomy.

The median age at respiratory intervention (≥ 6 hours/day for ≥ 7 days) or death and associated 95% confidence interval (CI) will be estimated using the Kaplan-Meier method. The proportion of subjects who meet such an event at different ages of interest will be estimated from the Kaplan-Meier curve.

The time point for respiratory intervention will be the first of either the date of death or tracheostomy or the 7th consecutive day of ventilator use at ≥ 6 hours. Subjects who do not meet the endpoint definition will be censored at the last occasion the subject was seen (either in-person visit or by telephone contact), irrespective of whether or not the subject has completed a full course of treatment, and whether the subject has completed the study or withdrawn prematurely. The exception to this is when a subject has begun a ventilator diary in which case the latest entry in the diary will be used as

the date of censoring. Of note, once a ventilator diary has been started, the diary will then need to be completed every day until the end of the study.

In all the time to event analyses, the reference time will be the date of birth and the age in months will be presented. One month will be considered to be 365.25/12 days.

5.4. Analysis methods for the secondary endpoints: < 6 weeks to 8 years

Where applicable, baseline for the endpoints assessed starting when subjects are < 6 weeks is defined as the closest assessment at or prior to first dose of ISIS 396443.

5.4.1. Proportion of subjects alive

The proportion of subjects alive at 13 months and 2, 3, 4, 5, 6, 7 and 8 years of age and a corresponding confidence interval will be estimated from a Kaplan-Meier survival curve. The follow-up will end on the last occasion the subject was seen (either in-person visit or by telephone contact), and censoring will occur on this date for subjects who did not die.

5.4.2. Proportion of subjects who have attained motor milestones – HINE, WHO

The proportion of subjects who achieve individual motor milestones as assessed by the HINE (Section 2) and WHO milestone charts will be estimated using the Kaplan-Meier method. Subjects who have not achieved the milestone as of their last assessment will be censored at their last assessment on the endpoint under consideration. Kaplan-Meier plots, the proportion of subjects achieving the milestones by 13 and 24 months of age and the median age at which subjects attain these milestones will be presented. For WHO motor milestones, the proportion of subjects achieving motor milestones at 3, 4, 5, 6, 7, and 8 years will also be presented.

For HINE motor milestones a number of items are capture in the eCRF but attainments of the 10 milestones are considered as part of this analysis and are as follows:

Milestone	Levels considered
Head Control	'All the time maintained'
Sitting	'Stable sit' or 'Pivots'
Voluntary Grasp	'Pincer grasp'
Ability to kick	'Touches toes'
Rolling	'Prone to supine' or 'Supine to prone'
Crawling	'Crawling on hands and knees'
Standing with support	'Stands with support' or 'Stands unaided'
Standing unaided	'Stands unaided'
Walking cruising	'Walking cruising' or 'Walking'
Walking	'Walking'

Where two levels are considered such as for the sitting milestone, then both would be considered to be achievement and movement between the two over time would not count as a loss. In this analysis only observed data will be utilized and missing assessments will be ignored.

For each of WHO and HINE motor milestones two approaches (main analysis and sensitivity analyses) will be performed. The first approach will be to select the first instance a milestone is observed at site and for HINE this will be considered the main analysis. A sensitivity analysis will be performed which will also require: i) Having achieved the milestone we don't see but no achievements at two or more consecutive visits where it is not demonstrated and ii) confirmation that the milestone was observed at the last assessment. For WHO, three analyses will be performed which also utilize caregiver reported dates of achievement and thus avoid interval censoring which occurs for the site assessments. In the main analysis, the first instance of either caregiver or site assessment is selected, however in a situation where the caregiver reported was chosen then it is expected that this is confirmed at the next site visit. A sensitivity analysis will be performed where simply the first instance of either caregiver or site is selected and no confirmation is required.

Summary of planned analyses

Description	Main/Sensitivity	Comment
HINE – Age at first achieved motor milestone	Main	Simply select first instance milestone is observed at site
HINE – Age at first achieved motor milestone with confirmation at last visit	Sensitivity	Select first instance observed at site but needs to be confirmed for >=2 consecutive visits and as of last visit*.
WHO – Age at first achieved milestone by caregiver or site, if caregiver then confirmation at subsequent visit by site	Main	First of site or caregiver reported date. A caregiver reported date needs to have a site confirmation at next visit**.
WHO – Age at first achieved milestone caregiver or site	Sensitivity	Simply select first instance milestone is observed by caregiver or site

*See further details described below "*Approach for site assessments with confirmation at last visit"*.
**See "*Further details for WHO on incorporating caregiver reported dates with confirmation at subsequent visit"* described below.

Approach for site assessments with confirmation at last visit

In identifying the age at which a subject is deemed to have achieved the milestone the first assessment where this was achieved will be considered and subsequent assessments will be examined. Consider the following scenarios where we have identified the first visit at which the milestone was achieved:

1. If all subsequent assessments indicate the subject had achieved the milestone then the first visit date will be utilized to determine the age achieved. [Scenario 1]
2. If at the last available assessment they have not achieved the milestone then they will be considered to have not achieved the milestone. [Scenario 2]

3. If between the first observed achievement and the last observed achievement a visit exists where the milestone was not observed or appeared to be lost then the first visit will still be utilized. [Scenario 3,4]. Here, for Scenario 4, Visit 8 value of missing is ignored.
4. If after first achieved we have two consecutive visits with no achievement then would not count the first achievement and we would look to select a later visit where we don't see two consecutive failures [Scenario 5,6]
5. Missing will be ignored when flanked by visits with achievements [Scenario 7, Scenario 8]

KEY: N = Not achieved, Y= Achieved, - = missing

Scenario	Visit						Comment
	3	4	5	6	7	8	
1	N	Y	Y	Y	Y	Y	Achieved at visit 4
2	N	Y	Y	Y	Y	N	Not achieved
3	N	Y	Y	-	N	Y	Achieved at visit 4
4	N	Y	Y	N	Y	-	Achieved at visit 4
5	N	Y	N	N	Y	Y	Achieved at visit 7
6	N	Y	N	Y	N	Y	Achieved at visit 4
7	Y	-	-	Y	Y	Y	Achieved at visit 3
8	Y	-	-	N	Y	Y	Achieved at visit 3

Further details for WHO on incorporating caregiver reported dates with confirmation at subsequent visit

Consider the following scenarios in order to illustrate how this will be evaluated.

- If the caregiver reported date is confirmed at the next visit by a site assessment and all subsequent assessments indicate the subject had achieved the milestone then the caregiver reported date will be utilized. [Scenario W1]
- If the caregiver reported achievement prior to visit 4 and at visit 4 the subject was judged unable to achieve the milestone then the caregiver reported date will be ignored. [Scenario W2]
- If the caregiver reported date is after the site reported date then the site date will be used [Scenario W3]
- If the caregiver reported date is not confirmed at site due to missing assessments then if the first non-missing site assessment is a confirmation the caregiver date will be used [Scenario W4]
- If the caregiver reported date is confirmed, then caregiver date will be used [Scenario W5]
- A caregiver reported date needs to be confirmed with a site assessment [Scenario W6]

KEY: N = Not achieved, Y= Achieved, - = missing, X = caregiver reported date

Scenario	Visit						Comment
	3	4	5	6	7	8	
W1	N	X Y	Y	Y	Y	Y	Use caregiver-reported date
W2	N	XN	Y	Y	Y	Y	Don't use caregiver-reported date
W3	N	Y	XY	-	N	Y	Don't use caregiver-reported date
W4	N	X -	-	Y	Y	Y	Achieved at visit 4
W5	N	X Y	N	N	Y	Y	Achieved at caregiver reported date
W6	N	X -	-	-	-	-	Don't use caregiver-reported date

In these analyses where a subject has not achieved a milestone they will be censored at the last 'N' response available for the scale under consideration. In the event that a subject discontinues or dies then this will be noted in the summary or display. If a subject has achieved a milestone at baseline, they will be removed from the analysis.

[redacted]

HINE motor milestone responder

The proportion of motor milestone responders will be presented. The definition of a motor milestone responder is based upon the motor milestones categories in Section 2 of the HINE, with the exclusion of voluntary grasp as follows:

i. Subject demonstrates at least a 2-point increase in the category of ability to kick or an increase to the maximal score on that category (touching toes), or a 1 –point increase in the motor milestones category of head control, rolling, sitting, crawling, standing, or walking AND
ii. Among the motor milestone categories with the exclusion of voluntary grasp, there are more categories where there is improvement as defined in (i) than worsening. Note: for the category of ability to kick, similar to the definition or improvement in (i) above, worsening is defined as at least a 2-point decrease or a decrease to the lowest possible score of no kicking. For the other 6 categories, worsening is defined as at least 1-point decrease.

iii. Subjects who die or withdraw from the study prior to the visit will be counted as non-responders and will be included in the denominator

To illustrate this responder definition, consider some examples. In all the examples below, it is assumed that there are no changes in other motor milestone categories.

i. A subject with a 2-point increase of ability to kick, a 1-point increase in rolling, and a 1 point decrease in head control is a responder.
ii. A subject with a 1-point increase of ability to kick from "touches legs" to "touches toes" is a responder.
iii. A subject with a 1-point increase of head control and a 1-point decrease rolling is a non-responder.
iv. A subject with a 1-point increase of rolling and a 2-point decrease in ability to kick is a non-responder.
v. A subject with a 1-point increase of rolling and a 1-point decrease of ability to kick from "upward vertically" to "kicks horizontal, legs do not lift" is a responder.
vi. A subject with a 1-point increase of rolling and a 1-point decrease of ability to kick from "kicks horizontal, legs do not lift" to "no kicking" is a non-responder.
vii. A subject with a 2-point increase of voluntary grasp is a non-responder.
viii. A subject with a 1-point increase of rolling and a 2 points decrease of voluntary grasp is a responder.
ix. A subject with maintenance of 'touching toes', i.e. 0-point change is a non-responder.

The responder classifications will be based on the motor milestones assessment at the last available visit where HINE-2 was assessed, which is expected to be Day 778 or earlier. Subjects who die or withdraw prior to Day 778 will be classified as non-responders.

Maintenance of WHO motor milestones

For each milestone, the proportion of subjects who have the following status to last visit will be presented as follows using observed data only:

- Inability at first visit
  - Achieved on study and demonstrated at all subsequent visits following the visit at which first achieved
  - Achieved at last visit
  - Inability at last visit

5.4.3. Change in CHOP INTEND

The change from baseline in CHOP INTEND overall score will be presented by visit using summary statistics. The change from baseline at last available assessment will also be presented.

The time to achieving a maximum score of 64 will be analyzed using the Kaplan-Meier method. Subject who have not reached a score of 64 will be censored at the last available assessment of CHOP INTEND.

A plot of the mean change in CHOP INTEND overall score from baseline over time will be presented.

A sensitivity analysis will be performed using the total score calculated using the results with a behavioral state of 4 and 5.

5.4.4. Change in growth parameters

The change from baseline to each visit will be summarized using descriptive statistics for the following growth parameters: weight for age, weight for length/height, head circumference, chest circumference, head to chest circumference ratio and arm circumference.

[redacted]

5.5. Analysis methods for the secondary endpoints: Age <6 weeks to 2 years

During this period, the 13- and 24-Month Visits are of most interest. The visit at Day 365 will be used for the assessment of the endpoint at 13 months and the visit at Day 700 will be used for the assessment of the endpoint at 24 months.

5.5.1. Proportion of subjects developing clinically manifested SMA

A subject will be considered as having clinically manifested SMA if any of the following occur:

- If at 13 or 24 months of age, the subject's weight has dropped below the 5th percentile according to the WHO criteria [WHO 2014]; or if compared to Baseline, a subject has decreased 2 or more major weight percentiles (3rd, 5th, 10th, 25th, 50th) ; or if a percutaneous gastric tube has been inserted.
- Failure to demonstrate the following as assessed by WHO motor milestones, as assessed by the investigator

  - At 13 and 24 months of age; ability to sit without support, standing with assistance, hands and knees crawling.
  - Additionally at 24 months of age; walking with assistance, standing alone and walking alone.
- Subjects who discontinue treatment or die before the visit scheduled for 13 or 24 months of age.

As this endpoint has several components, rather than using the exact date that the subjects is 13 months and 24 months the following approach will be used. For the 13 month of age assessment the CRF collected Day 365, motor milestone and weight values will be used in judging if the subject meets the definition of developing SMA. If a gastric tube was inserted at, or before the date of the Day 365 visit, or if the subject discontinued treatment or died prior to this visit they will be judged to have met the definition of developing SMA. Similarly, in assessing the subject at 24 months of age, the Day 700 assessment will be utilized. The date of insertion of a gastric tube will be identified using the preferred term 'gastrostomy' from the ancillary procedures page of the CRF.

In assessing, the achievement of WHO motor milestones at Day 365 or Day 700, missing data will be imputed as described in Section 5.1.3. In assessing weight, in a situation where a subject did not attend the visit then if necessary the measurement from the previous visit may be used.

The proportion of subjects who meet the definition of having clinically manifested SMA at each timepoint will be presented with a corresponding Wilson score confidence interval with continuity correction (Newcombe, 1998). The individual components will be presented as follows: the proportion of subjects who had a gastric tube inserted, died, or discontinued the study. For the subjects attending the clinic on Day 365 or Day 700, the number of subjects who provided a motor milestone assessment, or decreased 2 or more major weight percentiles and were deemed to have SMA on the basis of these will be presented.

5.6. Analysis methods for the secondary endpoints: Age 2 to 8 years

5.6.1. HFMSE total score

A number of presentations will be made to explore the HFMS-E score over time.

For HFMSE total score, the baseline is defined as first assessment since Day 700 (inclusive) where 6 or fewer items are missing.

Summary statistics will be displayed for both the score and change from baseline by visit.

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 visit will be displayed below the x-axis.

In addition, a mixed model will be performed to estimate the slope (rate of HFMSE change per year) with age of subjects at visit and SMN2 copy numbers as independent variables, assuming a subjects'

score at first assessment as random. Unstructured covariance will be used for slope estimates. The method may be adjusted depending on whether convergence is met.

Spaghetti plots of total HFMSE scores vs age at visit will be presented.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.12. Interim Analyses

An interim analysis was conducted when 10 subjects had the opportunity to attend the Day 64 assessment using a cut-off date of 21st January 2016. Further interim analyses have been conducted as described in Section 2, by assessing the progress of subjects in the study.

The Interim Efficacy Set is defined as the subset of subjects in the ITT Set who have the opportunity to be assessed at the Day 64 visit. Specifically, the Interim Efficacy Set include all subjects with a Day 64 or later visit at which motor milestones and CHOP INTEND were planned to be assessed; subjects who die or withdraw are included in the interim Efficacy Set provided the time difference between the date of first dose and the clinical cut-off date (e.g., 21st January 2016 for the 1st interim analysis) is greater than 71 days (64 plus a 7 day window).

The interim analyses are performed in the ITT population for the following efficacy endpoints:

- Primary efficacy endpoint,

- All time to event endpoints,
- Proportion of subjects alive, and
- Proportion of subjects achieving motor milestones-WHO or HINE
- Proportion of subjects developing clinically manifested SMA

For all remaining efficacy endpoints, the interim analyses are performed on interim efficacy sets that comprise all dosed subjects who have either attended the targeted visit of the analysis OR who would have had the opportunity to attend the visit had they not died or discontinued. Presentations included as part of the interim analysis of efficacy will be a subset of those defined for the final analysis.

For the presentations of study subjects and safety the analysis are performed on the ITT Set as described for the final analysis. It may be necessary to repeat some presentations of study subjects for additional efficacy sets for example Day 64 and Day 183. For some presentations, depending on the number of observed events it may not make sense to present summaries so listings are presented. In order to assess the progress of subjects in achieving WHO and HINE motor milestones at the time of interim analyses the status at the last observed study visit is included in by visit presentations.

6. Safety Data

Analyses of safety data will include adverse events (Section 6.1), laboratory data (Section 6.2), ECGs (Section 6.3), vital signs (Section 6.4), and neurological examinations (Section 6.5).

Analyses of safety data will be based on the Safety Set which is the same as ITT population. Baseline is defined as the last non-missing result prior to the first dose of ISIS 396443.

6.1. Clinical adverse events

All adverse events 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 ISIS 396443 and subsequently worsened in severity, or was not present prior to receiving the first dose of ISIS 396443 but subsequently appeared.

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

- The first AE record occurs prior to the first dose, the second AE record occurs on or after the first dose, and the severity increases: Only the second record will be counted as treatment-emergent.

- The first AE record occurs prior to the first dose, the second AE record occurs on or after the first dose, and the severity decreases: Neither record will be counted as treatment-emergent.

- Both records occur on or after the first dose: If the AE severity on the second record increases from the severity on the first record, then count both records as treatment-emergent. But, if the severity decreases, then only count the first record as treatment-emergent.

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

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

- 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 of study treatment;
- if the start date for a particular event is missing and the stop date/time falls after the first dose date/time, then the event is considered to have occurred on or after the first dose of study treatment;
- if the start time is missing and the start date is same as the first dosing date, then the event is considered to have occurred on or after the first dose of study treatment;
- If it cannot be determined whether or not 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 ISIS 396443, analyses of treatment-emergent adverse events will include all events reported during the study.

Adverse events will be coded using the appropriate version of 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 (participants) and frequency (event count) of treatment-emergent adverse events will be summarized. 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 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.

6.1.1. Adverse events over time

The incidence of AEs will be evaluated by time of onset by 360-day time intervals. For a given time interval, the number of subjects who were followed for adverse events during that time interval will be presented along with the incidence of adverse events during that time interval. Therefore, for a given System Organ Class (SOC) or preferred term (PT), subjects will be counted only once for a given time interval but may be counted more than once across time intervals.

6.1.2. Adverse events following dosing procedure

To examine the onset of any adverse events following dosing the incidence of events that occurred in the first 72 hours following lumbar puncture procedure will be provided. In these analyses, the time of injection of ISIS396443 will be the reference point after which AEs are reported.

6.1.3. Adverse events assessed as related to lumbar puncture procedure

The incidence of events that were judged possibly or related to LP procedure will be presented.

6.1.4. Adverse events by anti-ISIS 396443 antibody status

To determine the impact of the formation of anti-ISIS 396443 antibodies on the safety of ISIS 396443, the incidence of adverse events in those ‘persistently’ positive, ‘transiently’ positive, and antibody negative will be presented. The definition of persistence is given in Section 8.

6.1.5. Adverse events by severity

The investigator is to record the severity of each adverse event as mild, moderate, or severe. If a subject experiences the same adverse event multiple times, the event with the maximum severity will be counted. The incidence within each category will be presented. The incidence of severe events will be summarized.

6.1.6. Adverse events by relationship to study treatment

The investigator is to record the relationship assessment of each adverse event to the study drug (not related, unlikely or remotely related, possibly related, and related). If a subject experiences the same adverse event multiple times, the event with the most conservative assessment will be counted. The incidence within each category will be presented. The incidence of drug-related events as assessed by the PI (those categorized as possibly related or related) will be summarized.

6.1.7. Serious adverse events

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

6.1.8. Adverse events that led to discontinuation from treatment and/or withdrawal from study

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

6.1.9. Deaths

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

6.1.10. Presentations

The following presentations will be shown:

- an overall summary showing 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 serious event, an event that led to discontinuation of study drug, and an event that led to withdrawal from the study
- incidence of events by primary system organ class and preferred term
- incidence by events by preferred term
- incidence of mild, moderate and severe events by primary system organ class and preferred term
- incidence of severe events by primary system organ class and preferred term
- incidence of not related, unlikely or remotely to be related, possibly related, and related events by primary system organ class and preferred term
- incidence of drug-related events by primary system organ class and preferred term
- incidence of serious adverse events by primary system organ class and preferred term and a listing of serious adverse events
- incidence of serious adverse events by preferred term
- incidence of death and a listing of each death
- incidence of events that led to death and a listing of such events
- incidence of events leading to discontinuation of study drug by primary system organ class and preferred term and a listing of such events
- incidence of events leading to interruption of study drug by primary system organ class and preferred term and a listing of such events
- incidence of events leading to withdrawal from the study by primary system organ class and preferred term and a listing of such events
- incidence of events of in specific categories – AEs assessed as related to lumbar puncture procedure, AEs by antibody status etc, by primary system organ class and preferred term and a listing of such events.

- Incidence of adverse events by 360-day interval

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

6.2. Clinical laboratory data

Due to blood collection volume limitations for newborns, the laboratory safety assessments will be performed less frequently for subjects with a screening weight of < 3 kg, this will revert to the standard collection times at either the Day 183 or when weight for a subject reaches ≥ 5.4kg. The schedules are detailed in the protocol Section 14.2.

The following clinical laboratory parameters are to be assessed:

- Hematology: red blood cells, hemoglobin, hematocrit, platelets, white blood cells, white blood cell differential
- Blood chemistry: total protein, albumin, creatinine, creatine phosphokinase, blood urea nitrogen, total bilirubin (direct and indirect), alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, glucose, calcium, phosphorus, chloride, sodium, potassium, bicarbonate, gamma-glutamyl transferase.
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, blood, red blood cells, white blood cells, epithelial cells, bacteria, casts, crystals, Leukocyte esterase.
- Cystatin C (for subjects with Screening weight of ≥3 kg)
- Coagulation: aPTT, PT, INR

Coagulation testing was performed at baseline only from protocol version 1. From protocol version 6 this was introduced at every visit.

For a parameter if the local and central result are available with the same date and time then only the central analysis result will be considered for presentations by visit. In a situation where two or more results have the same date and time and are both central (or both local) then we will check with the Safety physician if it would be more appropriate or take the highest or lowest value.

As described below, laboratory data will be examined using an analysis of "shifts" and all available data will be considered for these irrespective if collected centrally or locally.

Each subject's laboratory values will be classified according to whether the test result is "low" (i.e., below the lower limit of normal [LLN]), "normal" (within the normal range), or "high" (i.e., above the upper limit of normal [ULN]). If a subject is missing a baseline value but had a post-baseline value, then the baseline assessment is labeled as "unknown". Likewise, if a subject had a baseline value but had no post-baseline values, then the minimum and maximum are labeled as "unknown". Post-baseline laboratory results are defined as any assessment taken after the first dose, including data collected from local laboratories. 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. From these, 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.

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-<3 x ULN, ≥3-<5 x ULN, ≥ 5-<10 x ULN, ≥ 10 x ULN for ALT/AST, >1-<2 x ULN, ≥ 2 x ULN for total bilirubin, and >1-1.5 x ULN and ≥ 1.5 x ULN for alkaline phosphatase.

Laboratory actual values and change from baseline will be presented.

6.3. ECG

ECGs are to be recorded at screening, and on Days 2, 29, 365, 700, 897, 1254, 1611, 1849, 2206, 2563, and 2891 (End of Study). These are assessed at a central reading laboratory and the results provided back to sites to be entered into the eCRF. ECG qualitative results include an overall interpretation of 'normal', 'abnormal but not clinically significant' or 'abnormal and clinically significant'. Quantitative results will not be captured in the clinical database.

The number and percentage of subjects with shifts from normal to each of the categorical values denoting an abnormal scan (abnormal not AE, abnormal AE) will be summarized by treatment group, where 'abnormal not AE' is equivalent to 'abnormal but not clinically significant' and 'abnormal AE equivalent to 'abnormal and clinically significant'. A listing of subjects with abnormal status in ECG will be presented.

6.4. Vital signs

Vital signs are to be measured at screening, pre-dosing and at varying intervals post-dosing on dosing days, plus, they are assessed once on days where dosing is not performed. At each of these times, temperature, heart rate, respiratory rate, systolic and diastolic blood pressure, and pulse oximetry awake will be measured.

Assessment of clinically relevant abnormalities will be determined from a medical review of listings.

The analysis of vital signs will be approached in two ways.

6.4.1. Acute effects after dosing

On each dosing day, the change in each vital sign from pre-dosing on that day to post-dosing (i.e., from pre-dosing to 1 hour post-dosing, to 2 hours post-dosing, etc., including next day of dosing) will be calculated. Summaries of actual values and change from pre-dosing for each dosing day will be presented.

6.4.2. Chronic effects

To examine for possible chronic effects, the change from baseline (the pre-dosing value on Day 1) to the pre-dosing value on later visits will be determined. Summaries of actual values and change from baseline for subsequent dosing days will be presented.

6.5. Neurological examinations

Neurological examinations are to be assessed at screening, pre-dosing and at varying timepoints post-dosing. Up to and including protocol version 5 these assessments were made using Sections 1 and 3 of the HINE. From protocol version 6, subjects were assessed using HINE up to and including 24 months of age and then after 24 months they were assessed using the standard neurological examination.

HINE

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

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

HINE will be analyzed for subjects assessed up to Day 778 (inclusive).

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

The scores of each item for each subject will be presented graphically by visit/timepoint.

Standard Neurological Examination

Neurological examinations include assessment of mental status, level of consciousness, cranial nerves, reflexes, motor system, coordination/cerebellar function and sensation – temperature and vibration.

The result collected for the majority of the tests is ‘normal’ or ‘abnormal’, however the assessment of sensations is reported as ‘present’ or ‘absent’ and the assessment of reflexes is captured on an ordinal scale. For each test it is recorded if secondary to SMA.

The Standard Neurological Examination will be analyzed for subjects assessed from Day 700. The first assessment at Day 700 or after will be defined as baseline.

For each test, the number and proportion of subjects with worsening shift at any post-baseline point will be presented. For binary assessments, worsening shift is defined as from Normal to Abnormal or from Present to Absent. For ordinal scales (reflex, level of consciousness, mood), the worsening shift for reflexes is a shift from score of 2 to 0, 1, 3 or 4; for level of consciousness, worsening is a decrease on scores and for mood, worsening is an increase from baseline to any post-baseline time points.

To examine for possible acute and chronic effects, the above analyses will be presented for dosing days (pre-dose and after-dose assessment – ie 3, 6 hours post dose and next day of dosing) and for any pre-dose assessment on dosing days or other post-baseline assessments, respectively.

Two sets of analyses will be performed, in the first only data not deemed secondary to SMA will be presented. In the second, all changes will be included regardless if they were deemed secondary to SMA.

Graphical presentations

Individual subject's assessment outcomes will be presented.

6.6. Echocardiogram

Echocardiogram assessment was introduced in Protocol Version 7 and was only assessed locally at the site as per clinical practice. The visits performed were Days 1849, 2206, 2563 and at EOS/Early termination visit.

Echocardiogram data will be listed. Number and proportion of subjects with abnormal findings along with abnormality clinically significant will be presented.

6.7. Interim safety analyses

Safety data is reviewed on an ongoing basis by the Sponsor and the Medical Monitor.

From the initiation of the study the safety data were reviewed on a quarterly basis by an independent DSMB. Details on the safety assessments, frequency of review, meeting schedules and access to data at are outlined in a DSMB Charter. Based on the DSMBs ongoing assessment of the safety and tolerability of ISIS 396443, they were able to provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned.

Interim analyses have been performed as described in Section 5.6.

7. Pharmacokinetic data

CSF and Plasma samples will be collected at protocol designated times for ISIS 396443 pharmacokinetic assessments in the Pharmacokinetic Population. The Pharmacokinetic Population

includes all subjects who are dosed and for which there is at least one evaluable post-dose procedure pharmacokinetic sample.

7.1. CSF concentration data

CSF concentrations of ISIS 396443, along with the scheduled (nominal) and actual sampling times (i.e., time from IT dosing) will be listed (when applicable) for each subject and day. Differences between scheduled and actual sampling times will also be listed for all subjects along with percentage of the differences. .

CSF concentrations below the lower limit of quantification (LLOQ) will be listed as "BLQ". LLOQ is 0.0500 ng/mL. For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for CSF concentrations, all BLQ values will be set to half of LLOQ. Summary statistics of the ISIS 396443 CSF concentrations will be tabulated by day and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling days or times, or large deviations between actual dose and nominal dose.

ISIS 396443 CSF concentration versus time (actual) profiles from Day 1 to End of study, for each subject will be presented graphically. Geometric mean along with 95% CI CSF concentration versus time (scheduled) profiles will be also presented graphically. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

Due to the limited CSF samples collected no CSF pharmacokinetic parameters will be calculated.

7.2. Plasma pharmacokinetics

Plasma concentrations of ISIS 396443, along with the scheduled (nominal) and actual sampling times (i.e., time from IT dosing) will be listed (when applicable) for each subject and day. Differences and percentage differences between scheduled and actual sampling times will also be listed for all subjects.

Plasma concentrations below the lower limit of quantification (LLOQ) will be listed as "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to be half of LLOQ. LLOQ is 0.0500 ng/mL. Summary statistics of the ISIS 396443 plasma concentrations will be tabulated by day and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

ISIS 396443 plasma concentration versus time (actual) profiles from Day 1 to End of study, for each subject will be presented graphically. Geometric mean along with 95% CI plasma concentration versus time (scheduled) profiles will be presented graphically. Samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

Due to the limited plasma samples collected no plasma pharmacokinetic parameters will be calculated.

Exposure-response relationships between selected efficacy and pharmacodynamic (including but not limited to CHOP INTEND) and pharmacokinetic measures (including but not limited to CSF concentrations and plasma trough concentrations) may also be explored (including with and without stratification by antibody status), where appropriate.

8. Immunogenicity data

Immunogenicity (IM) testing (anti-ISIS 396443 antibody positivity), using designated plasma samples collected from each study subject, is planned to be conducted and reported. Immunogenicity plasma samples will be collected in accordance to the Schedule of Activities provided in Appendix 1.

The 1% false positive rate for the confirmatory assay will be used for the analysis. Plasma samples collected at other time points for ISIS 396443 concentration determinations may also be evaluated for IM testing if of further interest and deemed warranted by the pharmacokinetic scientist.

An individual sample result will be designated 'antibody positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed 'antibody negative'.

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

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

Antibody positivity will also be categorized (when possible) as being either 'persistent' or 'transient'. Persistent is defined as having one positive test followed by another one more than 100 days after the first positive test. In addition, "persistent" is also defined as having one or more positive samples and no sample more than 100 days after the first positive sample. Transient is defined as having one or more positive results and not confirmed to be persistent.

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

- For subjects who are positive at baseline, for post-baseline status the number and percentage with treatment emergent positive, negative and no evaluable post-baseline result will be

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

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

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

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

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

When and where warranted, PK (e.g., elevated plasma trough level) and selected safety and efficacy (e.g., CHOP INTEND, HFMSE) results may be further explored (stratified) by antibody status (antibody negative versus positive subjects).

[redacted]

10. Additional Analyses

10.1. Assessment of COVID-19 Impact

Due to the impact of the COVID-19 pandemic, caused by the novel coronavirus (SARS-COV-2), on patient visits and monitoring, there may be potential issues with missed visits or efficacy assessments. To determine the impact of COVID-19, the following will be summarized overall:

- The number subjects who have missed a dose visit due to COVID-19.
- Duration of time between doses from January 2020.
- The number of subjects who had received a commercial dose due to COVID-19.
- The number of missed efficacy assessments (eg. WHO Motor Milestones, HFMSE, CHOP INTEND etc.).

10.2. Risdiplam Analyses

Spaghetti plot vs age at visit (not windowed) will be presented for subjects taking risdiplam, with risdiplam starting and endpoint flagged. This presentation will be for HFMSE but other secondary efficacy endpoints may also be presented if they cover the period risdiplam was administered.

11. Sample size justification

There are no formal sample size calculations for this study. Sample size is based upon feasibility.

12. References

WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development. Geneva: World Health Organization, 2006.

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Haataja L, Mercuri E, Regev R, Cowan F, Rutherford M, Dubowitz V, Dubowtiz L. Optimality score for the neurologic examination of the infant at 12 and 18 months of age. J Pediatr 1999; 135: 153-61.

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Matsumoto H, Clayton-Krasinski DA, Klinge SA, Gomex JA, Booker WA, Hman JE, Roye Jr. DP, Vitale MG. Development and initial validation of the assessment of caregiver experience with neuromuscular disease. J Pediatr Orthop 2011; 31: 284-292.

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13. Changes to previous versions of the SAP

Changes to Version 1

Several sections were updated to align with the CS3b SAP

- Section 4.4 – clarifications added to definition of a concomitant medication
- Section 5.1 – clarification and additional detail added to CHOP INTEND and motor milestones for WHO and HINE.
- Section 5.4.1 – Preferred term for Gastric tube corrected to be 'Gastrostomy'
- [redacted]
- Section 6.1 – additional detail added to clarify definition of an treatment emergent AE

Changes to Version 2

The following text was removed from Section 5.5:
The snapshots of data from the eCRF and external vendors for interim analyses will be subjected to database cleaning activities and freezing/locking of eCRF pages but without the formal investigator sign off on pages associated with the final database lock of a study.
In the future the scope of cleaning and signature for interim cuts of data will be detailed in the appropriate data-management document.

Section 5.1.3. Update to imputation section for HINE and WHO motor milestones to provide additional clarity.

Section 5.6 Added last observed study visit analysis for WHO, HINE MM for the interim.

Changes to Version 3

Protocol Version 6 added new visits and assessments up to 5 years of age to cover the following new endpoints:

- HFMSE [redacted]

The following safety endpoints were added:

- Neurological examination
- Coagulation laboratory testing

The SAP was updated as follows:

Section 1.2, 1.3 – new endpoints specified in protocol were added. [redacted]
Section 2- text updated to incorporate new visits out to Day 1830.
Section 5- Descriptions of new endpoints added and corresponding analysis methods.
Section 6.2- Add coagulation testing and clarify rules for by visit presentations.
Section 6.4.2 – Add neurological examinations
Section 8 – remove mention of 'ND'

Changes to Version 4

Protocol Versions 7 and 8 added language stating that onsite assessments are no longer required after study injection. In addition the assessment period was extended to Day 2891, with a window of 14 days.

The SAP was updated as follows:

[redacted]

Section 2 – language was added stating the change in the requirement of onsite assessments as specified in the protocol. Also added updated Schedule of Activities that incorporates new visits out to Day 2801.

Section 3 – updated language to specify that concomitant therapy for SMA will be allowed for subjects enrolled after approval of Protocol Version 8.

Section 5.4.3 – analysis of change in CHOP INTEND has been updated so that Kaplan-Meier estimates of subjects first achieving score of 64 will be performed. [redacted]

Section 5.6 – updated to reflect extension of study to age 8 years.

[redacted]

Section 8 – updated language on how immunogenicity data is to be analyzed, referring to analyses as per discretion of the Sponsor.

Section 10 – new section on additional analyses to assess impact of COVID-19 on the study.

Changes to Version 5

- Protocol Version 9 is followed for this SAP.
- [redacted]
- [redacted]
- [redacted] and Pharmcogenomics (Section 5.9) and therefore analyses language updated accordingly.
- [redacted]
- Section 2.2: Extended visits when subjects returned to the sites.
- Section 2.4: Schedule of activities moved to Appendix 1.
- Section 3: Per Protocol Set definition updated.
- Section 5: Baseline definitions are moved into or modified in analysis method for each individual endpoint section as necessary.

- Section 5.1.4 and 5.4.3: Added a sensitivity analysis for CHOP INTEND using behavior state of 4 or 5 to calculate total scores.
- [redacted]
- Section 5.4.2: Removed a couple of WHO MM sensitivity analyses. [redacted]
- Section 5.5.1: Sensitivity analysis on Proportion of subjects developing clinically manifested SMA.
- Section 5.6.1: Added mixed model analysis of HFMSE.
- [redacted]
- [redacted]
- Section 5.7.6: Added Analysis of the HINE-1 item suck-swallow
- Section 6: Provided more details or clarifications in subsections of Safety. Added Section 6.6. Echocardiogram.
- Section 6.1.3 Moved out data presentation (such as number of attempts etc.) related to LP procedure (Section 6.1.3) to Section 4.3.
- Section 6.2 Removed analysis on additional lab ranges (eg results significantly outside normal ranges)
- Section 7: Provided more details or clarifications.
- Section 8: Undated analysis of immunogenicity data mainly by introducing definitions of baseline and post-baseline anti-drug antibody status.
- [redacted] Added risdiplam analyses.
- Appendix: Added Appendix 4 for Analysis windowing on unscheduled/ETvisits and for HMFSE windowing

Appendix 1 Schedule of Activities

Table 1 Screening through Day 779

Study Period	Screen	Treatment/Follow-Up															
Study Day	D -21 to D -1	D1			D2	D15 (±1D)			D16	D29 (±1D)			D30	D64, D183, D302, D421, D540, D659, D778 (±14D)			D65, D184 D303, D422, D541, D660, D779[1]	D365, D700 (±14D)
		Pre-Dose	LP	Post-Dose		Pre-Dose	LP	Post-Dose		Pre-Dose	LP	Post-Dose		Pre-Dose	LP	Post-Dose		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X	X[2]																
Medical History	X																	
Sibling SMA Data	X																	
Vital Signs and Pulse Oximetry	X	X		4X[3]	X	X		4X[3]	X	X		4X Error! Reference source not found.	X	X		4X Error! Reference source not found.	X	X
Weight	X	X			X	X			X	X			X	X			X	X
Growth Parameters	X													X[4]				X
Physical Examination	X	X				X				X				X				X
Ventilator Use	X	X			X	X			X	X			X	X			X	X
[redacted]																		
Neurological Examination	X	X		2X[6]	X	X		2X Error! Refere	X	X		2X Error! Refere	X	X		2X Error! Refere	X	X

Study Period	Screen	Treatment/Follow-Up																
Study Day	D -21 to D -1	D1			D2	D15 (±1D)			D16	D29 (±1D)			D30	D64, D183, D302, D421, D540, D659, D778 (±14D)			D65, D184 D303, D422, D541, D660, D779[1]	D365, D700 (±14D)
		Pre-Dose	LP	Post-Dose		Pre-Dose	LP	Post-Dose		Pre-Dose	LP	Post-Dose		Pre-Dose	LP	Post-Dose		
								nce source not found.				nce source not found.				nce source not found.		
ECG	X				X							X						X
Laboratory Safety Tests[7]	X					X				X				X Error! Reference source not found.				X
Coagulation Laboratory Tests[8]	X	X				X				X				X				X
Immunogenicity		X												X Error! Reference source not found.				X
CSF PK [redacted]		X				X				X				X				
[redacted]																		
Plasma PK[9]				X										X Error! Referen				

Study Period	**Screen**	**Treatment/Follow-Up**															
Study Day	**D -21 to D -1**	**D1**			**D2**	**D15 (±1D)**			**D16**	**D29 (±1D)**			**D30**	**D64, D183, D302, D421, D540, D659, D778 (±14D)**			**D65, D184 D303, D422, D541, D660, D779[1]**	**D365, D700 (±14D)**
		Pre-Dose	**LP**	**Post-Dose**		**Pre-Dose**	**LP**	**Post-Dose**		**Pre-Dose**	**LP**	**Post-Dose**		**Pre-Dose**	**LP**	**Post-Dose**		
														ce source not found.				
Optional RNA/DNA Assessment																	X[10]	
Study Treatment Injection			X				X				X				X			
Inpatient Stay (24 hours)				X														
CHOP INTEND/ HFMSE[11]	X[12]													**XError! Reference source not found.**				X
HINE Motor Milestones	**XError! Reference source not found.**													**XError! Reference source not found.**				X
WHO Motor Milestones[13]	**XError! Reference source not found.**													**XError! Reference source**				X

Study Period	Screen	Treatment/Follow-Up																
Study Day	D -21 to D -1	D1			D2	D15 (±1D)			D16	D29 (±1D)			D30	D64, D183, D302, D421, D540, D659, D778 (±14D)			D65, D184 D303, D422, D541, D660, D779[1]	D365, D700 (±14D)
		Pre-Dose	LP	Post-Dose		Pre-Dose	LP	Post-Dose		Pre-Dose	LP	Post-Dose		Pre-Dose	LP	Post-Dose		
														not found.				
[redacted]																		
Con Med and Ancillary Procedure Recording	X----------X																	
AE Collection	X----------X																	

[redacted] AE = adverse event; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; [redacted] Con Med = concomitant medication; CSF = cerebrospinal fluid; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Exam; LP = lumbar puncture; PK = pharmacokinetic(s); [redacted] RNA = ribonucleic acid; SMA = spinal muscular atrophy; [redacted] Term = termination; WHO = World Health Organization.

Note: Monitoring telephone calls will occur on a monthly (±14 days) basis starting on Day 94 and continuing to Day 897. At telephone contact, changes in concomitant medications and AEs will be recorded, as well as information on the subject's ventilator use and SMA disease status. Videotaping of the motor milestone assessments, all motor function assessments, and physical examinations will be optional.

Error! Reference source not found. These safety monitoring visits will occur on the day after the subject receives an injection of study treatment. At the time of the implementation of Protocol Version 7, onsite safety assessments are no longer required per protocol on the day following injection of study treatment; however, a postdose follow-up email or phone call evaluation will be required within 1 to 7 days after the dosing visits on Days 64, 183, 302, 421, 540, 659, and 778.

Error! Reference source not found. Investigator to check for signs and symptoms consistent with SMA.

Error! Reference source not found. Vital signs will be collected at 4 timepoints postdose: 1, 2, 4, and 6 hours (±15 minutes).

Error! Reference source not found. These assessments may be performed up to 7 days prior to dosing, if necessary.

[redacted]

Error! Reference source not found. Neurological examinations will be conducted at 2 timepoints: 3 and 6 hours after dosing.

Error! Reference source not found. Serum chemistry, hematology, urinalysis, and urine total protein; see **Error! Reference source not found.**, **Error! Reference source not found.**, and **Error! Reference source not found.** of Protocol Version 9.0 for a list of analytes and collection timepoints based on the subject's weight at Screening. For subjects ≥3 kg at Screening, once they reach a weight of 5.4 kg or the Day 183 visit, whichever happens first, blood samples for all analytes should be collected according to the above schedule. The blood sample for Cystatin C analysis will not be collected at any timepoint for subjects with a Screening weight of <3 kg. Urinalysis will be conducted according to the above schedule, independent of a subject's weight.

Error! Reference source not found. Coagulation testing will be conducted up to 7 days prior to dosing at the time of the implementation of Protocol Version 7, and results must be reviewed prior to dosing.

Error! Reference source not found. See Table for the detailed PK sampling schedule. [redacted]

Error! Reference source not found. A blood sample for RNA and DNA assessments will be drawn on Day 184. For subjects who have already completed Day 184 at the time of the implementation of Protocol Version 4, blood samples should be obtained at the next visit. At the time of the implementation of Protocol Version 6, a blood sample for RNA and DNA assessments will be drawn on the same day as injection of study treatment (Day 183) or at the next visit.

Error! Reference source not found. CHOP INTEND will be assessed in subjects until they have a maximum score of 64. Once a score of 64 is achieved, CHOP INTEND will no longer be assessed. All subjects ≥2 years of age will be evaluated using the HFMSE. See Section **Error! Reference source not found.** and Section **Error! Reference source not found.**.

Error! Reference source not found. The CHOP INTEND, HINE, and WHO motor milestone assessments will be conducted as part of the initial screening assessments. If they are conducted within 7 days prior to dosing, they will only need to be performed once; otherwise, they will need to be repeated within 7 days prior to dosing.

Error! Reference source not found. WHO motor milestone assessments will be performed by the Investigator or physical therapist at study visits independently of the assessments made by the subject's caregiver.

[redacted]

Table 2 Day 897 Through Day 1730

Study Day	Treatment/Follow-Up (Each visit can be ±14 days)																							
	D897			D1016			D1135			D1254			D1373			D1492			D1611			D1730		
	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post
Sibling SMA Data	X									X									X					
Vital Signs and Pulse Oximetry[1]	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X		X
Weight	X			X			X			X			X			X			X			X		
Growth Parameters[2]	X[3]			X[3]			X[3]			X[3]			X[3]			X[3]			X[3]			X[3]		
Physical Examination	X			X			X			X			X			X			X			X		
Ventilator Use	X			X			X			X			X			X			X			X		
[redacted]																								
Neurological Examination[4]	X[3]		X	X[3]		X	X[3]		X	X[3]		X	X[3]		X	X[3]		X	X[3]		X	X[3]		X
[redacted]																								
ECG	X[3]									X[3]									X[3]					
Laboratory Safety Tests[5]	X[3]			X[3]			X[3]			X[3]			X[3]			X[3]			X[3]			X[3]		
Coagulation Laboratory Tests[6]	X			X			X			X			X			X			X			X		
Immunogenicity	X[3]			X[3]			X[3]			X[3]			X[3]			X[3]			X[3]			X[3]		
CSF PK [redacted]	X			X			X			X			X			X			X			X		

Study Day	Treatment/Follow-Up (Each visit can be ±14 days)																							
	D897			D1016			D1135			D1254			D1373			D1492			D1611			D1730		
	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post
[redacted]																								
Plasma PK[7]	X[3]			X[3]			X[3]			X[3]			X[3]			X[3]			X[3]			X[3]		
Study Treatment Injection		X			X			X			X			X			X			X			X	
CHOP INTEND/ HFMSE[8]	X[3]						X[3]						X[3]						X[3]					
WHO Motor Milestones[9]	X[3]						X[3]						X[3]						X[3]					
[redacted]																								
Con Med and Ancillary Procedure Recording	X----------X																							
AE Collection	X----------X																							

[redacted] AE = adverse event; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; [redacted] Con Med = concomitant medication; CSF = cerebrospinal fluid; D = day; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = End of Study; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Exam; LP = lumbar puncture; [redacted]; PK = pharmacokinetic(s); [redacted]; RNA = ribonucleic acid; SMA = spinal muscular atrophy; [redacted] Term = termination; WHO = World Health Organization.

Notes: Starting from Day 897, follow-up safety monitoring telephone calls or emails will occur 1 to 14 days postdose and every other month for the duration of the study, except for the months when in-clinic visits occur. At telephone contact or via email, changes in concomitant medications and AEs will be recorded, as well as information on the subject's

ventilator use and SMA disease status. Where possible, all visits from Day 897 through Day 1730 can be concluded in 1 day. The final visit will occur 90 days after the last study treatment injection. Videotaping of the motor milestone assessments, all motor function assessments, and physical examinations will be optional.

For growth parameters, [redacted], ECG, laboratory safety tests, CHOP INTEND/HFMSE, WHO motor milestones, [redacted] if an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

For study visits with a large number of planned assessments, assessments can be completed over 1 to 2 days and assessments for primary and secondary outcomes (e.g., motor milestones/functional assessments) should be prioritized.

Error! Reference source not found. Vital signs will be taken predose and approximately 1 hour postdose (±15 minutes) at every onsite visit throughout the study.

Error! Reference source not found. Growth parameters of body length and/or height (for all subjects), and head circumference, chest circumference, and arm circumference (for subjects up to 36 months of age) will be measured.

Error! Reference source not found. These assessments may be performed up to 7 days prior to dosing, if necessary.

Error! Reference source not found. Sections 1 and 3 of the HINE will be conducted on all subjects ≤24 months of age. For all subjects >24 months of age, standard neurological examinations, which include assessments of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes, will be conducted. Neurological examinations are conducted within 7 days of dosing and approximately 1 hour after dosing (or when sedation has worn off if it was used).

Error! Reference source not found. Among the laboratory measurements, quantitative urine total protein will be assessed at the local laboratory If urinary protein concentration is >0.2 g/L, repeat testing and further evaluation should be considered; quantitative urine total protein should be prioritized if there is not enough urine sample for all tests.

Error! Reference source not found. Coagulation testing will continue to be conducted at each visit or up to 7 days prior to dosing and results should be reviewed prior to dosing. In situations where predose verification of coagulation laboratory results is not feasible or optimal (e.g., prolonged sedation of the subject would be required to allow adequate time for lab processing), the Investigator may exercise discretionary clinical judgment and proceed with the LP procedure, based on the subject's clinical and coagulation lab history.

Error! Reference source not found. See Table 4 for the detailed PK sampling schedule. [redacted]

Error! Reference source not found. CHOP INTEND will be assessed in subjects until they have a maximum score of 64. Once a score of 64 is achieved, CHOP INTEND will no longer be assessed. All subjects ≥2 years of age will be evaluated using the HFMSE. See Section **Error! Reference source not found.** and Section **Error! Reference source not found.** of Protocol Version 9.0.

Error! Reference source not found. WHO motor milestone assessments will be performed by the Investigator or physical therapist at study visits independently of the assessments made by the subject's caregiver.

Table 3 Day 1849 Through Day 2891 (End of Study)

Study Day	Treatment/Follow-Up (Each visit can be ±14 days)																											PTFU
	D1849			D1968			D2087			D2206			D2325			D2444			D2563			D2682			D2801			D2891 (EOS)/ Early Term[1]
	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	
Sibling SMA Data				X									X									X						X
Vital Signs and Pulse Oximetry[2]	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X		X	X
Weight	X			X			X			X			X			X			X			X			X			X
Growth Parameters[3]	X[4]									X[4]									X[4]									X
Physical Examination	X			X			X			X			X			X			X			X			X			X
Ventilator Use	X			X			X			X			X			X			X			X			X			X
[redacted]																												
Neurological Examination[5]	X[4]		X	X[4]		X	X[4]		X	X[4]		X	X[4]		X	X[4]		X	X[4]		X	X[4]		X	X[4]		X	X
[redacted]																												
ECG	X[4]									X[4]									X[4]									X
Echocardiogram[7]	X[4]									X[4]									X[4]									X
Laboratory Safety Tests[8]	X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X
Coagulation Laboratory Tests[9]	X			X			X			X			X			X			X			X			X			X
Immunogenicity	X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X
CSF PK [redacted]	X			X			X			X			X			X			X			X			X			

Study Day	Treatment/Follow-Up (Each visit can be ±14 days)																											PTFU
	D1849			D1968			D2087			D2206			D2325			D2444			D2563			D2682			D2801			D2891 (EOS)/ Early Term[1]
	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	Pre	LP	Post	
[redacted]																												
Plasma PK[10]	X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			X[4]			
Optional RNA/DNA Assessment																												X
Study Treatment Injection		X			X			X			X			X			X			X			X			X		
CHOP INTEND/ HFMSE[11]	X[4]									X[4]									X[4]									X
WHO Motor Milestones[12]	X[4]									X[4]									X[4]									X
[redacted]																												
Con Med and Ancillary Procedure Recording	X----------X																											
AE Collection	X----------X																											

[redacted] AE = adverse event; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; [redacted] Con Med = concomitant medication; CSF = cerebrospinal fluid; D = day; [redacted] DNA = deoxyribonucleic acid; ECG = electrocardiogram; EOS = End of Study; HFMSE = Hammersmith Functional Motor Scale – Expanded; HINE = Hammersmith Infant Neurological Exam; LP = lumbar puncture; [redacted] PK = pharmacokinetic(s); [redacted] PTFU = Post-Treatment Follow-Up; [redacted] RNA = ribonucleic acid; SMA = spinal muscular atrophy; [redacted] Term = termination; US = United States; WHO = World Health Organization.

Notes: Starting from Day 897, follow-up safety monitoring telephone calls or emails will occur 1 to 14 days postdose and every other month for the duration of the study, except for the months when in-clinic visits occur. At telephone contact or via email, changes in concomitant medications and AEs will be recorded, as well as information on the subject's ventilator use and SMA disease status. Where possible, all visits from Day 1849 through Day 2891 can be concluded in 1 day. The final visit will occur 90 days after the last study treatment injection. Videotaping of the motor milestone assessments, all motor function assessments, and physical examinations will be optional.

For growth parameters, [redacted] ECG, echocardiogram, laboratory safety tests, CHOP INTEND/HFMSE, WHO motor milestones, [redacted], if an assessment is not performed at a visit, attempts should be made to perform the assessment at the subsequent dosing visit(s) until completed; however, an assessment should not be performed more than once at any visit.

For study visits with a large number of planned assessments, assessments can be completed over 1 to 2 days and assessments for primary and secondary outcomes (e.g., motor milestones/functional assessments) should be prioritized.

[1] At the Early Termination Visit, age-appropriate assessments should be performed.

[2] Vital signs will be taken predose and approximately 1 hour postdose (±15 minutes) at every onsite visit throughout the study.

[3] Growth parameters of body length and/or height (for all subjects), and head circumference, chest circumference, and arm circumference (for subjects up to 36 months of age) will be measured.

[4] These assessments may be performed up to 7 days prior to dosing, if necessary.

[5] Sections 1 and 3 of the HINE will be conducted on all subjects ≤24 months of age. For all subjects >24 months of age, standard neurological examinations, which include assessments of mental status, level of consciousness, sensory function, motor function, cranial nerve function, and reflexes, will be conducted. Neurological examinations are conducted within 7 days of dosing and approximately 1 hour after dosing (or when sedation has worn off if it was used).

[redacted]

[7] Echocardiogram will only be assessed locally at the site as per local practice.

[8] Among the laboratory measurements, quantitative urine total protein will be assessed at the local laboratory. If urinary protein concentration is >0.2 g/L, repeat testing and further evaluation should be considered; quantitative urine total protein should be prioritized if there is not enough urine sample for all tests.

[9] Coagulation testing will continue to be conducted at each visit or up to 7 days prior to dosing and results should be reviewed prior to dosing. In situations where predose verification of coagulation laboratory results is not feasible or optimal (e.g., prolonged sedation of the subject would be required to allow adequate time for lab processing), the Investigator may exercise discretionary clinical judgment and proceed with the LP procedure, based on the subject's clinical and coagulation lab history.

[10] See Table 4 for the detailed PK sampling schedule. [redacted]

[11] CHOP INTEND will be assessed in subjects until they have a maximum score of 64. Once a score of 64 is achieved, CHOP INTEND will no longer be assessed. All subjects ≥2 years of age will be evaluated using the HFMSE. See Section **Error! Reference source not found.** and Section **Error! Reference source not found.** of Protocol Version 9.0.

[12] WHO motor milestone assessments will be performed by the Investigator or physical therapist at study visits independently of the assessments made by the subject's caregiver.

[redacted]

[16] These assessments will be for US sites and for subjects 5 years of age and older at US sites who have English (US) as their primary language.

Table 4: Pharmacokinetic Sampling Schedule

Study Day	Timepoints	Blood Collection (mL)	CSF Collection (mL)[1]
D1	Predose	NA	0.5
	4 hr (±1 hr)	0.5	NA
D15	Predose	NA	0.5
D29	Predose	NA	0.5
D64	Predose	0.5	0.5
D183	Predose	0.5	0.5
D302	Predose	0.5	0.5
D421	Predose	0.5	0.5
D540	Predose	0.5	0.5
D659	Predose	0.5	0.5
D778	Predose	0.5	0.5
D897	Predose	0.5	0.5
D1016	Predose	0.5	0.5
D1135	Predose	0.5	0.5
D1254	Predose	0.5	0.5
D1373	Predose	0.5	0.5
D1492	Predose	0.5	0.5
D1611	Predose	0.5	0.5
D1730	Predose	0.5	0.5
D1849	Predose	0.5	0.5
D1968	Predose	0.5	0.5
D2087	Predose	0.5	0.5
D2206	Predose	0.5	0.5
D2325	Predose	0.5	0.5
D2444	Predose	0.5	0.5
D2563	Predose	0.5	0.5
D2682	Predose	0.5	0.5
D2801	Predose	0.5	0.5

CSF = cerebrospinal fluid; D = day; hr = hour; mRNA = messenger ribonucleic acid; NA = not applicable (no collection scheduled); PK = pharmacokinetic; SMA = spinal muscular atrophy.

Note: Details on sampling, preparation, and shipment are included in the Study Laboratory Manual.

[redacted]

[1] Four to 5 mL of CSF will be collected for analyses and for PK assessments (see Section **Error! Reference source not found.**), but only 0.5 mL will be used for the PK analysis.

Appendix 2 CHOP INTEND

Name: Diagnosis:
MR: Gestational age:
DOE: Time of evaluation: Time since last feeding:
DOB: Current health: URI☐ Gtube ☐ BIPAP☐ HRS/Day____HRSoff BIPAP at testing___

Item	Position	Test Procedure	Graded Response		Score	
1 Spontaneous movement (Upper extremity)	Supine	Observe throughout testing May unweight limb or stimulate infant to facilitate response	Antigravity shoulder movement (achieves elbow off surface)	4	L	Best side: State:
			Antigravity elbow movement (achieves hand and forearm off surface)	3		
			Wrist movement	2	R	
			Finger movement	1		
			No movement of limbs	0		
2 Spontaneous movement (Lower extremity)	Supine	Observe throughout testing May unweight limb or stimulate infant to facilitate response	Antigravity hip movement (achieves feet and knees off surface)	4	L	Best side: State:
			Antigravity hip adduction/internal rotation (knees off surface)	3		
			Active gravity eliminated knee movement	2	R	
			Ankle movement	1		
			No movement of limbs	0		
3 Hand grip	Supine	Grip strength: place finger in palm and lift until shoulder comes off surface observe when infant looses grasp May use toy of similar diameter for older children	Maintains hand grip with shoulder off bed	4	L	Best side: State:
			Maintains grip with elbow off surface (shoulders on surface)	3		
			Maintains grip with forearm off surface (elbow supported on surface)	2	R	
			Maintains grip only with no traction	1		
			No attempt to maintain grasp	0		
4 Head in midline with visual stimulation*	Supine head midline	Visual stimulation is given with toy. ***If head is maintained in midline for 5 seconds:*** Place head in maximum available rotation and provide visual stimulation to encourage midline	Rotates from maximum rotation to midline	4	L>R	Best side: State:
			Turns head part way back to midline	3		
			Maintains midline for 5 or more seconds	2	R>L	
			Maintains midline, less than 5 seconds	1		
			Head falls to side, no attempts to regain midline	0		
5 Hip adductors	Supine, no diaper	Hips flexed and adducted Feet hip width apart and thighs parallel, knees slightly apart	Keeps knee off surface of bed > 5 sec or lifts foot off surface	4	L	Best side: State:
			Keeps knees off surface of bed 1-5 sec	2		
			No attempt to maintain knees off surface	0	R	
6 Rolling: elicited from legs*	Supine (arms at side) Keep side tested up roll away from the Side tested	1. Holding infant's lower thigh, flex hip and knee and adduct across midline bringing pelvis vertical maintain traction and ***pause in this position***. 2. If infant rolls to side apply traction at a 45° diagonal to body and pause to allow infant to attempt to derotate body	When traction is applied at the end of the maneuver, rolls to prone with lateral head righting	4	To R	Best side: State:
			Rolls through side lying into prone without lateral head righting, clears weight-bearing arm to complete roll	3		
			Pelvis, trunk and arm lift from support surface, head turns and rolls onto side, arm comes thru to front of body	2	To L	
			Pelvis and trunk lift from support surface and head turns to side. Arm remains behind trunk	1		
			Pelvis lifted passively off support surface.	0		
7 Rolling: elicited from arms*	Supine (arms at side) Keep side tested up roll away from the Side tested	1. Hold infant at the elbow move toward opposite shoulder maintain traction on limb and ***pause with the shoulders vertical*** allow infant to derotate 2.if the pelvis achieves vertical continue to provide traction	Rolls to prone with lateral head righting	4	To R	Best side: State:
			Rolls into prone without lateral head righting; must clear weight-bearing arm completely to finish roll	3		
			Rolls onto side, leg comes thru and adducts, bringing the pelvis vertical	2	To L	
			Head turns to side and shoulder and trunk lift from surface	1		
			Head turns to side; body remains limp or shoulder lifts passively	0		

8 Shoulder and elbow flexion And horizontal abduction	Side-lying with upper arm at 30° of shoulder extension and elbow flexion and supported on body (restrain lower arm if needed)	Prompt reach for a toy presented at arms length at shoulder level (may provide stimulation and ***observe spontaneous movement***)	Clears hand from surface with antigravity arm movement	4	L	Best side:
			Able to flex shoulder to 45 degrees, without antigravity arm movement	3		
			Flexes elbow after arm comes off body	2		
			Able to get arm off body	1	R	State:
			No attempt	0		
9 Shoulder flexion & Elbow flexion	Sitting in lap or on mat with head and trunk support (20° recline)	Present stimulus at midline and at shoulder level at arms length (may provide stimulation and ***observe spontaneous movement***)	Abducts or flexes shoulder to 60 degrees	4	L	Best side:
			Abducts or flexes shoulder to 30 degrees	3		
			Any shoulder flexion or abduction	2		
			Flexes elbow only	1		State:
			No attempt to lift arm	0	R	
10 Knee extension	Sitting in lap or over edge of mat with head and trunk support (20° recline) thigh horizontal to ground	Tickle plantar surface of foot Or gently pinch toe	Extends knee to > 45 degrees	4	L	Best side:
			Extends knee 15 to 45 degrees	2		
			Any visible knee extension	1		
			No visible knee extension	0	R	State:
11 Hip flexion and foot dorsiflexion	Hold infant against your body with legs free, facing outward. Support at the abdomen with the child's head resting between your arm and thorax	Stroke the foot or pinch the toe	Hip flexion or knee flexion > 30°	4	L	Best side:
			Any hip flexion or knee flexion	3		
			Ankle dorsiflexion only	2		State:
			No active hip, knee or ankle motion	0	R	
12 Head control*	Sitting with support at the shoulders and trunk erect	Place the infant in ring sit with head erect and assistance given at the shoulders (front and back). ***(may delay scoring a grade of 1 and 4 until end of test)***	Attains head upright from flexion and turns head side to side	4		Score:
			Maintains head upright for >15 sec (for bobbing head control score a 2)	3		
			Maintains head in midline for >5 sec. with the head tipped in up to 30° of forward flexion or extension	2		
			Actively lifts or rotates head twice from flexion within 15 seconds (do not credit if movement is in time with breathing)	1		State:
			No response, head hangs	0		
13 Elbow flexion Score with item 14	Supine	**Traction response:** pull to sit extend arms at 45 degree angle, to point of nearly lifting head off surface	Flexes elbow	4	L	Best side:
			Visible biceps contraction without elbow flexion	2		
			No visible contraction	0	R	State:
14 Neck Flexion Score with item 13	Supine	**Traction response:** hold in neutral proximal to wrist and shoulder at 45°, ***to point of nearly lifting head off surface***	Lifts head off bed	4		Score:
			Visible muscle contraction of SCM	2		
			No muscle contraction	0		State:
15 Head/Neck Extension (Landau)	Ventral suspension: Prone, held in one hand upper abdomen	Stoke along spine from neck to sacrum. The coronal axis of the head when parallel to the bed surface = 0 degrees (horizontal)	Extends head ***to*** horizontal plane or above	4		Score:
			Extends head partially, but not to horizontal	2		
			No head extension	0		State:
16 Spinal Incurvation (Galant)	Ventral suspension: Prone, held in one hand upper abdomen	Stroke Right then Left throacolumbar paraspinals or tickle abdomen or foot or tilt in infants with integrated Galant For infant over 10 kg knees and head may touch	Twists pelvis towards stimulus off axis	4	L	Best side:
			Visible paraspinal muscle contraction	2		
			No response	0	R	State:
Total score, best score on each side for each item (maximum 64 points):						

* Adapted from the Test of Infant Motor Performance, Campbell, SK; et al. 2001.

Contractures :
L☐R☐Knee flexion
L☐R☐Ankle plantar flexion
(Present < 20 degrees knee extended)
L☐R☐Hip adductor L☐R☐ ITB contracture
(Note if leg cannot abduct and ext. rot. to contact surface in supine)
L☐R☐Shoulder protraction
L☐R☐Elbow flexion
L☐R☐Neck rotation
L☐R☐Neck lateral flexion
☐ Plagiocephaly
☐ Fixed spinal curve

Behavioral State : (Brazelton, TB.Neonatal Behavioral Assessment Scale, 2nd ed.,1984)

State 1	Deep sleep	State 2	Light sleep
State 3	Drowsy or semi-dozing	State 4	Alert, with bright look
State 5	Eyes open, considerable activity	State 6	Crying

Testing environment:
Ideally test first thing in the AM or same time of day about 1 hour after feeding
Test on a firm padded mat
Diaper /onesie only unless the infant is cold
Test with red wool ball on ring to encourage participation
May use pacifier only if needed to maintain state 4 or 5 (see definition).
Mark as CNT (could not test) if patient could not be tested DO NOT MARK 0

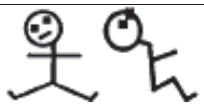
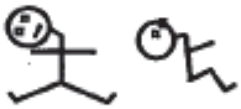
Appendix 3 Hammersmith Infant Neurological Examination (Section 1 AND 3)

SECTION 1: NEUROLOGICAL ITEMS

Assessment of cranial nerve function

	Score 3	Score 2	Score 1	Score 0	Comments
Facial appearance (at rest and when crying or stimulated)	smiles or reacts to stimuli by closing eyes and grimacing		closes eyes but not tightly; poor facial expression	expressionless; does not react to stimuli	
Eye appearance	normal conjugated eye movements		**intermittent** deviation of eyes or abnormal movements	**Continuous** deviation of eyes or abnormal movements	
Auditory response Test the response to rattle or bell	reacts to stimuli on both sides		doubtful reaction to stimuli or asymmetrical	does not react to stimuli	
Visual response Test the ability to follow a red ball or moving object	follows the object for a complete arc		follows the object for an incomplete arc, or asymmetry	does not follow the object	
Sucking/swallowing Watch the infant suck on breast or bottle	good suck and swallowing		poor suck and/or swallowing	no sucking reflex, no swallowing	

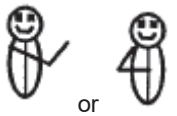
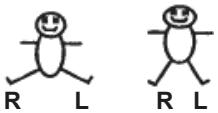
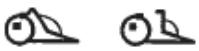
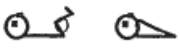
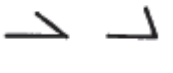
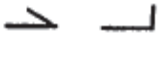
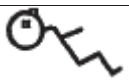
Posture

	Score 3	Score 2	Score 1	Score 0	Comment
Head In sitting	 straight; in midline		 slightly to side *or* backward *or* forward	 markedly to side *or* backward *or forward*	
Trunk In sitting	 straight		 slightly curved or bent to side	 very rounded rocking back bent sideways	
Arms At rest	In neutral position: central, straight *or* slightly bent		**slight** internal rotation *or* external rotation	**marked** internal rotation *or* external rotation or dystonic posture hemiplegic posture	
Hands	hands open		**intermittent** adducted thumb *or* fisting	**persistent** adducted thumb *or* fisting	
Legs In sitting In supine and In standing	able to sit with straight back, and legs straight or slightly bent (long sitting)  legs in neutral position: straight *or* slightly bent	**slight** internal rotation or external rotation	sit with straight back but knees bent at 15-20°  internal rotation *or* external rotation at hips	unable to sit straight unless knees markedly bent (no long sitting)  **marked** internal rotation *or* external rotation *or* fixed extension or flexion or contractures at hips and knees	
Feet In supine and In standing	central; in neutral position toes straight midway between flexion and extension		**slight** internal rotation *or* external rotation **intermittent** tendency to stand on tiptoes; *or* toes up or curling under	**marked** internal rotation *or* external rotation at the ankle **persistent** tendency to stand on tiptoes; *or* toes up or curling under	

Movements

	Score 3	Score 2	Score 1	Score 0	Comment
Quantity watch the infant lying in the supine	normal		excessive or sluggish	minimal or none	
Quality	free, alternating, smooth		jerky, slight tremor	• cramped & synchronous • extensor spasms • athetoid • ataxic • very tremulous • myoclonic spasm • dystonic	

Tone

	Score 3	Score 2	Score 1	Score 0	Comment
Scarf sign Take the infant's hand and pull the arm across the chest until there is resistance. Note the position of the elbow	Range:  R L R L		 R L	 or R L R L	
Passive shoulder elevation Lift arm next to the infant's head. Note resistance at shoulder and elbow	resistance; but overcome  R L		no resistance  R L	resistance, not overcome  R L	
Pronation/supination Steady upper arm while pronating and supinating forearm. Note resistance.	full pronation and supination, no resistance		full pronation and supination but resistance to be overcome	full pronation and supination not possible, marked resistance	
Adductors With the infant's legs extended, open them as far as possible. The angle formed by the legs is noted.	Range: 150º - 80º  R L R L	150º - 160º  R L	> 170º  R L	< 80 º  R L	
Popliteal angle Legs are flexed at the hip simultaneously on the side of the abdomen, then extended at the knee until there is resistance. Note angle between lower and upper leg.	Range: 150º - 110º  R L R L	150º - 160º  R L	~90º or >170º  R L R L	<80 º  R L	
Ankle dorsiflexion With knee extended, dorsiflex ankle. Note the angle between foot and leg.	Range: 30 - 85º  R L R L	20º - 30º  R L	< 20º or 90º  R L R L	> 90 º  R L	
Pulled to sit Pull infant to sit by wrists					
Ventral suspension Hold infant in ventral suspension; note position of the back, limbs, and head					

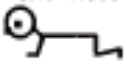
Reflexes and Reactions

	Score 3	Score 2	Score 1	Score 0	Comment
Tendon Reflexes	easily elicitable biceps knee ankle	mildly brisk bic knee ank	brisk biceps knee ankle	clonus or absent biceps knee ankle	
Arm protection Pull the infant by one arm from the supine position and note the reaction of the opposite side	 arm & hand extend **R** **L**		 arm semi-flexed **R** **L**	 arm fully flexed **R** **L**	
Vertical suspension Hold infant under axilla. Make sure legs do not touch any surface.	 kicks symmetrically		 kicks one leg more, or poor kicking	 no kicking even if stimulated, or scissoring	
Lateral tilting (describe side up). Infant held vertically, tilt quickly to horizontal. Note spine, limbs, and head.	 **R** **L**	 **R** **L**	 **R** **L**	 **R** **L**	
Forward parachute Infant held vertically and suddenly tilted forward. Note reaction of the arms	 (after 6 months)		 (after 6 months)		

SECTION 3: BEHAVIOR

	1	2	3	4	5	6	Comment
State of consciousness	unrousable	drowsy	sleepy but wakes easily	awake but no interest	loses interest	maintains interest	
Emotional State	irritable, not consolable	irritable, mother can console	irritable when approached	neither happy nor unhappy	happy, smiling		
Social Orientation	avoiding, withdrawn	hesitant	accepts approach	friendly			

HINE SECTION 2: Developmental milestones

Column	1	2	3	4	5	6
Head control	unable to mantain head upright (normal < 3 mo)	wobbles (normal at 4 mo)	all the time mantained upright (normal at 5 mo)			Observed: Reported (age):
12 m (%)			100			
18 m (%)			100			
Sitting	Cannot sit	With support  (normal at 4 mo)	Props  (normal at 6 mo)	Stable sit  (normal at 7 mo)	Pivots  (normal at 10 mo)	Observed: Reported (age):
12 m (%)				1	99	
18 m (%)					100	
Voluntary grasp	no grasp	uses whole hand	index finger and thumb but immature grasp	pincer grasp		Observed: Reported (age):
12 m (%)			3	97		
18 m (%)			2	98		
Ability to kick: (in supine)	no kicking	horizontally legs do not lift	upward (vertically)  (normal at 3 mo)	touches leg  (normal at 4-5 mo)	touches toes  (normal at 5-6 mo)	Observed: Reported (age):
12 m (%)					100	
18 m (%)					100	
Rolling	no rolling	rolling to side (normal at 4 mo)	prone to supine or supine to prone (normal at 6 mo)	supine to prone and prone to supine (normal at 7 mo)		Observed: Reported (age):
12 m (%)		1	1	98		
18 m (%)				100		
Crawling	Does not lift head	On elbow  (normal at 3 mo)	On outstretched hand  (normal at 4-5 mo)	Crawling flat on abdomen  (normal at 8 mo)	Crawling on hands and knees  (normal at 10 mo)	Observed: Reported (age):
			2	4	94	
					100	
Standing	Does not support weight	Supports weight (normal at 4-5 mo)	Stands with support (normal at 8 mo)	Stands unaided (normal at 12 mo)		Observed: Reported (age):
12 m (%)		3	18	79		
18 m (%)			2	98		
Walking		Bouncing (normal at 6 mo)	Cruising (walks holding on) (normal at 11 mo)	Walking (normal at 15 mo)		Observed: Reported (age):
12 m (%)		4	45	51		
18 m (%)			2	98		

Appendix 4 Analysis Visit Windowing Scheme

For secondary and [redacted] endpoints where applicable, analysis windowing is deemed necessary due to unscheduled visits or ET visits or assessments started at later stage of the trial due to age requirements. The windowing will be done for unscheduled/ET/EOS visits except for HFMSE, [redacted]. For HFMSE, the windowing will be done relative to its baseline which is defined as the first assessment since Day 700 (exclusive). [redacted]

Below are the details of windowing schemes for some endpoints. For the endpoints not listed, scheduled visits will be used as appropriate and windowing maybe still possible per the extent of unscheduled data.

Secondary endpoints

Growth parameters – Weight

Target Days	Intervals	Analysis Visit
0	<= 2	Day 0
15	2 < - <= 21	Day 15
29	22 =< - <= 46	Day 29
64	47 =< - <= 123	Day 64
183	124 =< - <= 242	Day 183
302	243 =< - <= 333	Day 302
365	334 =< - <= 392	Day 365
421	393 =< - <= 480	Day 421
540	481= < - <= 599	Day 540
659	600 =< - <= 679	Day 659
700	680 =< - <= 738	Day 700
778	739 =< - <= 837	Day 778
897	838 =< - <= 956	Day 897
1016	957 =< - <= 1075	Day 1016
1135	1076 =< - <= 1194	Day 1135
1254	1195 =< - <= 1313	Day 1254
1373	1314 =< - <= 1432	Day 1373
1492	1433 =< - <= 1551	Day 1492
1611	1552 =< - <= 1670	Day 1611
1730	1671 =< - <= 1789	Day 1730
1849	1790 =< - <= 1908	Day 1849
1968	1909 =< - <= 2027	Day 1968

2087	2028 =< - <= 2146	Day 2087
2206	2147 =< - <= 2265	Day 2206
2325	2266 =< - <= 2384	Day 2325
2444	2385 =< - <= 2503	Day 2444
2563	2504 =< - <= 2622	Day 2563
2682	2623 =< - <= 2741	Day 2682
2801	2742 =< - <= 2845	Day 2801
2891	>= 2846	Day 2891

Growth parameters – Other than Weight

Target Days	Intervals	Analysis Visit
0	<= 12	Day 0
64	13 =< - <= 123	Day 64
183	124 =< - <= 242	Day 183
302	243 =< - <= 333	Day 302
365	334 =< - <= 392	Day 365
421	393 =< - <= 480	Day 421
540	481 =< - <= 599	Day 540
659	600 =< - <= 679	Day 659
700	680 =< - <= 738	Day 700
778	739 =< - <= 837	Day 778
897	838 =< - <= 956	Day 897
1016	957 =< - <= 1075	Day 1016
1135	1076 =< - <= 1194	Day 1135
1254	1195 =< - <= 1313	Day 1254
1373	1314 =< - <= 1432	Day 1373
1492	1433 =< - <= 1551	Day 1492
1611	1552 =< - <= 1670	Day 1611
1730	1671 =< - <= 1789	Day 1730
1849	1790 =< - <= 1908	Day 1849
1968	1909 =< - <= 2027	Day 1968
2087	2028 =< - <= 2146	Day 2087
2206	2147 =< - <= 2265	Day 2206
2325	2266 =< - <= 2384	Day 2325
2444	2385 =< - <= 2503	Day 2444
2563	2504 =< - <= 2622	Day 2563
2682	2623 =< - <= 2741	Day 2682
2801	2742 =< - <= 2845	Day 2801

2891	>= 2846	Day 2891

LAB

Target Days	Intervals (inclusive)	Analysis Visit
0	<= Day 1	Day 0
15	Day 2 to 21	Day 15
29	Day 22 to 46	Day 29
64	Day 47 to 123	Day 64
183	Day 124 to 242	Day 183
302	Day 243 to 333	Day 302
365	Day 334 to 392	Day 365
421	Day 393 to 480	Day 421
540	Day 481 to 599	Day 540
659	Day 600 to 679	Day 659
700	Day 680 to 738	Day 700
778	Day 739 to 837	Day 778
897	Day 838 to 956	Day 897
1016	Day 957 to 1075	Day 1016
1135	Day 1076 to 1194	Day 1135
1254	Day 1195 to 1313	Day 1254
1373	Day 1314 to 1432	Day 1373
1492	Day 1433 to 1551	Day 1492
1611	Day 1552 to 1670	Day 1611
1730	Day 1671 to 1789	Day 1730
1849	Day 1790 to 1908	Day 1849
1968	Day 1909 to 2027	Day 1968
2087	Day 2028 to 2146	Day 2087
2206	Day 2147 to 2265	Day 2206
2325	Day 2266 to 2384	Day 2325
2444	Day 2385 to 2503	Day 2444
2563	Day 2504 to 2622	Day 2563
2682	Day 2623 to 2741	Day 2682
2801	Day 2742 to 2845	Day 2801
2891	>= 2846	Day 2891

Motor milestones – HINE

Target Days	Intervals	Analysis Visit

0	<=2	Day 0
64	3 =< - <= 123	Day 64
183	124 =< - <= 242	Day 183
302	243 =< - <= 333	Day 302
365	334 =< - <= 392	Day 365
421	393 =< - <= 480	Day 421
540	481 =< - <= 599	Day 540
659	600 =< - <= 679	Day 659
700	680 =< - <= 738	Day 700
778	>=739	Day 778

Motor milestones – WHO

Target Days	Intervals	Analysis Visit
0	<= 1	Day 0
64	2 =< - <= 123	Day 64
183	124 =< - <= 242	Day 183
302	243 =< - <= 333	Day 302
365	334 =< - <= 392	Day 365
421	393 =< - <= 480	Day 421
540	481 =< - <= 599	Day 540
659	600 =< - <= 679	Day 659
700	680 =< - <= 738	Day 700
778	739 =< - <= 837	Day 778
897	838 =< - <= 1015	Day 897
1135	1016 =< - <= 1253	Day 1135
1373	1254 =< - <= 1491	Day 1373
1611	1492 =< - <= 1729	Day 1611
1849	1730 =< - <= 2027	Day 1849
2206	2028 =< - <= 2384	Day 2206
2563	2385 =< - <= 2726	Day 2563
2891	>= 2727	Day 2891

CHOP INTEND

Target Days	Intervals	Analysis Visit
0	<= 1	Day 0
64	2 =< - <= 123	Day 64
183	124 =< - <= 242	Day 183

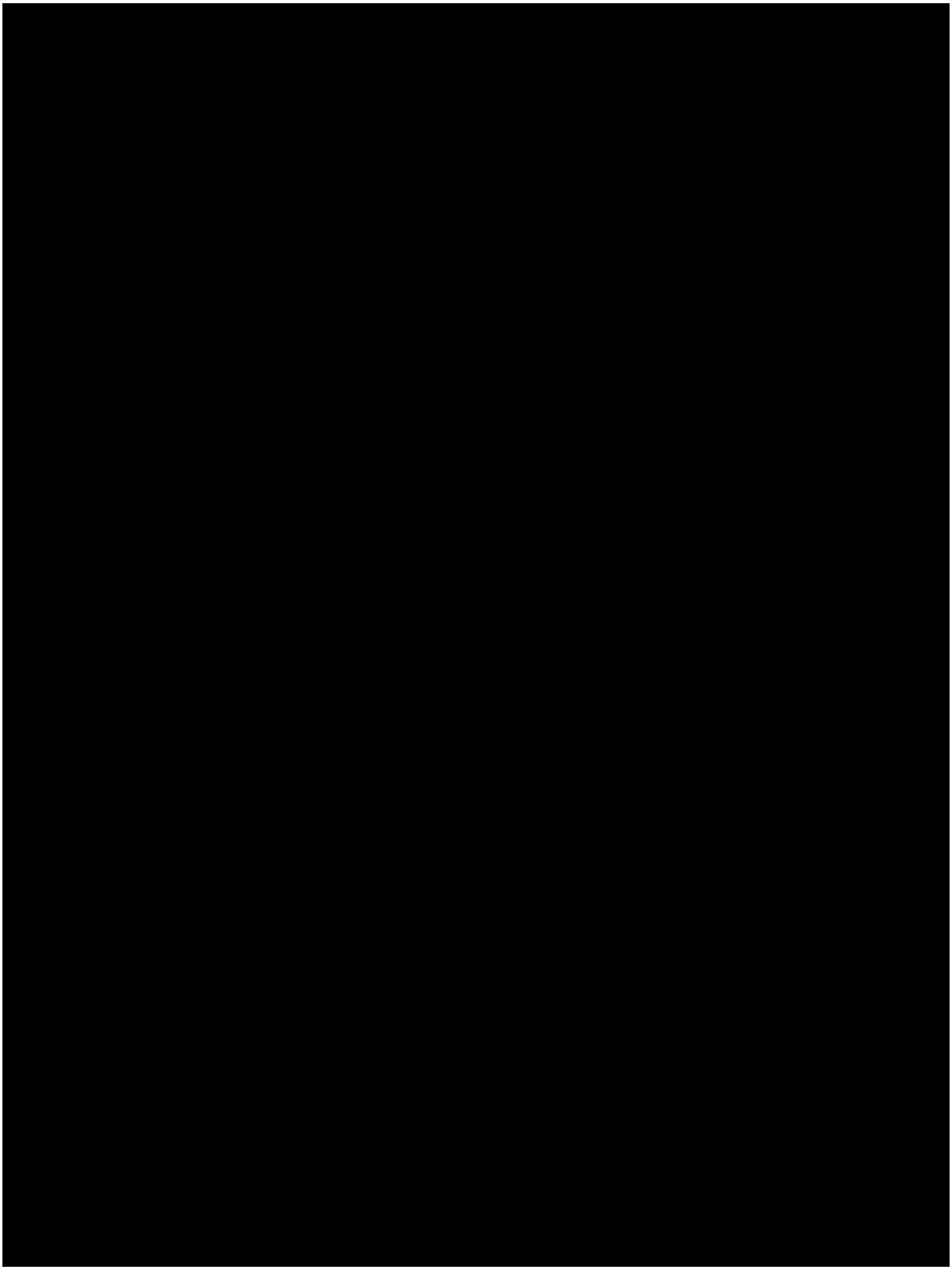
302	243 =< - <= 333	Day 302
365	334 =< - <= 392	Day 365
421	393 =< - <= 480	Day 421
540	481 =< - <= 599	Day 540
659	600 =< - <= 679	Day 659
700	680 =< - <= 738	Day 700
778	739 =< - <= 837	Day 778
897	838 =< - <= 1015	Day 897
1135	1016 =< - <= 1253	Day 1135
1373	1254 =< - <= 1491	Day 1373
1611	1492 =< - <= 1729	Day 1611
1849	1730 =< - <= 2027	Day 1849
2206	2028 =< - <= 2384	Day 2206
2563	2385 =< - <= 2726	Day 2563
2891	>= 2727	Day 2891

HFMSE

Target Days	Intervals	Analysis Visit (Day)	Analysis Visit (Month)
240	100 < - <=360	Day 240	Month 8
480	360 < - <=600	Day 480	Month 16
720	600 < - <=860	Day 720	Month 24
1080	860 < - <=1260	Day 1080	Month 36
1440	1260 < - <= 1620	Day 1440	Month 48
1800	1620 < - <= 1980	Day 1800	Month 60
2160	1980 < - <= 2340	Day 2160	Month 72

Note: Target days are relative to baseline which is defined as first assessment since Day 700 (exclusive).

[redacted]



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Document Pages: 83
Signatures: 3
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Record Tracking

Status: Original
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Signer Events	Signature	Timestamp
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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
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Payment Events	Status	Timestamps