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STATISTICAL ANALYSIS PLAN

TITLE: **AN OPEN-LABEL STUDY OF RISDIPLAM IN INFANTS WITH GENETICALLY DIAGNOSED AND PRESYMPTOMATIC SPINAL MUSCULAR ATROPHY**

PROTOCOL NUMBER: BN40703

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PLAN PREPARED BY: [redacted], Ph.D.

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STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
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1. BACKGROUND

This Statistical Analysis Plan (SAP) documents the statistical methods for summarizing and analyzing efficacy and safety data from Study BN40703 collected from patients with genetically diagnosed and presymptomatic spinal muscular atrophy (SMA) treated with risdiplam. The purpose of this document is to describe the data handling rules, derivation rules, and statistical analysis methods.

The SAP language and analysis supersedes the language in the protocol and protocol synopsis.

2. STUDY DESIGN

Study BN40703 is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of risdiplam in infants aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA but are not yet presenting with symptoms.

Infants will be enrolled in the study regardless of *SMN2* copy number. The primary efficacy analysis will be conducted in patients with two *SMN2* copies (excluding the known *SMN2* gene mutation c.859G>C) and a baseline compound muscle action potential (CMAP) amplitude $\geq$ 1.5mV. Recruitment will be closed when one of the following conditions have been met:

1. At least 25 patients, including a minimum of 5 patients who meet the criteria for the primary efficacy analysis population are enrolled, OR
2. A total of 10 patients who meet the criteria for the primary efficacy analysis population are enrolled.

The study consists of a screening period, treatment period, open-label extension phase and a follow-up, with a total treatment duration of at least 5 years for each patient:

- Screening: up to 42 days prior to first dose (bearing in mind the maximum age of the infant at first dose is 42 days).
- Treatment period: 24 months from the start of dosing, with the primary analysis conducted after the last patient enrolled reaches 12 months of treatment.
- Open-label extension: after completion of 24 months of treatment, each patient will continue to receive treatment in an open-label extension phase. The open-label extension phase is planned to run for 3 years for each patient (Month 24 to Month 60). Thereafter, the patient may continue until end of study, provided that risdiplam is not commercially available in the country of the site at which the patient is enrolled or until the Sponsor ceases producing or studying risdiplam. The overall study will not exceed a total of 5 years after the last patient is enrolled.
- Follow-up: all patients should have a follow-up call 30 days after the study completion/early withdrawal visit, as described in the Schedule of Activities (SoA).

The end of study is defined as the date when the last patient, last visit (LPLV) occurs. LPLV is expected to occur at the latest when the last patient enrolled in the study has completed 2 years in the treatment phase and 3 years in the open-label extension phase. The study will continue until the end of study, or as per local regulation, or per the Sponsor's decision to terminate risdiplam development.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Activities in Appendix 2.

2.2 ENDPOINTS

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of patients who are sitting without support after 12 months of treatment as assessed by item 22 ("Sits without support for 5 seconds") of the Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III). All patients with two *SMN2* copies (excluding the known *SMN2* gene mutation c.859G>C) and a baseline CMAP amplitude ≥1.5mV will be included in the primary efficacy analysis.

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

Development of Clinically Manifested SMA

- Proportion of patients developing clinically manifested SMA at Month 12 and Month 24 of treatment.

Survival and Ventilation-Free Survival

- Time to death (from enrollment).
- Time to permanent ventilation (from enrollment). Permanent ventilation is defined as $\geq$16 hours of non-invasive ventilation per day or intubation for $>$21 consecutive days in the absence of, or following the resolution of, an acute reversible event; or tracheostomy.
- Time to death or permanent ventilation (from enrollment).
- Proportion of patients who are alive without permanent ventilation at Month 12 and Month 24 of treatment.
- Proportion of patients who are alive at Month 12 and Month 24 of treatment.

Motor Function and Development Milestones

- Proportion of patients who achieve the attainment levels of the motor milestones assessed in the Hammersmith Infant Neurological Examination Module 2 (HINE-2; head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing and walking) at Month 12 and Month 24 of treatment.

- Proportion of patients with two copies of the *SMN2* gene (independent of the CMAP value at baseline) sitting without support for 5 seconds at Month 12 of treatment (as assessed in item 22 of the BSID-III Gross Motor Scale).
- Proportion of patients sitting without support for 5 seconds at Month 24 of treatment (as assessed in item 22 of the BSID-III Gross Motor Scale).
- Proportion of patients sitting without support for 30 seconds at Month 12 and Month 24 of treatment (as assessed in item 26 ["Sits without support for 30 seconds"] of the BSID-III Gross Motor Scale).
- Proportion of patients standing at Month 24 of treatment (as assessed in item 40 ["Stands alone"] of the BSID-III Gross Motor Scale).
- Proportion of patients walking at Month 24 of treatment (as assessed in item 42 ["Walks alone"] of the BSID-III Gross Motor Scale).
- Gross motor function as measured by the raw and scaled scores of the BSID-III Gross Motor Scale at Month 12, Month 24 and Month 42 of treatment.
- Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations (SD) of the chronological reference standard at Month 24 and Month 42 of treatment, as assessed through the use of the BSID-III Gross Motor Scale.
- Change from baseline score in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) motor function scale at Month 12 of treatment.
- Proportion of patients who achieve a score of 40 or higher in the CHOP-INTEND motor function scale at Month 12 of treatment.
- Proportion of patients who achieve a score of 50 or higher in the CHOP-INTEND motor function scale at Month 12 of treatment.
- Proportion of patients who achieve a score of 60 or higher in the CHOP-INTEND motor function scale at Month 12 of treatment.
- Proportion of patients who meet CHOP-INTEND stopping criteria at any time up to Month 24 of treatment.
- Change from baseline (Month 24) in the Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 60 of treatment.

Respiratory

- Proportion of patients who do not receive any pulmonary care at Month 12 and Month 24 of treatment.

Growth Measures

- Number and proportion of patients within the 3rd percentile of normal range for weight-for-age, length/height-for-age and weight-for-length/height at Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment, based on the World Health Organization (WHO) Child Growth Standards.

- Number and proportion of patients within the 3rd percentile of normal range for head circumference-for-age at Month 12 and Month 24 of treatment, based on the WHO Child Growth Standards.
- Change from baseline percentiles for weight-for-age, length/height-for-age and weight-for-length/height at Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment.
- Change from baseline percentiles for head circumference-for-age at Month 12 and Month 24 of treatment.
- Change from baseline in chest circumference at Month 12 and Month 24 of treatment.
- Ratio between the chest and head circumferences at Month 12 and Month 24 of treatment.

Nutrition

- Proportion of patients with the ability to swallow at Month 12, Month 24, Month 36, Month 48, and Month 60 of treatment.
- Proportion of patients with the ability to feed orally at Month 12, Month 24, Month 36, Month 48, and Month 60 of treatment.

Muscle Electrophysiology

- Change from baseline in the CMAP negative peak amplitude at Month 12 and Month 24 of treatment.

2.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

- Cognition as measured by the raw and scaled scores of the BSID-III Cognitive Scale at Month 12, Month 24, and Month 42 of treatment.
- Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 SD of the chronological reference standard at Month 24 and Month 42 of treatment, as assessed through the use of the BSID-III Cognitive Scale.
- Fine motor function as measured by the raw and scaled scores of the BSID-III Fine Motor Scale at Month 12, Month 24 and Month 42 of treatment.
- Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 SD of the chronological reference standard at Month 24 and Month 42 of treatment, as assessed through the use of the BSID-III Fine Motor Scale.
- Total walk distance as assessed by the 6-minute walk test (6MWT) at Month 60 of treatment (ambulant patients only).
- Proportion of patients who attain motor milestones as assessed by WHO criteria at Month 48 and Month 60 of treatment.
- Speech development as assessed by neurological examination at Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment.

- Change from baseline in the Infant Toddler Quality of Life (ITQOL)-SF47 Questionnaire domains and single item scores at Month 12 and Month 24 of treatment.
- Number of hospitalizations (for any reason, except if for study purpose only [e.g., to facilitate study assessments]) per patient-year and number of nights admitted to hospital per patient at Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment.
- Proportion of patients with no hospitalizations by Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment.
- Proportion of patients who experience at least one disease-related adverse event by Month 12 and Month 24 of treatment.
- Number of disease-related adverse events per patient-year at Month 12 and Month 24 of treatment.

2.2.4 Pharmacokinetic Endpoints

The PK endpoints are as follows:

- Concentration per time-point listed.
- Peak plasma concentration (C_{max}).
- Area under the curve (AUC).
- Concentration at the end of a dosing interval (C_{trough}).
- Other PK parameters as appropriate.

2.2.5 Pharmacodynamic Endpoints

The PD endpoints are as follows:

- Change from baseline in full-length *SMN2* mRNA in blood at each time-point.
- Change from baseline in Δ7 *SMN2* mRNA in blood at each time-point.
- Absolute SMN protein in blood at each time-point.
- Change from baseline in SMN protein in blood at each time-point.

2.2.6 Safety Endpoints

The safety endpoints are as follows:

- Incidence of adverse events (overall, by severity and by relationship to study medication).
- Incidence of serious adverse events.
- Incidence of treatment discontinuations due to adverse events.
- Incidence of laboratory abnormalities.
- Incidence of electrocardiogram (ECG) abnormalities.
- Incidence of vital sign abnormalities.
- Incidence of clinically significant findings on ophthalmological examination.

2.3 DETERMINATION OF SAMPLE SIZE

The primary purpose of the study is to estimate the proportion of patients with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude ≥1.5mV who are sitting without support after 12 months of treatment and to test whether this proportion is higher than a performance criterion set at 5%. The 5% threshold was chosen based on the natural history of the disease (typically patients with Type 1 SMA never achieve sitting without support by definition) and based on the assumption that there is a 97% chance that a presymptomatic patient with two *SMN2* copies will develop Type 1 SMA (Feldkotter et al. 2002).

The target sample size to be enrolled in the study is 10 patients in the primary efficacy analysis population, i.e., patients with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude ≥1.5mV. A sample size of 10 patients provides 83% power to test the null hypothesis H_0: p≤5% versus alternative hypothesis H_a: p>5%, if the true proportion of patients who would sit after 12 months of treatment is 40%. This is based on an exact binomial test with a one-sided 5% significance level. The minimum number of patients needed to be observed sitting without support is 3 out of 10 for a statistically significant result. If 3 out of 10 patients sit without support, the lower limit of the two-sided 90% Clopper-Pearson (exact) confidence interval (CI) would be above 5%.

If recruitment is completed prior to enrolling 10 patients in the primary efficacy analysis population, the minimum number of patients needed to be observed sitting without support for a statistically significant result (the critical value) may differ. The power and critical value based on the number of patients in the primary efficacy analysis population are presented below:

Number of patients in primary efficacy analysis population	Critical value	Power (%)
5	2	66.3
6	2	76.7
7	2	84.1
8	3	68.5
9	3	76.8
10	**3**	**83.3**

In each case, the lower limit of the two-sided 90% Clopper-Pearson (exact) CI would be above 5%.

No allowance has been made for patients who withdraw early as these patients will be classified as a non-responder/non-sitter and included within the primary analysis.

A total of approximately 25 patients with SMA (any *SMN2* copy number) are expected to be enrolled in the study. Recruitment will be closed when at least 25 patients, including

a minimum of 5 patients who meet the criteria for the primary efficacy analysis population are enrolled, OR a total of 10 patients who meet the criteria for the primary efficacy analysis population are enrolled.

2.4 ANALYSIS TIMING

A database lock for the purpose of the primary analysis and analyses of the 12-month secondary and exploratory endpoints will occur once the last patient enrolled has either completed his or her 12-month assessment or has been withdrawn (and all other patients have either completed the 12-month assessment or have been withdrawn). A fixed-cutoff data cut will be used with a clinical cutoff date based on the date of the Month 12 visit of the last patient enrolled. The clinical cutoff date will be the same for all patients, and all data collected on or before the clinical cutoff date will be included in the data cut. At the time of the primary analysis, all available interim efficacy data post Month 12 will be reported. All available safety data will also be reported.

A database lock for the analyses of the 24-month secondary and exploratory endpoints will occur once the last patient enrolled in the study has either completed his or her 24-month assessment or has been withdrawn (and all other patients have either completed the 24-month assessment or have been withdrawn). A fixed-cutoff data cut will be used with a clinical cutoff date based on the date of the Month 24 visit of the last patient enrolled. The clinical cutoff date will be the same for all patients, and all data collected on or before the clinical cutoff date will be included in the data cut. At the time of the Month 24 analysis, all available interim efficacy data post Month 24 collected as part of the open-label extension period will be reported. All available safety data will also be reported.

Subsequent locks of the database may occur in order to perform exploratory efficacy or safety analyses of the data at further time-points in response to information that may emerge during the course of the study. The final database lock will occur at the end of the study (i.e., last patient, last observation).

As this is an open-label study, once at least 3 out of 10 patients (if 10 patients have been enrolled in the primary efficacy analysis population) have met the primary endpoint of sitting without support at Month 12 (as assessed by the independent central readers), the minimum number of patients needed for a statistically significant result will have been achieved and the primary objective of the study will be considered achieved at this earlier time-point. The study will not be stopped early if the primary objective has been reached, and all patients enrolled will continue to receive 12 months of treatment in order to provide an unbiased estimate of the proportion of patients sitting without support at Month 12.

An interim analysis may also be performed to summarize descriptively the safety and efficacy data to support the registration of risdiplam in presymptomatic patients and patients below the age of 2 months.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Study BN40703 is a non-randomized, single-arm, open-label study, and all patients will receive risdiplam at a dose selected to achieve the target exposure of an $AUC_{0\text{-}24,\ ss}$ of close to 2000 ng·hr/mL (the dose may be adapted as patients grow and mature), with the average exposure of all patients not predicted to exceed 2000 ng·hr/mL.

3.2 INDEPENDENT REVIEW FACILITY

3.2.1 BSID-III Gross Motor Scale and Sitting, Standing, Walking Series

The sitting, standing, walking series consists of seven items assessed in the BSID-III Gross Motor Scale:

- Sitting items: item 16 (“Sits with support briefly”), item 19 (“Sits with support for 30 seconds”), item 22 (“Sits without support for 5 seconds” [primary endpoint]), item 26 (“Sits without support for 30 seconds”) and item 27 (“Sits without support and holds object”)
- Standing item: item 40 (“Stands alone”)
- Walking item: item 42 (“Walks alone”)

The sitting, standing, walking series should be administered prior to the standard BSID-III Gross Motor Scale (which takes into account the designated starting point in the scale and the discontinuation and reversal rules) at each visit.

The evaluation of the sitting, standing, walking series and the BSID-III Gross Motor Scale will be video-recorded at study sites in a standardized manner and centrally reviewed by two independent readers (in addition to the site clinical evaluator assessment). There will be two videos for each patient, one for the initial sitting, standing, walking assessment and one for the full BSID-III Gross Motor Scale. These videos will be merged for the purpose of central review.

The two independent central readers will review all recorded items of the sitting, standing, walking series and the full BSID-III Gross Motor Scale assessment, but will only complete scoring of items 16, 19, 22, 26, 27, 40, and 42, taking into account items completed at any point in the recording. If an item is performed as part of the sitting, standing, walking series and the full BSID-III Gross Motor Scale assessment, the best score will be provided.

The assessment by the central readers will be used for the analysis of the primary endpoint (item 22 “Sits without support for 5 seconds”) and for the analysis of the six other scored items in the sitting, standing, walking series. The role and process of the reading center is described in a separate charter.

The scores provided by the two independent readers will be evaluated to determine concordance in the seven scored items of the sitting, standing, walking series. For items 16, 19, 22, 26, 27, 40 and 42 to be classified as confirmed, both independent central readers should classify the milestone (i.e., item) to have been achieved by the patient (a score of 1). If the independent central readers both classify the milestone as not being achieved (a score of 0 [or "Cannot Test (CNT)"]), then the milestone will be classified as not confirmed, regardless of the site clinical evaluator's own assessment.

If the scores of the independent central readers are discordant for any of the scored items on the first reading, then both central readers will be asked to re-score the patient. If the scores of the independent central readers are concordant on re-score, i.e., both central readers classify the item as (not) being achieved, those milestones will be classified as confirmed (or not confirmed). If the two independent central readers are not in agreement after they have re-scored the patient, then the motor milestone will be classified as not confirmed (i.e., not achieved).

Table 1 Central Reader Scoring – Analysis of Scored Item (Example: Item 22 "Sits Without Support for 5 Seconds")

Site Clinical Evaluator Score	Reader 1 Score	Reader 2 Score	Discordance/ Re-score Needed	Reader 1 Re-Score	Reader 2 Re-Score	Confirmed for Primary Endpoint
1 – sitting achieved	1	1	No	N/A	N/A	Yes
1	0	0	No	N/A	N/A	No
1	1	0	Yes	Asked to re-score		
				1	0	No
				1	1	Yes
				0	0	No
				0	1	No
0 – sitting not achieved	0	0	No	N/A	N/A	No
0	1	1	No	N/A	N/A	Yes
0	1	0	Yes	Asked to re-score		
				1	0	No
				1	1	Yes
				0	0	No
				0	1	No

N/A = Not applicable

3.2.2 Ophthalmological Assessments

Images obtained from the spectral domain optical coherence tomography (SD OCT) and fundus photography examinations will be reviewed by an independent reader from the Annesley EyeBrain Center (AEBC), Vickie and Jack Farber Institute for Neuroscience at Jefferson Health Partnered with Wills Eye Hospital. This includes an assessment of clinically significant changes from baseline in these examinations at each time-point. These assessments will be used to determine the incidence of clinically significant findings in the SD OCT and fundus photography examinations. The role and process of the reading center is described in a separate charter.

3.2.3 Permanent Ventilation

The occurrence of permanent ventilation events will be determined by an independent permanent ventilation adjudication committee. This committee will review all pertinent data for patients who may meet the definition of permanent ventilation and confirm if this endpoint has been met. The assessment of the committee will be used in the analysis of time to death or permanent ventilation and time to permanent ventilation. The role and process of the committee is described in a separate charter.

3.3 DATA MONITORING

An external independent Data Monitoring Committee (iDMC) has been established to monitor patient safety during the study. The iDMC will meet on a regular basis (approximately every 3 months) over the course of the study to review emerging data, and may also meet on an ad-hoc basis as required (e.g., if any unexpected safety concerns arise). After every meeting, the iDMC will make a recommendation to the Sponsor for the study conduct. The iDMC can make any of the following recommendations to the Sponsor:

- Recommend to continue the trial without modification.
- Recommend increases or decreases to the dose of risdiplam.
- Recommend to stop the trial.
- Recommend to put enrollment on hold pending further safety evaluations.
- Recommend a protocol amendment.

Analyses required for the iDMC's safety data review will be performed as described in the iDMC Charter. Data displays will be prepared by the Sponsor.

The iDMC will continue to meet and review patient safety until 12 months after the last patient is enrolled in this study.

Interim analyses for efficacy will be performed by the Sponsor and the results presented to the iDMC. The iDMC will be requested to review all available safety data and be asked to provide an independent assessment of the benefit-risk profile of risdiplam in the

presymptomatic SMA population at this earlier time-point. The final decision based on the iDMC recommendation will be made by the Sponsor.

A Sponsor Clinical Pharmacologist (who is not a member of the iDMC) will regularly review the PK and PD data from the study in order to be able to adjust the dose of individual patients if required, ensuring not to exceed the mean exposure cap, and to continue treatment at the targeted exposure level, as patients grow and their body systems mature. The iDMC will be informed of any individual dose changes at the next scheduled iDMC meeting.

The roles, responsibilities, membership, scope of activities, time of meetings, and communication plan for the iDMC are documented in a separate charter. The external iDMC will be chaired by a medically qualified individual with experience in SMA and will include another physician experienced in neurology, a clinical pharmacologist, an ophthalmologic expert, and a biostatistician. No member of the iDMC will participate in the study as an investigator or sub-investigator.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all enrolled patients, regardless of whether they receive risdiplam or not. The ITT population will be used for all secondary and exploratory efficacy summaries.

4.1.2 Primary Efficacy Analysis Population

The primary efficacy analysis population is defined as all patients in the ITT population with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude $\geq$1.5mV. The primary efficacy analysis population will be the population for the primary efficacy analysis. All secondary and exploratory efficacy endpoints will also be analyzed for this population. Any hypothesis testing if performed will be limited to the primary efficacy analysis population.

4.1.3 Pharmacokinetic Analysis Population

All patients with at least one time-point with a measureable drug concentration will be included in the analysis data sets. Patients will only be excluded from the analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable, not plausible, or incomplete, that may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion.

4.1.4 Pharmacodynamic Analysis Population

All patients with at least one time-point with a measureable PD marker will be included in the analysis data sets. Patients will only be excluded from the analysis population if they

significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable, not plausible, or incomplete, that may influence the PD analysis. Excluded cases will be documented together with the reason for exclusion.

4.1.5 Safety Population

All patients who receive at least one dose of risdiplam will be included in the safety population.

4.2 ANALYSIS OF STUDY CONDUCT

4.2.1 Study Enrollment

The number of patients in each of the ITT, primary efficacy analysis and safety populations will be summarized, and the number of patients excluded from each of the populations will be summarized by reason for exclusion. Patients excluded from the analysis populations will also be listed.

The number of patients enrolled at each country and site will be summarized.

4.2.2 Protocol Deviations

The major protocol deviations will be identified according to the Procedures for Managing Protocol Deviations document. Major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. The number and percentage of patients with major protocol deviations will be summarized by protocol deviation category.

4.2.3 Patient Disposition

The number of patients who were enrolled, discontinued, continuing treatment at the time of the analysis or have completed the main study phase (i.e., completed the 24-month treatment period and the open-label extension phase) will be summarized. Reasons for premature study withdrawal will be listed and summarized. The number of patients entering the open-label extension will also be summarized. The number of patients discontinuing between 0 and 12 months, between 12 and 24 months, and during the open-label extension phase, and the reasons for discontinuation, will be summarized.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and other baseline characteristics will be summarized overall and by *SMN2* copy number (copy number 2, 3 or ≥4; patients with an “atypical 3-4” result will be included in the copy number ≥4 group) for the ITT population, and for the primary efficacy analysis population using descriptive statistics, means, standard deviations, medians, interquartile ranges (IQRs) and ranges for continuous variables and numbers and percentages for categorical variables, as appropriate. Any patients with the *SMN2* gene modifier mutation c.859G>C will be summarized separately.

Baseline will be defined as the last measurement recorded prior to the first study drug administration, unless specified otherwise. If an assessment is performed at both the screening visit and the baseline visit, the baseline assessment will be used, unless this is missing and the screening assessment is available.

General medical history and baseline conditions, and previous and concomitant medications and surgeries and procedures will be summarized for the safety population.

4.3.1 Demographics and Baseline Characteristics

Summary statistics will be presented for the following demographic and baseline characteristics: age at enrollment (in days), age at first dose (in days), sex, race, ethnicity, weight, body length/height, head circumference, chest circumference, and chest to head circumference ratio (head circumference will be the denominator of the ratio). The number and percentage of patients enrolled in each country and in each of the following geographical regions: Europe, North America, rest of world, will be presented. The rest of world category may be further subdivided depending on the final recruitment pattern.

Growth charts will be used to track a patient's growth over time and to monitor his or her growth in relation to a reference population of healthy children. A patient's percentile on the growth chart indicates the percentage of the reference population that his or her value equaled or surpassed for a given growth parameter. The standard deviation score (SDS or z-score) indicates to what extent the patient's value deviated from the median of the reference population. Because of the relationship between a patient's z-score and percentile on the growth chart, a standard normal distribution table can be used to obtain a patient's z-score from his or her growth chart percentile, and vice versa.

Baseline weight-for-age, length/height-for-age, weight-for-length/height, and head circumference-for-age percentiles will be summarized. The number and percentage of patients in the 3rd, 5th, 10th, 25th, 50th, 75th and >75th percentiles for weight-for-age, length/height-for-age, weight-for-length/height, and head circumference-for-age will also be presented. Percentiles will be based on World Health Organization (WHO) Child Growth Standards (2006 and 2007). z-scores will be calculated using the methods described in the WHO Child Growth Standards (2006 and 2007), with percentiles derived directly from the z-score and standard normal cumulative distribution function.

For the derivation of weight-for-age, length/height-for-age and head circumference-for-age percentiles, age (in days) will be calculated as date of assessment – date of birth.

4.3.2 SMA History and Disease Characteristics

Summary statistics will be presented for the following parameters: *SMN2* copy number, SMA identification method (newborn screening, family history, other), baseline CHOP-INTEND and HINE-2 scores, and baseline CMAP amplitude values (including the number and percentage of patients with values <1.5mV and ≥1.5mV).

4.3.3 General Medical History and Baseline Conditions

For all medical conditions, the term entered by the investigator describing the condition (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) and system organ class based on the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA). All analyses will be performed using these preferred terms and body systems.

The number and percentage of patients with previous conditions and conditions concurrent at screening will be summarized. Multiple occurrences of the same condition in an individual patient (i.e., same coded term) will be counted only once in the calculation of the event frequency. The overall number of patients with at least one condition and the total number of conditions will also be presented.

Previous conditions (conditions that resolved prior to screening) and conditions concurrent at screening will be summarized separately.

4.3.4 Previous and Concomitant Medications

For all medications, the term entered by the investigator describing the medication (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) and drug class based on the most up-to-date version of the World Health Organization Drug Dictionary (WHODrug Global B3 Format Dictionary). All analyses will be performed using these preferred names and medication classes.

The number and percentage of patients taking each medication will be presented. Multiple occurrences of the same medication in an individual patient (i.e., same coded term) will be counted only once. The overall number of patients taking at least one medication and the total number of medications will also be presented.

Previous medications (medications with an end date before the first dose date), medications present at baseline (medications that start prior to the first dose date and have no end date or an end date after the first dose date) and concomitant medications (medications with a start date on or after the first dose date) will be summarized separately.

Treatments given for an adverse event will be summarized separately.

4.3.5 Previous and Concomitant SMA Related Surgeries and Procedures

For all surgeries and procedures, the term entered by the investigator describing the event (the “verbatim term”) will be assigned to a standardized term (the “preferred term”) and system organ class based on the most up-to-date version of MedDRA. All analyses will be performed using these preferred terms and body systems.

The number and percentage of patients who had any relevant SMA related surgeries or procedures will be presented. Multiple occurrences of the same procedure in an individual patient (i.e., same coded term) will be counted only once. The overall number of patients who have undergone at least one procedure and the total number of procedures reported will also be presented.

SMA related surgeries or procedures performed prior to the first dose date and those performed on or after the first dose date will be summarized separately.

Surgeries and procedures that are not related to SMA will be summarized similarly.

4.4 EFFICACY ANALYSIS

The primary efficacy analysis population (patients with two *SMN2* copies [excluding the known *SMN2* gene modifier mutation c.859G>C] and a baseline CMAP amplitude ≥1.5mV) will be the primary population for efficacy analyses. Secondary and exploratory efficacy endpoints will be summarized for the primary efficacy analysis population and for the ITT population (overall and by *SMN2* copy number [copy number 2, 3 or ≥4; patients with an "atypical 3-4" result will be included in the copy number ≥4 group]). Any patients with the *SMN2* gene modifier mutation c.859G>C will be summarized separately. Hypothesis testing, if performed, will be limited to the primary efficacy analysis population.

For efficacy analyses, a time window will be created for each study visit according to the schedule for the specific assessment. The time window will start midway between the visit and the previous study visit where the assessment is due to be performed, and end midway between that visit and the next study visit where the assessment is due to be performed (if applicable). Post-baseline efficacy assessments, including assessments performed at an unscheduled visit or early withdrawal visit, will be assigned to the appropriate scheduled study visit based on these time windows. If multiple valid values for a variable are recorded in the same time window, the assessment performed closest to the scheduled study day of the visit will be used for summary of the data. If there are assessments equidistant from the scheduled study day, the latest assessment will be used.

4.4.1 Primary Efficacy Endpoint

All enrolled patients with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude ≥1.5mV will be included in the primary efficacy analysis. The primary endpoint of the study is the proportion of patients who are sitting without support after 12 months of treatment. Sitting is defined as "sits alone without support for at least 5 seconds" as assessed in item 22 of the BSID-III Gross Motor Scale. As per the scoring manual (Bayley 2006), item 22 will not be considered achieved if the patient sits alone for less than 5 seconds before losing balance and falling over, or if the patient uses his or her arms to prop him- or herself up in order to sit for 5 seconds. The assessment performed by the independent central

readers will be used for the primary analysis (as described in Section 3.2.1). Both central readers should classify the milestone as achieved for the endpoint to be confirmed. Patients who do not achieve sitting, have not maintained sitting achieved at an earlier time-point, or have been withdrawn, or died, will be classified as non-responders (i.e., non-sitters) for the primary analysis. Patients who are ongoing in the study and have a missing assessment at Month 12 will be excluded from the analysis.

The number and percentage of patients sitting after 12 months of treatment (i.e., at Month 12) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. An exact binomial test will be performed. The hypothesis to be tested is that the proportion of patients who sit on treatment (p) is:

$$H_0: p \leqslant 5\% \text{ (null) versus } H_a: p > 5\% \text{ (alternative).}$$

If the one-sided p-value is $\leq 5\%$ (type 1 error rate), then the null hypothesis will be rejected. If the lower limit of the two-sided 90% CI is above the 5% threshold, the primary objective of the study will be considered achieved.

The number and percentage of patients sitting at each time-point will also be presented, using the same responder/non-responder definition described above. A listing of individual responses, including the assessment of the site clinical evaluator and each assessment made by the independent central readers and whether or not they are concordant, will be produced.

4.4.2 Secondary Efficacy Endpoints

Analyses of the secondary efficacy endpoints will be performed using all data available at the time of the 12-month, 24-month and further analysis reporting events. All secondary endpoints will be summarized by time-point (except for the time to event endpoints) for the ITT population (overall and by *SMN2* copy number) and for the primary efficacy analysis population using descriptive statistics. The two-sided 90% confidence intervals will also be presented as appropriate.

The secondary efficacy endpoints in the study are as follows:

4.4.2.1 Development of Clinically Manifested SMA

The number and percentage of patients developing clinically manifested SMA at Month 12 and Month 24 of treatment will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion.

Patients will be considered to have developed clinically manifested SMA if at least one of the following criteria, (a) or (b), are met:

a) (i) When assessing this endpoint at Month 12: Failure to achieve sitting without support at Month 12 as assessed by both the HINE-2 (i.e., a score below 3

[corresponding to “Stable sit”] for the sitting milestone), and item 22 of the BSID-III Gross Motor Scale (i.e., a score of 0) using the assessment by the two independent central readers.

(ii) When assessing this endpoint at Month 24: Failure to achieve walking at Month 24 as assessed by both the HINE-2 (i.e., a score below 3 [corresponding to “Walking independently”] for the walking milestone), and item 42 of the BSID-III Gross Motor Scale (i.e., a score of 0) using the assessment by the two independent central readers.

a) Age-adjusted weight of ≤3rd percentile at Month 12 or Month 24 or decrease of ≥2 major percentile lines (3rd, 10th, 25th, 50th, 75th, 90th, and 97th) compared with baseline at Month 12 or Month 24, in combination with tongue fasciculation or feeding/swallowing abnormalities (as assessed in the SMA Neurological Examination); or a gastric tube placement for nutritional support in the absence of a non-SMA related indication (as recorded on the SMA related surgeries and procedures electronic Case Report Form [eCRF]) at Month 12 or Month 24. Gastric tube placement will include all procedures with a MedDRA preferred term of “gastrostomy,” “gastrointestinal tube insertion,” “jejunostomy,” or “feeding tube user,” or a MedDRA lowest level term of “gastrojejunostomy.” Gastric tube removal will include all procedures with a MedDRA preferred term of “gastrostomy tube removal,” “gastrointestinal tube removal” or “jejunostomy closure.”

Patients who have died prior to Month 12 or Month 24 will be counted as having developed clinically manifested SMA. Patients who have been withdrawn from treatment for any other reason prior to Month 12 or Month 24 will be counted as having developed clinically manifested SMA if the reason for withdrawal is determined to be related to the study drug (safety, tolerability or lack of efficacy) or underlying disease progression.

If a patient withdraws from treatment, the reason for withdrawal will be classified as “related to study drug or disease progression” or “not related to study drug or disease progression” based on the information provided in the study drug completion/early discontinuation eCRF. If the category of reason for withdrawal is vague (e.g., physician decision, withdrawal by subject, other), the site will be required to provide further details in the eCRF free-text field in order to allow an appropriate classification. The study team will review the reasons for withdrawal (including free-text fields) on an ongoing basis, and queries may be raised to the site to obtain additional information as needed. In case of ambiguity in assigning the reason for withdrawal, a conservative approach will be taken and the reason will be classified as “related to study drug or disease progression.” The classification of all reasons for withdrawal will be made and documented prior to the analysis of any efficacy data.

A withdrawal will be classified as “related to study drug or disease progression” if one of the following reasons is reported in the eCRF: adverse event, death, lack of efficacy, progressive disease, disease relapse or symptomatic deterioration.

If one of the following reasons is reported: lost to follow-up, protocol deviation, non-compliance with study drug, withdrawal by subject, physician decision or other, there will be a manual review of the eCRF free-text fields to determine if the reason for withdrawal is "related to study drug or disease progression" or not. If a patient withdraws from treatment to start an alternative medication intended for the treatment of SMA, this will be classified as "related to study drug or disease progression." Withdrawal from treatment due to Coronavirus Disease 2019 (COVID-19), family relocation or to receive commercial risdiplam (Evrysdi) will be classified as "not related to study drug or disease progression."

If the reason for withdrawal is classified as "not related to study drug or disease progression," the patient will be excluded from the analysis. Patients will also be excluded from the analysis if the reason for withdrawal is study terminated by Sponsor.

Patients who are ongoing in the study and have a missing motor milestone assessment, and a missing weight and/or SMA Neurological Examination at Month 12 or Month 24 will be excluded from the analysis.

If a partial date is provided for the placement of a gastric tube, the day will be replaced with the first day of the month (assuming the month and year are known). If a partial date is provided for the removal of a gastric tube, the day will be replaced with the last day of the month (assuming the month and year are known).

4.4.2.2 SMA Neurological Examination

The number and percentage of patients with abnormal findings in the SMA Neurological Examination at each time-point will be presented overall and by type of finding. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

4.4.2.3 Survival and Ventilation-Free Survival

4.4.2.3.1 Ventilation-Free Survival

Time to death or permanent ventilation will be presented graphically using Kaplan-Meier curves. Permanent ventilation is defined as:

- ≥16 hours of non-invasive ventilation (e.g., bilevel positive airway pressure [BiPAP]) per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event; or
- tracheostomy.

An acute reversible event will include any of the following events that occur between 7 days prior and 7 days after the onset of ≥16 hours of non-invasive ventilation per day or intubation:

- Fever

- Laboratory diagnosis of a viral, bacterial or fungus infection either by direct examination of a sample (e.g., sputum, tissue etc.), culture, serology or polymerase chain reaction (PCR)
- Leukocytosis
- Imaging studies demonstrating an active infection
- Surgical procedure

The patient will be given a grace period of 7 days after the event to recover and begin extubation or weaning off ventilation support before the endpoint can be confirmed, i.e., the endpoint will not be met until the patient requires ≥16 hours of non-invasive ventilation per day or intubation for >21 consecutive days starting 7 days after the resolution of the acute reversible event.

The occurrence of a permanent ventilation event and the date of the event will be determined by the independent permanent ventilation adjudication committee, and will be recorded on the permanent ventilation eCRF. Non-invasive ventilation use during the study will be collected via a patient diary.

The median time to death or permanent ventilation (and 90% CI) and the proportion of patients who are alive without permanent ventilation at Month 12 and Month 24 of treatment will be estimated using Kaplan-Meier methodology, when possible. Ninety percent CIs for the proportion of patients surviving without permanent ventilation at Month 12 and Month 24 will be presented. CIs will be calculated using the complementary log-log transformation for the estimated survivor function $\hat{S}(t)$, with standard errors computed via Greenwood's formula.

Time to death or permanent ventilation is defined as the time in months from the date of enrollment into the study until the date of death from any cause or date of permanent ventilation, whichever event occurs first. The date of permanent ventilation will be the first of the >21 days of non-invasive ventilation support or intubation required for the endpoint to be confirmed, or the date of tracheostomy. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff at which they were known to be alive and without permanent ventilation. Individual listings will also be provided for the time to death or permanent ventilation (and the individual components).

Note: the date of enrollment occurs at least one day before the first study drug administration.

A partial event date will be replaced by the first day of the month (assuming the month and year are known), unless there is evidence that the patient was event-free within that month, in which case the date the patient was last known to be event-free within that month (plus one day) will be used as the event date. If the month is missing, the date the patient was last known to be event-free (plus one day) will be used.

Patients who have been withdrawn from treatment with no event reported prior to withdrawal will be censored at the date of withdrawal. The patient diary will not be available to provide information about the use of non-invasive ventilation once a patient has been withdrawn from treatment and is no longer receiving study drug. If a patient has reached ≥16 hours of non-invasive ventilation support per day or has been intubated continuously within the last 21 days prior to withdrawal, he or she will be followed by telephone contact in order to confirm the outcome of the endpoint.

4.4.2.3.2 Survival

Time to death will be presented graphically using Kaplan-Meier curves. The median time to death (and 90% CI) and the proportion of patients who are alive at Month 12 and Month 24 of treatment will be estimated using Kaplan-Meier methodology, when possible. Ninety percent CIs for the proportion of patients alive at Month 12 and Month 24 will be presented. Time to death is defined as the time in months from the date of enrollment until the date of death from any cause. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff at which they were known to be alive. Patients who have been withdrawn from treatment with no event reported prior to withdrawal will be censored at the date of withdrawal.

4.4.2.3.3 Permanent Ventilation

Time to permanent ventilation will be presented graphically using Kaplan-Meier curves. The median time to permanent ventilation (and 90% CI) and the proportion of patients who are without permanent ventilation at Month 12 and Month 24 of treatment will be estimated using Kaplan-Meier methodology, when possible. Ninety percent CIs for the proportion of patients who are without permanent ventilation at Month 12 and Month 24 will be presented. Time to permanent ventilation is defined as the time in months from the date of enrollment into the study until the date of permanent ventilation. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff at which they were known to be without permanent ventilation. Patients who have been withdrawn from treatment with no event reported prior to withdrawal will be censored at the date of withdrawal.

4.4.2.4 Motor Function and Development Milestones

4.4.2.4.1 HINE-2

The HINE-2 evaluates 8 developmental milestones scored on a 3, 4, or 5-point scale, with 0 indicating inability to perform a task and a score of 2, 3, or 4 (depending on the task) indicating full milestone achievement. Milestones include head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. The total score is calculated by summing the item scores to give a maximum possible score of 26.

The HINE-2 is designed to assess patients up to 2 years of age. Therefore, from the Month 24 visit, this assessment will be stopped for each patient once the maximum

score is achieved at two consecutive visits. The final HINE-2 evaluation for each patient will be at Month 24 at the earliest.

The number and percentage of patients within each attainment response category of the HINE-2 motor milestones at Month 12 and Month 24 of treatment (and all other time-points) will be presented. "Cannot test (CNT)" will be included as a separate response category for each milestone. The number and percentage of patients who had been withdrawn or died by that visit will also be presented. Patients who are ongoing in the study and have a missing assessment at a visit or are no longer performing the HINE-2 assessment after achieving the maximum score at two consecutive visits will be excluded from the analysis.

The HINE-2 total score and change from baseline score at each time-point will also be summarized using descriptive statistics. If an individual item is missing or "Cannot Test (CNT)" is recorded, the item score will be set to 0. No imputation for missing HINE-2 assessments will be performed. In addition, the mean total scores and corresponding 90% CIs over time will be presented graphically (by *SMN2* copy number).

4.4.2.4.2 BSID-III Gross Motor Scale

The BSID-III assesses the developmental progress of infants and young children, and is primarily used to identify children with developmental delays and to evaluate the impact of intervention efforts. The BSID-III consists of a core battery of five scales: three scales are administered with child interaction, the Cognitive Scale, the Language Scale (Receptive Communication and Expressive Communication), and the Motor Scale (Fine Motor and Gross Motor); two additional scales (Social-Emotional and Adaptive Behavior) are conducted with parent/caregiver questionnaires (Bayley 2006).

Patients in this study will be administered the Cognitive and Motor (Fine Motor and Gross Motor) scales. The BSID-III is designed to evaluate young children up to 42 months of age, so these assessments will be stopped after the Month 42 visit for all patients. The sitting, standing, walking series (consisting of seven items assessed in the BSID-III Gross Motor Scale) will also be stopped after the Month 42 visit.

The BSID-III Gross Motor Scale is used to assess the attainment of motor milestones including static positioning (e.g., head control, sitting), dynamic movement including locomotion and co-ordination (e.g., crawling), quality of movement (e.g., kicking), balance and motor planning (Bayley 2006).

Motor Milestones: Sitting, Standing, Walking Series

The number and percentage of patients sitting without support for 30 seconds (defined as "Sits without support for 30 seconds" as assessed in item 26 of the BSID-III Gross Motor Scale) at Month 12, and the number and percentage of patients (1) sitting without support for 5 seconds (defined as per the primary endpoint), (2) sitting without support

for 30 seconds (defined as “Sits without support for 30 seconds” as assessed in item 26 of the BSID-III Gross Motor Scale), (3) standing (defined as “Stands alone” as assessed in item 40 of the BSID-III Gross Motor Scale), and (4) walking (defined as “Walks alone” as assessed in item 42 of the BSID-III Gross Motor Scale) at Month 24 (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Patients who do not achieve the milestone, have not maintained the milestone achieved at an earlier time-point, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients who are ongoing in the study and have a missing assessment at a visit will be excluded from the analysis.

For the primary efficacy analysis population only, the proportion of patients who at 12 months of treatment are sitting without support for 30 seconds and the proportion of patients who at 24 months of treatment are (1) sitting without support for 5 seconds, (2) sitting without support for 30 seconds, (3) standing, and (4) walking will be analyzed as for the primary endpoint (using the same performance criterion of 5%; Section 4.4.1) testing the null hypothesis that the proportion of patients who achieve the motor milestone (p) is ≤5% (null) versus p>5% (alternative). If the one-sided p-value is ≤5%, then the null hypothesis will be rejected.

The number and percentage of patients with two *SMN2* copies (independent of the CMAP amplitude at baseline) sitting without support for 5 seconds at Month 12 of treatment (and all other time-points) will also be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Patients who do not achieve sitting, have not maintained sitting achieved at an earlier time-point, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients who are ongoing in the study and have a missing assessment at a visit will be excluded from the analysis.

The age at which patients first achieve these motor milestones (items 22, 26, 40 and 42 of the BSID-III Gross Motor Scale) will be summarized using descriptive statistics and compared graphically to the windows of achievement among healthy children described in the WHO Multicentre Growth Reference Study (2006) for the milestones of sitting without support, standing alone and walking alone (1st to 99th percentiles).

In addition, the number and percentage of patients achieving the other motor milestones assessed in the sitting, standing, walking series (items 16 [“Sits with support briefly”], 19 [“Sits with support for 30 seconds”] and item 27 [“Sits without support and holds object”]) at each time-point will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Patients who do not achieve the milestone, have not maintained the milestone achieved at an earlier time-point, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients who are ongoing in the study and have a missing assessment at a visit will be excluded from the analysis.

The assessment performed by the independent central readers will be used for the analysis of these motor milestones (as described in Section 3.2.1). Both central readers should classify the milestone as achieved for the endpoint to be confirmed.

Summary Scores

The BSID-III Gross Motor Scale (and all other subscales) will be administered as described in the BSID-III manual (Bayley 2006). The patient's age in months and days determines the start point for administration. Reversal and discontinue rules are utilized to ensure that the most appropriate items are administered to the patient. The patient must receive a score of 1 on the first three consecutive items at his or her age-specific start point to go forward (i.e., achieve the basal). If the patient obtains a score of 0 on any of the first three items, administration should go back to the start point for the previous age with those items administered in a forward direction. The reversal rule also applies to this new start point. Items are administered in a forward direction until the discontinue criterion is met, which establishes when testing is complete. Administration is stopped when the patient has received a score of 0 for five consecutive items (i.e., the ceiling has been achieved). Credit (i.e., a score of 1) is given for all items preceding the basal that are not administered.

The BSID-III Gross Motor Scale consists of 72 items scored as 0 (criteria for item not achieved) or 1 (criteria for item achieved). The total raw score is calculated by adding the total number of items for which the patient receives a score of 1 and the number of items preceding the basal to give a maximum possible score of 72.

Scaled scores are derived from the total raw scores (based on the age of the patient; age will be calculated as described in the scoring manual) and range from 1-19, with a mean of 10 and standard deviation of 3.

The total raw score and scaled score of the BSID-III Gross Motor Scale and change from baseline scores at Month 12, Month 24 and Month 42 of treatment (and all other time-points) will be summarized using descriptive statistics. Item scores will be based on the assessment of the site clinical evaluator. For the calculation of the total raw score, if an individual item that is expected to be scored is missing, the item score will be set to 0. Any item scores provided after the discontinuation rule has been met (i.e., the discontinuation rule was not applied correctly) will also be set to 0. If a score is provided in error for an item below the basal, the item score will be set to 1. Assessments where the reversal rule was not applied correctly will be excluded from the analysis. No imputation for missing assessments will be performed.

The total raw score and scaled score of the BSID-III Gross Motor Scale will also be presented graphically using individual patient plots (versus age at the time of the assessment) and mean plots with corresponding 90% CIs (by *SMN2* copy number).

The number and percentage of patients with a scaled score within 1.5 standard deviations of the chronological reference standard (i.e., with a scaled score ≥5.5) at Month 24 and Month 42 of treatment (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

4.4.2.4.3 CHOP-INTEND

The CHOP-INTEND is a measure of motor function that consists of 16 items scored from 0 to 4, with a higher score indicating better motor skills. For items where both the left and right sides are scored, the maximum score is selected for the final item score. The total score is calculated by summing the item scores to give a maximum possible score of 64.

The CHOP-INTEND is designed to evaluate patients up to 2 years of age, so this assessment will be stopped for all patients after the Month 24 visit. However, after the Month 12 visit, the CHOP-INTEND can be discontinued prior to Month 24 if the patient has demonstrated the ability to sit without support (based on item 22 of the BSID-III Gross Motor Scale, as assessed by the site clinical evaluator during the sitting, standing, walking series or the full BSID-III Gross Motor Scale assessment) at two consecutive visits and has achieved a CHOP-INTEND total score ≥60 at the same two consecutive visits at any time up to Month 24.

The CHOP-INTEND total score and change from baseline score at Month 12 of treatment (and all other time-points) will be summarized using descriptive statistics. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed. CHOP-INTEND scores will also be presented graphically using individual patient plots for the total score (versus age at the time of the assessment), mean plots with corresponding 90% CIs for the total score and change from baseline score (by *SMN2* copy number), and waterfall plots for the change from baseline score at Month 12 and Month 24.

The number and percentage of patients who achieve a total score of 40 or higher, 50 or higher, or 60 or higher in the CHOP-INTEND at Month 12 of treatment (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

The number and percentage of patients who meet the stopping criteria for the CHOP-INTEND (as defined above) at any time up to Month 24 will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Patients who do not meet the stopping criteria for the CHOP-INTEND, or have been withdrawn, or died, will be classified as non-responders for the analysis.

Handling of Missing Data

If an item of the CHOP-INTEND is missing at any visit, or if "CNT" is recorded for an item, the item score will be imputed as follows:

- If an item is missing or "CNT" is recorded at baseline, the item score will be imputed as the median of the non-missing values in the stratum to which the patient belongs. Patients will be classified into the following strata, based on the *SMN2* copy number, for the purpose of identifying non-missing data for imputation:
    - *SMN2* copy number 2 and baseline CMAP amplitude <1.5mV
    - *SMN2* copy number 2 and baseline CMAP amplitude ≥1.5mV
    - *SMN2* copy number ≥3

  If there is no data available in that stratum at baseline (i.e., no scores have been recorded), the item score will be imputed as the median of the non-missing values in the other strata.
- If an item is missing or "CNT" is recorded at a post-baseline visit, and this visit is flanked by visits where the item score is available, the item score will be imputed using linear interpolation with the result rounded to the nearest integer score.

  If an item is missing or "CNT" is recorded at a post-baseline visit, and the visit is not flanked by visits where the item score is available (i.e., this is the patient's last assessment, or the item is missing or "CNT" is recorded either at the previous or subsequent visit), the item score will be imputed as the minimum of the non-missing values in the stratum to which the patient belongs. If there is no data available in that stratum at that visit, the item score will be set to 0.

  These rules will not be applied for patients who have died or been withdrawn from treatment before the visit, unless the patient has an assessment that falls in the corresponding visit window.

This imputation will be applied for all CHOP-INTEND analyses.

4.4.2.4.4 HFMSE

The HFMSE was developed to assess the motor function ability of individuals aged 2 years or older, thus the first assessment time-point in this study will be the Month 24 visit. This will be considered the baseline assessment for all patients.

The HFMSE consists of 33 items scored on a 3-point scale (0-2), with a higher score indicating better motor function. The total score is calculated by summing the item scores to give a maximum possible score of 66.

The HFMSE total score and change from baseline (Month 24) score at Month 60 of treatment (and all other time-points) will be summarized using descriptive statistics.

If 6 items or fewer are missing, the missing items will be imputed to 0 (unable to perform the task) prior to the calculation of the total score. If more than 6 items are missing, the total score will not be calculated and will be considered as missing. No imputation for missing assessments will be performed.

HFMSE scores will also be presented graphically using individual patient plots for the total score (versus age at the time of the assessment) and mean plots with corresponding 90% CIs for the total score and change from baseline score (by *SMN2* copy number).

4.4.2.5 Growth Measures

Anthropometric measurements in this study will include weight, length/height, head circumference and chest circumference (head circumference and chest circumference will only be measured until the Month 24 visit).

If length/height cannot be measured directly (e.g., if the patient is unable to stand but he or she is too long to be assessed using a fixed board) ulnar length will be used to calculate a surrogate height measure. Height will be derived from the measurement of ulnar length using the following formulae (for patients aged 2-18 years old; Gauld et al. 2004):

Female: height (cm) = 4.459 * ulnar length (cm) + 1.315 * age (years) + 31.485

Male: height (cm) = 4.605 * ulnar length (cm) + 1.308 * age (years) + 28.003

The number and percentage of patients within the 3rd percentile (i.e., ≤3rd percentile) for weight-for-age, length/height-for-age and weight-for-length/height at Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment (and all other time-points), based on the WHO Child Growth Standards, will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. The number and percentage of patients within the 3rd percentile for head circumference-for-age at Month 12 and Month 24 (and all other time-points up to Month 24), based on the WHO Child Growth Standards, will also be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

The weight-for-age, length/height-for-age and weight-for-length/height percentiles, and change from baseline percentiles at Month 12, Month 24, Month 36, Month 48, and Month 60 of treatment (and all other time-points) will be summarized using descriptive statistics. The head circumference-for-age percentiles, and change from baseline percentiles at Month 12 and Month 24 (and all other time-points up to Month 24) will also be summarized. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

In addition, actual values and change from baseline values for weight and length/height will be summarized at each time-point. The chest and head circumference and change from baseline values at Month 12 and Month 24 (and all other time-points up to Month 24) will be summarized. The chest to head circumference ratio and change from baseline ratio at each time-point will also be summarized. The head circumference will

be the denominator of the ratio. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

The number and percentage of patients in the 3rd, 5th, 10th, 25th, 50th, 75th, and >75th percentiles of the WHO growth charts will be presented for weight-for-age, length/height-for-age, weight-for-length/height and head-circumference-for-age. Shift tables for each parameter to compare the patient's percentile at baseline (≤3rd, >3rd-≤5th, >5th-≤10th, >10th-≤25th, >25th-≤50th, >50th-≤75th and >75th) to each time-point post-baseline will be presented.

Individual growth charts will be presented for each patient in the ITT population. One chart will present the weight of the patient over time, with reference lines for the 3rd, 10th, 25th, 50th, 75th, 90th, and 97th percentiles for weight-for-age from the WHO growth charts displayed. The following parameters will also be presented: age ability to swallow is lost or regained and age at time of feeding tube (gastrostomy, nasogastric tube or jejunostomy tube) placement. This will include all procedures with a MedDRA preferred term of "gastrostomy," "gastrointestinal tube insertion," "jejunostomy," or "feeding tube user," or a MedDRA lowest level term of "gastrojejunostomy." A second chart will display the length/height of the patient over time with reference lines for length/height-for-age. Both charts will also present the age at first dose, age at time of permanent ventilation, age at treatment/study discontinuation and age at death, as applicable.

Individual patient weight and length/height values over time will also be presented grouped by sex with corresponding reference lines for the 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentiles from the WHO growth charts displayed.

Mean percentiles for weight-for-age and length/height-for-age and corresponding 90% CIs will be plotted over time.

4.4.2.6 Nutrition

The number and percentage of patients with the ability to feed orally ("oral" or "combination of oral and tube feeding") at Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

The number and percentage of patients fed exclusively orally, via a feeding tube, or via a combination of oral and tube feeding at each time-point will be presented. Percentages will be calculated based on the number of patients with a valid assessment at each time-point. For patients fed via a combination of oral and tube feeding, the percentage of feedings delivered through the tube will be summarized at each time-point. The number and percentage of patients with the ability to feed themselves will also be presented.

The number and percentage of patients with the ability to swallow at Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Percentages will be calculated based on the number of patients with a valid assessment at each time-point. A shift table comparing the status of each patient at baseline (able to swallow, unable to swallow, missing) to each time-point post baseline (able to swallow, unable to swallow, missing [including withdrawals and deaths]) will also be presented.

In addition, the number and percentage of patients who have lost or regained the ability to swallow (if applicable) will be presented, and the age the ability to swallow is lost or regained will be summarized.

A partial date for loss of swallowing will be replaced by the first day of the month (assuming the month and year are known), unless there is evidence of an assessment where the patient was able to swallow within that month, in which case the date of the last assessment within that month (plus one day) will be used. If the month is missing, the date the patient was last known to be able to swallow (plus one day) will be used.

The number and percentage of patients who can swallow water, nectar (or similar), rice pudding (or similar), purées, and solid food, and the primary food intake type at each time-point will be presented.

In each summary table, percentages will be calculated based on the number of patients with a valid assessment at each time-point.

4.4.2.7 Muscle Electrophysiology

The CMAP negative peak amplitude (and area) and change from baseline values at Month 12 and Month 24 of treatment (and all other time-points) will be summarized using descriptive statistics. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed. The CMAP negative peak amplitude will also be presented graphically using individual patient plots for the actual value (versus age at the time of the assessment) and mean plots with corresponding 90% CIs for the actual values and change from baseline values (by *SMN2* copy number).

4.4.2.8 Respiratory

4.4.2.8.1 Level of Respiratory Support

The number and percentage of patients who do not receive any pulmonary care (invasive or non-invasive) at Month 12 and Month 24 of treatment (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

The number and percentage of patients who require cough assistance (used daily for therapy or with an illness) or BiPAP support (<16 hours per day or ≥16 hours per day) and who have ventilation provided prophylactically (including type of ventilation, if applicable) at each time-point will also be presented. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

4.4.2.8.2 Respiratory Plethysmography

Respiratory plethysmography has been removed from the Schedule of Activities as of protocol version 3. Respiratory plethysmography results (including phase angle, rib cage contribution to inspiratory volume, respiratory rate, respiratory time total, peak expiratory flow ratio and labored breathing index) will be listed for all patients with an available assessment. Each variable will be calculated as the mean of all valid breaths observed within a 10-minute time window (as determined by Vivonoetics). The mean will only be calculated if there are a minimum of 8 valid breaths, otherwise the variable will be considered missing. No imputation for missing assessments will be performed.

4.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints in the study are as follows:

4.4.3.1 BSID-III Fine Motor Scale

The BSID-III Fine Motor Scale is used to assess young children's fine motor skills including visual tracking, reaching, object manipulation and grasping (Bayley 2006). It consists of 66 items scored as 0 (criteria for item not achieved) or 1 (criteria for item achieved). The total raw score is calculated by adding the total number of items for which the patient receives a score of 1 and the number of items preceding the basal to give a maximum possible score of 66.

The total raw score and scaled score of the BSID-III Fine Motor Scale and change from baseline scores at Month 12, Month 24 and Month 42 of treatment (and all other time-points) will be summarized using descriptive statistics. For the calculation of the total raw score, if an individual item that is expected to be scored is missing, the item score will be set to 0. Any item scores provided after the discontinuation rule has been met (i.e., the discontinuation rule was not applied correctly) will also be set to 0. If a score is provided in error for an item below the basal, the item score will be set to 1. Assessments where the reversal rule was not applied correctly will be excluded from the analysis. No imputation for missing assessments will be performed.

The number and percentage of patients with a scaled score within 1.5 standard deviations of the chronological reference standard (i.e., with a scaled score ≥5.5) at Month 24 and Month 42 of treatment (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

4.4.3.2 BSID-III Cognitive Scale

The BSID-III Cognitive Scale assesses sensorimotor development, exploration and manipulation, object relatedness, concept formation and other aspects of cognitive processing, and includes items such as attention to familiar and unfamiliar objects, looking for a fallen object and pretend play (Bayley 2006). It consists of 91 items scored as 0 (criteria for item not achieved) or 1 (criteria for item achieved). The total raw score is calculated by adding the total number of items for which the patient receives a score of 1 and the number of items preceding the basal to give a maximum possible score of 91.

The total raw score and scaled score of the BSID-III Cognitive Scale and change from baseline scores at Month 12, Month 24 and Month 42 of treatment (and all other time-points) will be summarized using descriptive statistics. For the calculation of the total raw score, if an individual item that is expected to be scored is missing, the item score will be set to 0. Any item scores provided after the discontinuation rule has been met (i.e., the discontinuation rule was not applied correctly) will also be set to 0. If a score is provided in error for an item below the basal, the item score will be set to 1. Assessments where the reversal rule was not applied correctly will be excluded from the analysis. No imputation for missing assessments will be performed.

The number and percentage of patients with a scaled score within 1.5 standard deviations of the chronological reference standard (i.e., with a scaled score ≥5.5) at Month 24 and Month 42 of treatment (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

4.4.3.3 6-Minute Walk Test

The 6MWT measures the maximum distance that a person can walk in 6 minutes over a 25-meter linear course. The total distance walked is recorded as well as the distance walked in each minute. The first assessment time-point in this study will be Month 42 for patients who are able to walk unassisted for at least 10 meters (i.e., without braces, crutches or calipers, or person [e.g., hand-held] assistance). This will be considered the baseline assessment for all patients.

The total walk distance and the distance walked in each minute at Month 60 of treatment (and all other time-points) will be summarized using descriptive statistics for ambulant patients only. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

The total distance walked at Month 60 may also be compared to a population of healthy children, with the percent predicted value at this time-point summarized using descriptive statistics.

4.4.3.4 WHO Motor Milestones

The WHO motor milestones evaluate gross motor development based on 6 motor milestones: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone and walking alone. The first assessment time-point in this study will be Month 48.

The number and percentage of patients who achieve these motor milestones as assessed by the WHO criteria at Month 48 and Month 60 of treatment (and all other time-points) will be presented with corresponding 90% Clopper-Pearson (exact) CIs. Patients who do not achieve the milestone, have not maintained this milestone achieved at an earlier time-point, or have been withdrawn, or died, will be classified as non-responders for the analysis. Patients who are ongoing in the study and have a missing assessment at a visit will be excluded from the analysis.

4.4.3.5 Speech Development

The number and percentage of patients with abnormal findings in speech development, as assessed in the SMA Neurological Examination, at Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Percentages will be calculated based on the number of patients with a valid assessment at each time-point.

4.4.3.6 Parent/Caregiver Reported Outcomes

4.4.3.6.1 ITQOL-SF47

The ITQOL-SF47 contains three single-item scores (Overall Health, Change in Health, and Family Cohesion) and eight multi-item domains (Physical Abilities [6 items], Growth and Development [5], Bodily Pain/Discomfort [2], Temperament and Moods [6], Behavior [12], General Health Perceptions [5], Parent Impact-Emotional Health [4] and Parent Impact-Time Limitations [4]). Items are scored using a Likert-type scale with five response options (except Parent Impact-Time Limitations which has 4 response options). Where applicable, item scores are reversed so that higher scores indicate better health.

For each domain, items are summed and transformed to a 0 (worst health) to 100 (best health) scale as defined in the scoring manual. Raw scores are calculated by computing the algebraic mean of the items completed. Scores are imputed for those individuals with missing items, provided that the respondents answered at least half of the items in the scale. This is done by using a denominator for each respondent based on the number of items in the scale that were completed. As per the ITQOL-SF47 scoring manual, domain scores will not be calculated if more than half of the items within a domain are missing. The transformed score is calculated as:

> Transformed raw score = [(actual raw score – lowest possible raw score) / possible raw score range] * 100

The “actual raw score” is the mean of the item responses in a domain (sum of item responses / number of completed items). The “possible raw score range” is the highest possible raw score minus the lowest possible raw score.

The total score and change from baseline score in the ITQOL-SF47 domains and single item scores at Month 12 and Month 24 of treatment (and all other time-points) will be summarized. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

Behavior Scales and Change in Health items are not appropriate for patients younger than 12 months of age, so should not be assessed at the baseline visit (the maximum age at first dose in this study is 42 days). Only summary scores will be presented for these domains at Month 12 and Month 24 of treatment (and all other time-points); any scores provided for patients younger than 12 months of age at the time of the assessment will be excluded from the analysis.

In addition, the Change in Health score at Month 12 and Month 24, and the change from baseline score in the Overall Health domain at Month 12 and Month 24 will be presented graphically using waterfall plots.

4.4.3.6.2 Parent/Caregiver Reported Motor Milestones

The number and percentage of patients who experience any significant life events (loss or achievement of the following motor milestones: kicked legs upward vertically, head control in ventral suspension, head control whilst carried upright, rolled from side to back, rolled from back to side, rolled completely, sat supported, sat unsupported, crawled combat style, crawled 4 point, stood with support, stood without support, walked with support, walked without support) by Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment will be presented. This will be based on the report from the parent/caregiver. The number and percentage of patients who were withdrawn from treatment and the number and percentage of patients who had died by Month 12, Month 24, Month 36, Month 48 and Month 60 will also be presented.

In addition, patients’ age at the attainment of a new motor milestone (or at the loss of a motor milestone gained during or before the study) will be summarized.

If a partial date is provided for the attainment of a motor milestone, the day will be replaced with the last day of the month (assuming the month and year are known). If a partial date is provided for the loss of a motor milestone, the day will be replaced with the first day of the month (assuming the month and year are known).

4.4.3.7 Healthcare Utilization

The number of hospitalizations (for any reason; except if for study purpose only [e.g., to facilitate study assessments]) per patient-year and corresponding exact 90% CIs, and the total number of hospitalizations at Month 12, Month 24, Month 36, Month 48 and

Month 60 of treatment will be presented. The number of nights admitted to hospital per patient at these time-points will also be summarized. The number of hospitalizations per patient-year is computed as:

> Number of hospitalizations per patient-year = number of hospitalizations observed by Month 12 (or 24, 36, 48, 60) / total patient-years at risk

and

> Total patient-years at risk = sum across all patients of the time intervals (in years) between start of study therapy and the earliest date of {treatment withdrawal or completion of 12 (or 24, 36, 48, 60) months of treatment}

The number and percentage of patients with no hospitalizations by Month 12, Month 24, Month 36, Month 48 and Month 60 of treatment and corresponding 90% Clopper-Pearson (exact) CIs will also be presented.

Hospitalizations will include all hospital admissions which span at least two days, and which are not due to study requirements.

4.4.3.8 Disease-Related Adverse Events

Disease-related adverse events (AEs) will be collected through the AE reporting of the study and events will be identified by applying prospectively defined baskets of MedDRA lowest level and preferred terms to the AE dataset:

- Narrow, prospectively defined baskets of MedDRA lowest level terms suggestive of SMA-related AEs defined based on a group of Centers for Disease Control and Prevention (CDC) terms selected from an age- and gender-matched case control study comparing CDC code rates observed in patients with and without SMA using commercially available insurance claim data (CLAIMS and MarketScan data). These selected ICD9 codes were then manually linked to the corresponding MedDRA lowest level terms and grouped by medical concepts in different baskets, using the latest version of MedDRA.
- Broad, prospectively defined baskets with events suggestive of SMA-related events selected at the MedDRA preferred term level from all AEs reported in ongoing risdiplam clinical trials up to January 2019 (i.e., prior to unblinding of Part 2 of Study BP39055 [SUNFISH]).

A basket of terms has been defined for each of the following medical concepts: gastro-intestinal disorders, lower respiratory tract infections, respiratory impairment, neuro-musculo-skeletal and connective tissues, nutrition and growth, cardiac not elsewhere classified (NEC), and other NEC. These baskets will be updated twice a year due to MedDRA version upgrades.

Note: the same term may be applicable to more than one medical concept and will therefore be included in more than one basket.

The number and percentage of patients who experience at least one disease-related AE by Month 12 and Month 24 of treatment and corresponding 90% Clopper-Pearson (exact) CIs will be presented overall and by medical concept. The total number of disease-related AEs will also be presented overall and by medical concept. A listing of all terms searched will be produced.

For each AE recorded, the term entered by the investigator describing the event (the "verbatim term") will be assigned to a standardized term, the "lowest level term," which will be mapped to a second higher level of standardized term, the "preferred term," based on the most up-to-date version of MedDRA. Data displays of disease-related AEs for each medical concept will be performed using the lowest level terms for the narrow baskets and the preferred terms for the broad baskets. For summaries of AE incidences, patients who experienced the same event on more than one occasion will be counted once in the calculation of the event frequency at the highest intensity reported.

The number of disease-related AEs per patient-year at Month 12 and Month 24 of treatment and corresponding exact 90% CIs will also be presented overall and by medical concept, where

> Number of disease-related AEs per patient-year = number of events observed by Month 12 (or 24) / total patient-years at risk

and

> Total patient-years at risk = sum across all patients of the time intervals (in years) between start of study therapy and the earliest date of {treatment withdrawal or completion of 12 (or 24) months of treatment}

4.4.4 Sensitivity Analyses

4.4.4.1 Site Evaluation of Sitting without Support for 5 Seconds

For the primary efficacy endpoint of the proportion of patients sitting without support for 5 seconds at Month 12 of treatment, the analyses described in Section 4.4.1 will be performed using the assessment of the site clinical evaluator instead of the assessment of the two independent central readers.

4.4.4.2 Alternative Definition of Sitting without Support

Sensitivity analyses will be performed using an alternative definition of sitting without support.

The proportion of patients sitting without support at Month 12 of treatment will be analyzed as described in Section 4.4.1 with sitting defined by the HINE-2 categories of "Stable sit" or "Pivots (rotates)." Patients within either of these response categories for the milestone of sitting at Month 12 will be classified as responders.

4.4.5 Subgroup Analyses

Subgroup analyses will be performed for patients with two *SMN2* copies for the following endpoints:

- Proportion of patients sitting without support for 5 seconds at Month 12 and Month 24 of treatment (as assessed in item 22 of the BSID-III Gross Motor Scale)
- Proportion of patients sitting without support for 30 seconds at Month 12 and Month 24 of treatment (as assessed in item 26 of the BSID-III Gross Motor Scale)
- Proportion of patients standing at Month 24 of treatment (as assessed in item 40 of the BSID-III Gross Motor Scale)
- Proportion of patients walking at Month 24 of treatment (as assessed in item 42 of the BSID-III Gross Motor Scale)

Analyses will be presented for the subgroups defined below:

- Age at enrollment (≤median age, >median age)
- Sex
- Baseline CHOP-INTEND score (≤median score, >median score)
- Baseline CMAP amplitude (<1.5mV, ≥1.5mV)

The number and percentage of patients who achieve the motor milestone and corresponding 90% Clopper-Pearson (exact) CIs will be presented for each subgroup using forest plots.

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Non-linear mixed effects modeling (using software NONMEM) will be used to analyze the sparse samples of concentration-time data of risdiplam (and its metabolites if deemed necessary). Population and individual PK parameters will be estimated and the influence of various covariates (such as age, sex, and body weight) on these parameters will be investigated. Data may be pooled with data from other studies with risdiplam in order to improve the parameter estimates from the model. Secondary PK parameters (such as C_{max} and AUC) may be derived from the model for each individual included in the PK analysis and will be presented descriptively. All PK parameters will be presented using listings and descriptive summary statistics.

Additional PK analyses and exploratory analyses on exposure versus selected safety and efficacy parameters may be conducted as deemed necessary for patients who meet the criteria for the primary efficacy analysis population or by *SMN2* copy number. This may include scatterplots of AUC versus change from baseline in the CHOP-INTEND total score, BSID-III Gross Motor Scale score and HINE-2 total score at Month 12 and Month 24 of treatment; and boxplots of AUC for patients who achieve/do not achieve sitting without support at Month 12 and Month 24, and patients who achieve/do not achieve standing and walking at Month 24, as assessed by items 22, 26, 40, and 42 of

the BSID-III Gross Motor Scale, respectively. Depending on the adverse event profile, correlations between exposure and adverse events may be explored.

The details of the modeling and exploratory analyses may be reported in a document separate from the clinical study report.

Assessment of protein binding will be performed on pre-dose samples (and may also be performed on PK samples throughout the study, as required) and reported.

All PD parameters (SMN mRNA and SMN protein in blood) will be presented by listings, descriptive summary statistics and mean or median plots over time, as appropriate.

Exploratory analyses on PD parameters versus selected efficacy parameters may also be performed as deemed necessary for patients who meet the criteria for the primary efficacy analysis population or by *SMN2* copy number, including, e.g., scatterplots of absolute SMN protein level and percent change from baseline in SMN protein level versus change from baseline in the CHOP-INTEND total score, BSID-III Gross Motor Scale score and HINE-2 total score at Month 12 and Month 24 of treatment; and boxplots of absolute SMN protein level and percent change from baseline in SMN protein level for patients who achieve/do not achieve sitting without support at Month 12 and Month 24, and patients who achieve/do not achieve standing and walking at Month 24, as assessed by items 22, 26, 40, and 42 of the BSID-III Gross Motor Scale, respectively.

4.6 SAFETY ANALYSES

All safety analyses will be based on the safety population. Safety data will be summarized descriptively for the first 12-month period (i.e., 12-month data for each individual patient) at the time of the 12-month analysis reporting event and for all available interim safety data collected at the time of the analysis (i.e., all data up to the clinical cutoff date for the analysis). Similar summaries for the first 24-month period will be presented at the time of the 24-month analysis reporting event. Safety data will be summarized descriptively for all patients (overall and by *SMN2* copy number [copy number 2, 3 or ≥4; patients with an “atypical 3-4” result will be included in the copy number ≥4 group]). The baseline CMAP amplitude (<1.5mV and ≥1.5mV) will also be indicated in patient listings. Any patients with the *SMN2* gene modifier mutation c.859G>C will be summarized separately.

Visit windows for safety analyses will be defined as described in Section 4.4. If multiple valid values for a variable are recorded in the same time window (including assessments performed at an unscheduled visit or an early withdrawal visit), the last record will be selected for summary of the data, except for laboratory data, where the worst record will be selected for summary of the data.

4.6.1 Exposure of Study Medication

The following extent of exposure to study drug will be summarized: duration of treatment (including the number and percentage of patients with duration of treatment from 0-≤6 months, >6-≤12 months, >12-≤18 months, >18-≤24 months etc.), number of doses taken, number of doses missed, number of partial doses taken (actual dose administered <90% of planned dose), number of overdoses (actual dose administered >110% of planned dose), dose intensity, and cumulative dose.

The duration of total treatment intake will be calculated from the patient's first day of study treatment to the last day of study treatment:

Duration of treatment = date of the last dose[#] – date of the first dose + 1 day

[#]Note: for outputs displaying all available interim exposure data, if dose administration is ongoing at the time of the clinical cutoff date, the last dose date will be replaced by the clinical cutoff date for the analysis.

All dose records with a start date on or before the clinical cutoff date will be included in the data cut.

Dose intensity will be calculated as:

Dose intensity = number of non-missing doses taken * 100 / number of doses expected to be taken

The number and percentage of patients with dose intensity <80% and ≥80% will be presented.

The route of administration of study drug and the number of dose adjustments per patient (if applicable) will also be summarized.

4.6.2 Adverse Events

For each AE recorded, the term entered by the investigator describing the event (the "verbatim term") will be assigned to a standardized term (the "preferred term") based on the most up-to-date version of MedDRA. Data displays of AEs will be performed using the system organ class and preferred terms. For summaries of AE incidences, patients who experienced the same event on more than one occasion will be counted once in the calculation of the event frequency at the highest intensity reported. Each table will also present the overall number of patients experiencing at least one AE and the total number of AEs reported. All AEs with an onset date on or before the clinical cutoff date for the analysis will be included in the data cut, regardless of the end date.

AEs will be considered treatment emergent if (a) the onset date is on or after the first day of the study drug; or (b) the onset date is prior to the first dose day with the end date on or after the first dose day or the AE is unresolved, and the most extreme intensity is greater than the initial intensity.

All treatment emergent AEs, AEs resulting in death, serious AEs (SAEs), AEs leading to withdrawal of study treatment and AEs leading to dose modification or interruption will be summarized. AEs will also be summarized by intensity/severity (National Cancer Institute-Common Terminology Criteria for Adverse Event [NCI-CTCAE] grade) and by relationship to study treatment (as assigned by the treating investigator). Most common AEs (reported in ≥10% of patients) will be summarized by preferred term. AE outcomes (recovered/resolved [including recovered/resolved with sequelae, recovering/resolving], not recovered/not resolved, fatal, unknown) will also be summarized by preferred term, with counts based on the number of events. In addition, an overall AE profile summary table will be presented. Individual listings will be generated for AEs, SAEs, AEs leading to withdrawal of study treatment and AEs leading to dose modification or interruption.

The AE and SAE rate adjusted for patient-years at risk (all occurrences, by preferred term) and corresponding exact 90% CIs for the event rate will also be presented. The AE rate per 100 patient-years is computed as follows:

AE rate = (number of AEs observed / total patient-years at risk) * 100

where

Total patient-years at risk = sum across all patients of the time intervals (in years) between start of study therapy and the earliest of {clinical cutoff date, date of study completion/early withdrawal or last treatment date + 30 days}

AEs, SAEs and AE/SAE rates adjusted for patient-years at risk will also be presented in 6- and 12-month intervals.

In addition, the overall AE profile summary table will be presented by baseline CMAP amplitude (<1.5mV and ≥1.5mV).

The following AEs of special interest (pre-defined in the protocol) will be summarized separately:

- Cases of potential drug-induced liver injury that include an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (>3 x upper limit of normal [ULN]) in combination with either an elevated total bilirubin (>2 x ULN) or clinical jaundice, as defined by Hy's law.
- Suspected transmission of an infectious agent by the study drug.

Non-treatment emergent AEs, including the SAEs caused by a protocol-mandated intervention (e.g., SAEs related to invasive procedures such as biopsies), for which the onset date is before the date of the start of study medication (after informed consent has been obtained but prior to initiation of study drug), will be listed.

The following rules will be applied for AEs with missing onset and/or end dates:

- Events that are missing both onset and end dates will be considered treatment emergent, given that a patient had at least one dose of study drug.
- If the onset date is missing and the end date is on or after the first dosing date, then the event will be considered treatment emergent.
- If the end date is missing and the onset date is on or after the first dosing date, then the event will be considered treatment emergent.
- If the end date is missing and the extreme intensity is worse than the initial intensity, and the onset date is prior to the first dosing date, then the event will be considered treatment emergent.
- The duration will be set to missing.

4.6.3 Death

Patient listings will be generated containing all details for each patient who died during the protocol-specified AE reporting period (up to 30 days after the study completion/early withdrawal visit). If progressive disease is specified as the cause of death, the associated AE will also be reported.

4.6.4 Laboratory Data

Laboratory data will be listed for patients with values outside the normal ranges (based on local laboratory ranges). In addition, shift tables to compare the status at baseline to each time-point post-baseline and overall will be presented. The number and percentage of patients with elevated ALT or AST levels at any time-point post-baseline will also be presented.

4.6.5 Vital Signs

Vital signs, including body temperature, respiratory rate, pulse rate and blood pressure, will be measured throughout the study. Vital signs data will be listed for patients with values outside the normal ranges. The normal ranges will be based on the age of the patient at the time of the assessment. In addition, shift tables to compare the status at baseline to each time-point post-baseline and overall will be presented.

The following normal ranges will be used:

Age (months)	Heart/Pulse Rate (beats/min)	Respiratory Rate (breaths/min)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)
0-≤3	100-150	35-55	65-85	45-55
>3-≤6	90-120	30-45	70-90	50-65
>6-≤12	80-120	25-40	80-100	55-65
>12-≤24	70-110	20-30	90-105	55-70
>24-≤72	70-130			
>24-≤144		18-30	90-125	60-80

For temperature, the following normal ranges will be used:

Age (months)	Temperature (°C)
0-≤24	36.4-38.0
>24-≤144	35.5-37.8

4.6.6 Electrocardiogram

ECG data will be listed for patients with values outside the normal ranges. The normal ranges will be based on the age of the patient at the time of the assessment. Triplicate and average ECG results will be listed, where the average ECG result is defined as the average of the valid (non-missing and non-zero) triplicate measurements.

In addition, shift tables for each parameter (PR duration, QT duration, QRS duration, RR duration, QTc [Bazett] [QTcB], QTc [Fridericia] [QTcF], T-wave, U-wave and interpretation [ECG result]) to compare the status at baseline to each time-point post-baseline and overall will be presented.

If ECG assessments are also evaluated by a local cardiologist (clinician), data for these patients will be listed.

The following normal ranges will be used:

Age (months)	PR Duration (ms)	QT Duration (ms)	QRS Duration (ms)	RR Duration (ms)	QTcB (ms)	QTcF (ms)
0-≤24	80-120	230-420	50-90		370-450	370-450
>24-≤144	80-160	260-390	40-90		380-450	380-450
0-≤3				400-600		
>3-≤6				500-670		
>6-≤12				500-750		
>12-≤24				450-860		
>24-≤72				460-860		

The number and percentage of patients with PR duration, QRS duration, QT duration, QTcB and QTcF in the following ranges at each time-point will be presented:

ECG Parameter	Raw Value	Increase from Baseline
PR duration (ms) 0-≤24 months >24-≤144 months	 ≤120 >120 ≤160 >160	
QRS duration (ms)	≤90 >90	
QT duration (ms)	≤450 >450 and ≤480 >480 and ≤500 >500	≤30 >30 and ≤60 >60
QTcB (ms)	≤450 >450 and ≤480 >480 and ≤500 >500	≤30 >30 and ≤60 >60
QTcF (ms)	≤450 >450 and ≤480 >480 and ≤500 >500	≤30 >30 and ≤60 >60

4.6.7 Ophthalmological Assessments

Ophthalmological assessments will be classified into three main categories:

- Imaging (including SD OCT and fundus photography)
- Ophthalmological examination (including fundus examination, ocular examination [slit lamp and visual testing] and intraocular pressure)
- Visual function (including fix and follow assessment)

An overall ophthalmology profile summary table showing the number and percentage of patients with an abnormal or potentially clinically significant result at any time-point and at the last available time-point (based on the criteria defined below) will be presented for each assessment. The total number of abnormal or potentially clinically significant results will also be presented.

In addition, the number and percentage of patients with an abnormal or potentially clinically significant result and the total number of abnormal or potentially clinically significant results at each time-point will be presented for each assessment. The

number and percentage of patients with an abnormal or potentially clinically significant result in both eyes will also be presented.

Listings will be produced for all patients with an abnormal or potentially clinically significant result in any ophthalmological assessment.

Short patient summaries will be provided for patients with an abnormal or potentially clinically significant result at the last available time-point in order to provide an assessment on whether the finding may constitute a sign of risdiplam-related retinal toxicity.

4.6.7.1 Imaging

SD OCT

An abnormal or potentially clinically significant result in the SD OCT assessment is defined as:

1. A clinically significant change from baseline (as assessed by AEBC); or
2. An abnormal macula OCT assessment; or
3. A result other than “Not Applicable” for the macula OCT diagnosis

Fundus photography

An abnormal or potentially clinically significant result in the fundus photography assessment is defined as:

1. A clinically significant change from baseline (as assessed by AEBC); or
2. An abnormal photograph assessment; or
3. A result other than “Not Applicable” for the photograph diagnosis; or
4. A result of “Yes” for pigmentation observed

4.6.7.2 Ophthalmological Examination

Fundus examination

An abnormal or potentially clinically significant result in the fundus examination is defined as:

1. A clinically significant change (worse) from baseline (as assessed by the local ophthalmologist); or
2. An abnormal result; or
3. A retinal break; or
4. A retinal detachment

Ocular examination (slit lamp and visual testing)

An abnormal or potentially clinically significant result in the slit lamp or visual testing assessment is defined as:

1. A clinically significant change (worse) from baseline (as assessed by the local ophthalmologist); or
2. An abnormal result

Intraocular pressure

An abnormal or potentially clinically significant result in the intraocular pressure assessment is defined as:

1. A clinically significant change (worse) from baseline (as assessed by the local ophthalmologist); or
2. An abnormal result

4.6.7.3 Visual Function

Fix and follow

An abnormal or potentially clinically significant result in the fix and follow assessment is defined as:

1. A clinically significant change (worse) from baseline (as assessed by the local ophthalmologist); or
2. An abnormal result

4.7 MISSING DATA

The handling of missing data for efficacy variables is described in the corresponding sections within this SAP.

No imputation will be performed for missing safety variables.

4.8 INTERIM ANALYSES

As this study is open-label, once at least 3 of the 10 patients in the primary efficacy analysis population (if 10 of these patients have been enrolled) have met the primary endpoint of sitting without support at Month 12 (as assessed by the independent central readers), the minimum number of patients needed for a statistically significant result will have been achieved and the primary objective of the study will be considered achieved at this earlier time-point. The study will not be stopped and all patients enrolled will continue to receive 12 months of treatment in order to provide an unbiased estimate of the proportion of patients sitting at Month 12.

An interim analysis may also be performed to summarize descriptively the safety and efficacy data to support the registration of risdiplam in presymptomatic patients and patients below the age of 2 months.

Interim analyses for efficacy will be performed by the Sponsor and the results presented to the iDMC. The iDMC will be requested to review all available safety data and asked to provide an independent assessment of the benefit-risk profile of risdiplam in the presymptomatic SMA population at this earlier time-point. The final decision based on the iDMC recommendation will be made by the Sponsor.

4.9 ANALYSES RELATED TO COVID-19 PANDEMIC

On 11 March 2020, the World Health Organization (WHO) characterized the outbreak of Coronavirus Disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a pandemic. Government restrictions on the population were implemented to varying degrees globally in response to the COVID-19 pandemic. Measures, such as restrictions of movement and travel and, therefore, visits to healthcare facilities, as well as the increased demands on the health service due to the pandemic and changes to study staff availability pose various challenges to the conduct of clinical studies. In addition, patients may have been required to self-isolate, which introduces difficulties for Investigators to maintain their medical oversight. Therefore, the COVID-19 pandemic may have had an impact on the conduct of clinical studies of medical products, on study patients, and on the collection and analysis of clinical study data.

It is difficult to determine the start of the COVID-19 outbreak and the Sponsor decided to use 01 December 2019 based on early cases reported in Mainland China. Study BN40703 began in 2019 (i.e., first patient in [FPI] occurred in August 2019) and enrollment is ongoing as of May 2021, which includes the period during which the COVID-19 pandemic was occurring globally. Direct and indirect impacts of the COVID-19 pandemic will be evaluated for their potential effects on the interpretation of study results.

4.9.1 Protocol Deviations

The number and percentage of patients with major protocol deviations due to COVID-19 will be presented with deviations summarized by the primary reason for the deviation. COVID-19 related major protocol deviations, including descriptions and reasons for each deviation, will also be listed.

4.9.2 Patient Disposition

The number and percentage of patients who discontinued early from treatment and/or study due to reasons related to COVID-19 (e.g., COVID-19 infection or study disruption) will be presented. Discontinuations due to indirect COVID-19 impacts will be based on a

manual review of discontinuation reasons reported in the study drug completion/early discontinuation and subject disposition eCRF free-text fields.

4.9.3 Safety Analyses

Based on the first reports of COVID-19 infection globally, the Sponsor determined that the window for all analyses of COVID-19 associated events would start from 01 December 2019, until the clinical cutoff date for each reporting event.

Two new safety analysis concepts were created to identify COVID-19 related AEs:

- Confirmed or suspected COVID-19: This includes all AEs in the COVID-19 Standardized MedDRA Query (SMQ; narrow). The preferred terms of this SMQ allow for the assessment of COVID diagnoses, infections, treatment and carrier status.
- COVID-19 associated events: This includes all of the confirmed/suspected AEs from the COVID-19 SMQ (narrow) plus any AEs reported in patients with confirmed COVID-19 infection or positive PCR test (as defined by a pre-defined list of preferred terms from the COVID-19 SMQ [narrow]). The additional AEs are included if they occurred within ≤7 days before and ≤30 days after the start date of the confirmed COVID-19 events. With this analysis concept, the impact of COVID-19 infection on the AE profile of patients with a positive COVID-19 diagnosis can be assessed including any complications that may have occurred in patients with a positive COVID-19 diagnosis.

A listing of confirmed and suspected COVID-19 AEs (events in the COVID-19 SMQ) will be produced. COVID-19 associated AEs, including confirmed/suspected COVID-19 infections plus, for those patients with confirmed COVID-19 infection or positive PCR test, any other AEs occurring within ≤7 days before and ≤30 days after the start date of all the confirmed COVID-19 events, will also be listed.

5. REFERENCES

Bayley N. Bayley scales of infant and toddler development–third edition: Administration manual. 2006. San Antonio, TX: Harcourt Assessment, Inc.

Feldkotter M, Schwarzer V, Wirth R, et al. Quantitative analyses of *SMN1* and *SMN2* based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet 2002;70:358-68.

Gauld LM, Kappers J, Carlin JB et al. Height prediction from ulna length. Dev Med Child Neurol 2004;46:475-80.

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.

WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards: Head circumference-for-age, arm circumference-for-age, triceps skinfold-for-age and subscapular skinfold-for-age: Methods and development. Geneva: World Health Organization, 2007.

WHO Multicentre Growth Reference Study Group. WHO Motor Development Study: Windows of achievement for six gross motor development milestones. Acta Paediatr Suppl 2006;450:86-95.

Appendix 1
Protocol Synopsis

TITLE:	**AN OPEN-LABEL STUDY OF RISDIPLAM IN INFANTS WITH GENETICALLY DIAGNOSED AND PRESYMPTOMATIC SPINAL MUSCULAR ATROPHY**
PROTOCOL NUMBER:	BN40703
VERSION NUMBER:	4
EUDRACT NUMBER:	2018-002087-12
IND NUMBER:	128972
TEST PRODUCT:	Risdiplam (RO7034067)
PHASE:	II
INDICATION:	Spinal muscular atrophy
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants genetically diagnosed with spinal muscular atrophy (SMA) but not yet presenting with symptoms. Specific objectives and corresponding endpoints for the study are outlined below.

Efficacy Objectives

Primary Efficacy Objective

In line with the study population expected to predominantly include presymptomatic infants who, without any treatment, would develop a phenotype of Type 1 SMA, the primary efficacy objective for this study is to evaluate the efficacy of risdiplam in patients with two copies of the *survival motor neuron* (*SMN)2* gene (excluding the known SMN2 gene modifier mutation c.859G > C) and baseline compound muscle action potential (CMAP)) amplitude ≥ 1.5 mV, as determined by the proportion of patients who are sitting without support after 12 months of treatment. Sitting is defined as “sits without support for 5 seconds” as assessed in Item 22 of the Bayley Scales of Infant and Toddler Development®, Third Edition (BSID-III) Gross Motor Scale.

Secondary Efficacy Objectives

The secondary efficacy objectives along with the corresponding endpoints for this study are as follows:

- To evaluate the efficacy of risdiplam on the development of clinically manifested SMA on the basis of the following endpoints:
  - Proportion of patients developing clinically manifested SMA (at Month 12 and Month 24 of treatment)
- To evaluate the efficacy of risdiplam on survival and permanent ventilation on the basis of the following endpoints
  - Time to death
  - Time to permanent ventilation
  - Time to death or permanent ventilation
  - Proportion of patients alive without permanent ventilation (at Month 12 and Month 24 of treatment)

Proportion of patients alive (at Month 12 and Month 24 of treatment)

- To evaluate the efficacy of risdiplam on the achievement of motor milestones defined in the BSID-III and by the Hammersmith Infant Neurological Examination (HINE) on the basis of the following endpoints:

  Proportion of patients who achieve the attainment levels of the motor milestones assessed in the HINE-2 (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) (at Month 12 and Month 24 of treatment)

  Proportion of patients with two copies of the *SMN2* gene sitting without support (at Month 12 of treatment [as assessed in Item 22 of BSID-III Gross Motor Scale]) for 5 seconds (independent of the CMAP value at baseline)

  Proportion of patients sitting without support (at Month 24 of treatment [as assessed in Item 22 of BSID-III Gross Motor Scale] for 5 second

  Proportion of patients sitting without support (at Month 12 and Month 24 of treatment [as assessed in Item 26 of BSID-III Gross Motor Scale]) for 30 seconds

  Proportion of patients standing (at Month 24 [defined as “Stands Alone” for at least 3 seconds as assessed in Item 40 of the BSID-III Gross Motor Scale])

  Proportion of infants walking (at Month 24 [defined as “Walks Alone” takes at least 3 steps as assessed in Item 42 of the BSID-III Gross Motor Scale])

  Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of the chronological reference standard (at Months 24 and 42 [as assessed through the use of the BSID−III Gross Motor Scale])

- To evaluate the efficacy of risdiplam on motor function on the basis of the following endpoints:

  Change from baseline in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale (at Month 12 and Month 24 of treatment)

  Proportion of patients who achieve a score of 40 or higher, 50 or higher, and 60 or higher in the CHOP INTEND motor function scale (at Month 12 of treatment)

  Proportion of patients who meet CHOP INTEND stopping criteria at any point up to Month 24 of treatment

  Change from baseline (Month 24) in the Hammersmith Functional Motor Scale Expanded (HFMSE) (at Month 60 of treatment).

- To evaluate the efficacy of risdiplam on growth measures upon treatment on the basis of the following endpoints:

  Number and proportion of patients within 3rd percentile of normal range for weight-for-age, length/height-for-age and weight-for-length/height (at Months 12, 24, 36, 48, and 60 of treatment based on the WHO Child Growth Standards) (WHO 2019)

  Number and proportion of patients within 3rd percentile of normal range for head circumference-for-age (at Month 12 and Month 24 of treatment, based on the WHO Child Growth Standards) (WHO 2019)

  Change from baseline percentiles for weight-for-age, length/height-for-age and weight-for-length/height (at Months 12, 24, 36, 48 and 60 of treatment)

  Change from baseline percentiles for head circumference-for-age (at Month 12 and Month 24 of treatment)

  Change from baseline in chest circumference (at Month 12 and Month 24 of treatment)

  Ratio between chest and head circumferences (at Month 12 and Month 24 of treatment)

- To evaluate the efficacy of risdiplam on the nutritional status of the patients upon treatment with risdiplam on the basis of the following endpoint:

  Ability to swallow and to feed orally (at Months 12, 24, 36, 48, and 60 of treatment)

- To evaluate the efficacy of risdiplam on the degree of innervation upon treatment with risdiplam on the basis of the following endpoint:

  Change from baseline in CMAP amplitude (at Month 12 and 24 of treatment)
- To evaluate the pharmacodynamic (PD) effects of risdiplam on the basis of the following endpoints:

  SMN mRNA levels in blood

  SMN protein levels in blood

Exploratory Efficacy Objectives

The exploratory efficacy objectives along with the corresponding endpoint for this study are as follows:

- To evaluate the efficacy of risdiplam to achieve other developmental milestones as defined by BSID-III and WHO milestones on the basis of the following endpoints:

  Cognition assessed through the use of the BSID–III Cognitive Scale (at Months 12, 24, and 42 of treatment)

  Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of chronological reference standard (at Months 24 and 42 of treatment [as assessed through the use of the BSID–III Cognitive Scale])

  Fine motor function assessed through the use of the BSID–III Fine Motor Scale (at Months 12, 24, and 42 of treatment)

  Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of chronological reference standard (at Months 24 and 42 of treatment [as assessed through the use of the BSID–III Fine Motor Scale])

  Proportion of patients who attain motor milestones as assessed by WHO criteria (at Months 48 and 60 of treatment)
- To evaluate the efficacy of risdiplam on motor function on the basis of the following endpoint:

  Total Walk Distance in the six-minute walk test (6MWT; ambulant patients only) (at Month 60 of treatment)
- To explore the treatment effect on speech development on the basis of the following endpoint:

  Speech development as assessed during the neurological examination (at Months 12, 24, 36, 48, and 60 of treatment).
- To explore the effect of treatment with risdiplam on the number of hospitalizations on the basis of the following endpoints:

  Number of hospitalizations (for any reason, except if for study purpose only [e.g., to facilitate study assessments]) per patient-year and number of nights admitted to hospital per patient (at 12, 24, 36, 48, and 60 months of treatment).

  Proportion of patients with no hospitalizations (at 12, 24, 36, 48, and 60 months of treatment).
- To explore the treatment effect on pre-specified disease-related adverse events on basis on the following endpoint:

  Pre-specified disease-related adverse events by 12 and 24 months of treatment

Safety Objectives

The safety objective for this study is to evaluate the safety of risdiplam on the basis of the following endpoints:

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5
- Incidence and severity of serious adverse events
- Incidence of treatment discontinuation due to adverse events

- Incidence of abnormal laboratory values
- Incidence of abnormal ECG values
- Vital signs abnormalities, including body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate
- Ophthalmological examination as appropriate for age (e.g., red reflex, external ocular examination, pupillary examination/response, cover/uncover, fix and follow test, corneal light reflex, fundus examination including ophthalmoscopy/slit lamp examination, SD-OCT, and fundus photography)
- Physical examination, including detailed examination of the skin and mouth

Pharmacokinetic Objective

The pharmacodynamic (PK) objective for this study is to characterize the PK profile of risdiplam on the basis of the following endpoints:

- Plasma concentration of risdiplam and its metabolite(s), as appropriate, at specified timepoints
- Area under the concentration–time curve (AUC)
- Concentration at the end of a dosing interval to assess steady-state
- Other PK parameters as appropriate

Biomarker Objective

The exploratory biomarker objective for this study is to identify biomarkers that are predictive of response to risdiplam (i.e., predictive biomarkers), are early surrogates of efficacy, are associated with progression to a more severe disease state (i.e., prognostic biomarkers), are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation (i.e., safety biomarkers), can provide additional evidence of risdiplam activity (i.e., PD biomarkers), or can increase the knowledge and understanding of disease biology and drug safety, on the basis of the following endpoints:

- Relationship between exploratory biomarkers in blood and efficacy, safety, PK, or other biomarker endpoints
- Relationship of genetic, epigenetic, or genomic markers with efficacy, safety, PK, or other biomarker endpoints related to SMA

Health Status Utility Objective

The exploratory health status utility objective for this study is to evaluate parent (or caregiver)-rated health status and health-related quality of life on the basis of the following endpoint:

- Change from baseline in Infant/Toddler Quality of Life Questionnaire™ (at 12 and 24 months of treatment)

Study Design

Description of Study

The study is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants aged from birth to 6 weeks who have been (at first dose) genetically diagnosed with SMA but are not yet presenting with symptoms.

There will be a screening, treatment, open-label extension (OLE) phase, and a follow-up. Screening will be up to 42 days prior to first dose, bearing in mind the maximum age of the patient at first dose of study drug is 42 days. Screening assessments may be repeated before enrollment to confirm eligibility. Patients will be enrolled in the study regardless of *SMN2* copy number. Recruitment will be global (e.g., at sites in United States, European Union, Russia, Brazil, Australia, Taiwan, Saudi Arabia and National Medical Products Administration recognized sites in China). All patients will receive risdiplam orally once daily for 2 years at a dose selected to achieve the targeted exposure range of close to 2000 ng • hr/mL (the dose

may be adapted as patients grow and mature), followed by an OLE phase of at least 36 months and a follow-up, for a total treatment duration of at least 5 years for each infant enrolled.
Enrollment will be closed when one of the following conditions have been met:

At least 25 patients, including a minimum of 5 patients who meet the criteria for the primary efficacy population are enrolled,

OR

A total of 10 patients who meet the criteria for the primary efficacy population are enrolled.

The OLE phase (Month 24 up to Month 60) will continue as per the main study in regards to dosing and will include regular monitoring of safety, tolerability, pharmacokinetics, and efficacy. Thereafter, the patient may continue until end of study, provided that risdiplam is not commercially available in the country of the site or until the Sponsor ceases producing or studying risdiplam. However, the overall study will not exceed a total of 5 years after the last patient is enrolled in the study.

All patients should have a follow-up call 30 days after the study completion/early withdrawal visit.

The primary endpoint is defined as the proportion of patients sitting without support after 12 months of treatment, as assessed on BSID-III Gross Motor Scale (defined as sitting without support for 5 seconds). Additional secondary endpoints will include longer-term (after 24 months) evaluation of motor milestone achievements and other developmental milestones.

Data will be reviewed on an ongoing basis by the Sponsor and an independent Data Monitoring Committee (iDMC).

Number of Patients

Approximately 25 patients with SMA will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by a legally authorized representative for the patient in accordance to International Council on Harmonisation (ICH) and local regulations
- Males and females aged from birth (1 day) to 6 weeks (42 days) of age at the time of first dose (Day 1); a minimum age of 7 days at first dose is required for the first infant to be enrolled
- Gestational age of 37–42 weeks for singleton births; gestational age of 34–42 weeks for twins
- Body weight $\geq 3^{rd}$ percentile for age, using appropriate country-specific guidelines
- Genetic diagnosis of 5q-autosomal recessive SMA, including confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the *SMN1* gene
- Absence of clinical signs or symptoms at screening (Day –42 to Day –2) or at baseline (Day –1) that are, in the opinion of the investigator, strongly suggestive of SMA
- Receiving adequate nutrition and hydration at the time of screening, in the opinion of the investigator
- Adequately recovered from any acute illness at baseline and considered well enough to participate in the study, in the opinion of the investigator
- Able and expected to be able to safely travel to the study site for the entire duration of the study and in accordance to the frequency of required study visits, in the opinion of the investigator
- Able to complete all study procedures, measurements, and visits, and the parent (or caregiver), in the opinion of the investigator, has adequately supportive psychosocial circumstances

- Parent (or caregiver) is willing to consider nasogastric, naso-jejunal, or gastrostomy tube placement during the study to maintain safe hydration, nutrition, and treatment delivery, if recommended by the investigator
- Parent (or caregiver) is willing to consider the use of non-invasive ventilation during the study, if recommended by the investigator

Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Concomitant or previous participation in any investigational drug or device study at any time
- Concomitant or previous administration of an SMN2-targeting antisense oligonucleotide, SMN2-splicing modifier, or gene therapy either in a clinical study or as part of medical care
- Presence of significant concurrent syndromes or diseases
- In the opinion of the investigator, inadequate venous or capillary blood access for the study procedures
- Requiring invasive ventilation or tracheostomy
- Requiring awake non-invasive ventilation
- Awake hypoxemia ($SaO2 < 95\%$) with or without ventilator support
- Multiple or fixed contractures and/or hip subluxation or dislocation at birth
- Systolic blood pressure or diastolic blood pressure or heart rate considered to be clinically significant by the investigator
- Presence of clinically relevant ECG abnormalities before study drug administration; corrected QT interval using Bazett's method > 460 ms; personal or family history (first degree relatives) of congenital long QT syndrome indicating a safety risk for patients as determined by the investigator. First-degree atrioventricular block or isolated right bundle branch block are allowed.
- The infant (and the mother, if breastfeeding the infant) taking any of the following:

  Any inhibitor of CYP3A4 taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing, including but not limited to: ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, cimetidine

  Any inducer of CYP3A4 taken within 4 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing, including but not limited to: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John's wort

  Use of any OCT 2 and MATE substrates within 2 weeks prior to dosing (including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine)

  Use of any known FMO1 or FMO3 inhibitors or substrates
- Clinically significant abnormalities in laboratory test results (e.g., Grade > 1 anemia, ALT values exceeding $1.5\times$ the upper limit of normal unless the elevated ALT level is considered of muscular origin [i.e., in the absence of other evidence of liver disease that is confirmed by elevated creatine kinase and lactate dehydrogenase]). Out of range creatine kinase levels should be reviewed in light of the underlying SMA pathology of the patient; elevated levels per se do not disqualify the patient from the study. In the case of uncertain or questionable results, tests performed during screening may be repeated before enrollment to confirm eligibility.
- Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to risdiplam or to the constituents of its formulation (see the Risdiplam Investigator's Brochure)
- Treatment with oral salbutamol or another $\beta 2$ adrenergic agonist taken orally for SMA is not allowed. Use of inhaled $\beta 2$ adrenergic agonists (e.g., for the treatment of asthma) is allowed.

- Anticipated need for thioridazine, vigabatrin, retigabine, or any other drug known to cause retinal toxicity during the study. Infants exposed to thioridazine, vigabatrin, retigabine, or drugs with known retinal toxicity given to mothers during pregnancy (and lactation) should not be enrolled.
- Diagnosis of ophthalmic diseases (e.g., glaucoma, central serous retinopathy, inflammatory/infectious retinitis unless clearly inactive, retinal detachment, intraocular trauma, retinal dystrophy or degeneration, optic neuropathy, or optic neuritis) that would interfere with the conduct of the study as assessed by an ophthalmologist. Any other abnormalities detected with SD-OCT during screening *prior to enrollment* (e.g., retinal layer abnormalities, edema, cystic or atrophic changes) must be discussed with the investigator, ophthalmologist, and with the Sponsor, who will jointly determine if the infant may be enrolled in the study. Infants in whom SD-OCT measurement of sufficient quality cannot be obtained at screening will not be enrolled. *In the event that an OCT of sufficient quality cannot be obtained prior to enrollment, one must be obtained by Day 14.*

End of Study

The end of study (EOS) is defined as the date when the last patient, last visit (LPLV) occurs.

Length of Study

The study will continue until the EOS, or as per local regulation, or per the Sponsor's decision to terminate risdiplam development. However, the length of the study will not exceed a total of 5 years after the last patient is enrolled in the study.

After completion of 2 years treatment, each patient will continue to receive treatment in the OLE phase for at least 3 years. After a patient has completed 3 years in the OLE, the patient may continue until EOS, provided that risdiplam is not commercially available in the country of the site.

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product for this study is risdiplam.

Throughout the study, the study drug (risdiplam) should be taken orally once daily in the morning, except when site visits are planned and study medication will be administered at the clinical site. In patients able to swallow, study drug will be administered with a syringe inserted between gum and cheek of the patient as described in the study drug administration instructions for use. Patients unable to swallow the study medication and who have a naso-gastric or gastrostomy tube in situ should receive the study medication by bolus via the tube.

Statistical Methods

Primary Analysis

All enrolled infants with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude $\geq$ 1.5 mV will be included in the primary efficacy analysis. The primary endpoint of the study is the proportion of infants who are sitting without support after 12 months of treatment. Infants who do not achieve sitting, or have not maintained sitting achieved earlier, have been withdrawn, or died, will be classified as non-responders (i.e., non-sitters) for the primary analysis. Sitting is defined as "sits without support for 5 seconds" as assessed in Item 22 of the BSID-III Gross Motor Scale. The assessment of the independent central readers will be used for the primary analysis.

The proportion of infants who are alive and sitting after 12 months of treatment will be presented with a two-sided 90% Clopper-Pearson (Exact) confidence interval. An exact binomial test will be performed. The hypothesis to be tested will be that the proportion of infants who sit on treatment (p) is:

Ho: $p \leq 5\%$ (null) versus Ha: $p > 5\%$ (alternative).

If the one-sided p-value is $\leq$ 5% (Type 1 error rate), then the null hypothesis will be rejected. If the lower limit of the two-sided 90% confidence interval is above the 5% threshold, the primary objective of the study will be considered achieved. The number and percentage of

infants sitting at each timepoint will also be presented, using the same responder/non-responder definition described above.

As this is an open-label study, once at least 3 out of 10 infants *(if 10 patients in the primary analysis population are enrolled)* have met the primary endpoint of sitting without support at Month 12 (as assessed by the independent central readers), the minimum number of infants needed for a statistically significant result will have been achieved and the primary objective of the study will be considered achieved at this earlier timepoint. *The primary analysis will be conducted once the last patient enrolled (irrespective of SMN2 copy number) has reached 12 months of treatment, in order to assess the primary endpoint, and to allow the assessment of the 12 month secondary and exploratory endpoints in all patients*. The study will not be stopped early if the primary objective has been reached, and all infants enrolled will continue to receive 12 months of treatment to provide an unbiased estimate of the proportion of infants sitting at Month 12.

Determination of Sample Size

The purpose of the study is to estimate the proportion of infants with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude ≥1.5 mV who are sitting without support after 12 months of treatment and to test whether this proportion is higher than a performance criterion set at 5%. The 5% threshold was chosen based on the natural history of the disease (typically patients with Type 1 SMA never achieve sitting without support by definition) and based on the assumption that there is a 97% chance that a presymptomatic infant with two *SMN2* copies develops Type 1 SMA.

The target sample size to be enrolled in the study is 10 patients with two SMN2 copies and a baseline CMAP amplitude ≥1.5 mV. The sample size of 10 patients provides 83% power to test the null hypothesis Ho: p≤5% versus alternative hypothesis Ha: p> 5%, if the true proportion of infants who would sit after 12 months on treatment is 40%. This is based on an exact binomial test with a one-sided 5% significance level. The minimum number of infants needed to be observed sitting without support is 3 out of 10 for a statistically significant result. If 3 out of 10 infants sit without support, the lower limit of the two-sided 90% Clopper-Pearson (Exact) confidence interval would be above 5%.

If recruitment is completed prior to enrolling 10 patients with two SMN2 copies and a baseline CMAP amplitude ≥1.5 mV, the number of patients needed to be observed sitting without support for a statistically significant result may differ. The table below shows the minimum number of patients that would need to achieve the primary endpoint (based on the number enrolled), in order for the endpoint to meet statistical significance (the critical value). In each case, the lower limit of the two-sided 90% Clopper-Pearson (Exact) confidence interval would be above 5%.

Number of Patients in the Primary Analysis Population Needed to Achieve the Primary Endpoint

Number of Patients in the Primary Population	*Critical Value*	*Power (%)*
5	*2*	*66.3*
6	*2*	*76.7*
7	*2*	*84.1*
8	*3*	*68.5*
9	*3*	*76.8*
10	*3*	*83.3*

Interim Analyses

As this study is open-label, once at least 3 of the 10 infants *(if 10 of these patients have been enrolled)* have met the primary endpoint of sitting without support at Month 12 (as assessed by the independent central readers), the minimum number of infants needed for a statistically significant result will have been achieved and the primary objective of the study will be considered achieved at this earlier timepoint. The study will not be stopped and all infants enrolled will continue to receive 12 months of treatment in order to provide an unbiased estimate of the proportion of infants sitting at Month 12.

An interim analysis may also be performed to summarize descriptively the safety and efficacy data to support the initial filing and registration of risdiplam in pre-symptomatic patients and patients below the age of 2 months.

Interim analyses for efficacy will be performed by the Sponsor and the results presented to the iDMC. The iDMC will be requested to review all available safety data and asked to provide an independent assessment of the benefit–risk profile of risdiplam in the pre-symptomatic SMA population at this earlier timepoint.

Appendix 2
Schedule of Activities

Week	Screen.	Wk1			Wk2	Wk4	Wk8	Wk16	Wk28	Wk40	Wk52	Wk64	Wk78	Wk92	Wk104	OLE [a]	SC/ EW [b]	FU (30D after SC/EW)
Day	D –42 to D –2	D –1 [c]	D 1	D 2	D 14	D 28	D 56	D 112	D 196	D 280	D 364	D 448	D 546	D 644	D 728			
Visit Window					±1	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±14	+7
Assessments																		
Site visit	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Follow-up call [d]	x	x																x
Informed consent	x																	
Enrollment		x																
Eligibility	x	x																
Demography	x																	
Medical history	x																	
SMA family history	x																	
Physical and neurologic examination [e]	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	
Weight, height, head and chest circumferences [f]	x	x			x [f]	x [f]	x	x	x	x	x	x	x	x	x	x [f]	x	
Vital signs [g]	x	x	x (+4 hr)		x	x	x	x	x	x	x	x	x	x	x	x	x	
ECG-12 lead [h]	x	x	x (+4 hr)		x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 2
Schedule of Activities (cont.)

Week	Screen.	Wk1		Wk2	Wk4	Wk8	Wk16	Wk28	Wk40	Wk52	Wk64	Wk78	Wk92	Wk104	OLE [a]	SC/ EW [b]	FU (30D after SC/EW)
Day	D –42 to D –2	D –1 [c]	D 1	D 2	D 14	D 28	D 56	D 112	D 196	D 280	D 364	D 448	D 546	D 644	D 728	±7	Day	
Visit Window					±1	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7			
Assessments																		
Administration of study medication [i]			x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Study medication dispensation/return [j]			x		x													
Diary of time of drug administration			Daily															
Clinical genotyping [k]	x																	
Fluid PD sample [k, l]			x				x		x		x				x		x	
Protein binding sample [k]	x																	
PK blood sample [k]			3 [m]	1 [m, n]	1 [m]	4	4	1	4	1	4	1	4	1	4	1	x	
Safety laboratory (hematology and blood chemistry) [k]	x				x		x	x	x	x	x	x	x	x	x	x	x	
Ophthalmology assessments [o]	x [o]						x		x		x				x	x	x	
Developmental milestones (BSID®-III) [p]		x				x	x	x	x	x	x	x	x	x	x	x [p]	x [p]	

Appendix 2
Schedule of Activities (cont.)

Week	Screen.	Wk1			Wk2	Wk4	Wk8	Wk16	Wk28	Wk40	Wk52	Wk64	Wk78	Wk92	Wk104	OLE [a]	SC/ EW [b]	FU (30D after SC/EW)
Day	D –42 to D –2	D –1 [c]	D 1	D 2	D 14	D 28	D 56	D 112	D 196	D 280	D 364	D 448	D 546	D 644	D 728		Day	
Visit Window					±1	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	Visit Window	
Assessments																		
HINE-2		x				x	x	x	x	x	x	x	x	x	x [q]	x [q]	x [q]	
CHOP INTEND [r]		x				x	x	x	x	x	x	x	x	x	x		x [r]	
HFMSE															x	x	x	
6MWT [s]																x [s]	x	
WHO milestones [t]																x [t]	x	
Level of respiratory support	x	x			x	x	x	x	x	x	x	x	x	x	x	x	x	x
CMAP	x	x						x	x	x	x	x	x	x	x	x	x	
Nutritional check [u]	x	x					x	x	x	x	x	x	x	x	x	x	x	
Infant Toddler Quality of Life Questionnaire		x						x		x	x		x		x	x	x	

Appendix 2
Schedule of Activities (cont.)

Week	Screen.	Wk1			Wk2	Wk4	Wk8	Wk16	Wk28	Wk40	Wk52	Wk64	Wk78	Wk92	Wk104	OLE [a]	SC/ EW [b]	FU (30D after SC/EW)
Day	D –42 to D –2	D –1 [c]	D 1	D 2	D 14	D 28	D 56	D 112	D 196	D 280	D 364	D 448	D 546	D 644	D 728		Day	
Visit Window					±1	±3	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7		
Assessments																		
Previous and concomitant treatments [v]	x	x																
Significant life events (including family)	x	x																
Adverse events	x [w]	x																

6MWT = six-minute walk test; BSID®-III = Bayley Scales of Infant and Toddler Development®, Third Edition; CHOP INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP = compound muscle action potential; D = day; EW = early withdrawal; FU = follow-up; HINE-2 = Hammersmith Infant Neurological Examination–Module 2; HFMSE = Hammersmith Functional Motor Scale Expanded; OLE = open-label extension; PD = pharmacodynamic; PK = pharmacokinetic; SC = study completion; Screen. = screening; SD-OCT = spectral-domain optical coherence tomography; SMA = spinal muscular atrophy; SMN = survival motor neuron (protein); Wk = week.

[a] Visits every 26 weeks after the Week 104 visit until the completion of the OLE.

[b] If a patient withdraws within 4 weeks of an OLE visit, only the following assessments need to be repeated at the study completion/early withdrawal visit: study drug return, diary return, adverse event, and concomitant medication. EOS is when the last patient completes five years in the study. All patients should attend an SC/EW visit. If risdiplam is approved in the country of the site before the Week 260 (Year 5) visit, then the final visit for the patient will be at 260 weeks – in this case the SC/EW visit be performed in place of the Week 260 visit. If risdiplam is not approved in the country of the site at the time of the Week 260 visit, the patient should attend the Week 260 visit, and all OLE visits beyond Week 260 until risdiplam is approved or until EOS (whichever occurs first), ensuring that the final site visit is the SC/EW visit.

[c] Assessments should be performed in the following order: adverse events, previous/concomitant medication, confirmation of eligibility, IxRS enrollment call, all required assessments according to the order of assessments specified in Appendix 4 of the study protocol.

Appendix 2
Schedule of Activities (cont.).

[e] See Section 4.5.4 of the study protocol for details on physical and neurologic examinations. Photographs may be taken to document the nature of skin findings (or other adverse events).

[f] See Section 4.5.3 of the study protocol for details on anthropometric measurements. Only weight needs to be measured at Week 2 and Week 4. Measuring of the patient's weight during an unscheduled visit is allowed at the discretion of the investigator, i.e., if weight change is >10% according to parent/caregiver reporting or a dose adjustment has been requested. During OLE, as visits are 26 weeks apart, unscheduled visits to assess weight may be expected. If patients are attending site for any other reason during OLE, it is advisable to also take the opportunity to measure weight. During OLE, head circumference and chest circumference will not be measured.

[g] Vital signs will include measurements of blood pressure, pulse rate, respiratory rate, and body temperature (oral or tympanic). Measurements should be taken 4 hours post dose on Day 1. See Section 4.5.5 of the study protocol for details.

[h] ECG recordings must be performed after the patient has been resting in a relaxed (e.g., semi-supine/supine) position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Measurements should be taken 4 hours post dose on Day 1. See Section 4.5.6 of the study protocol for details.

[i] Oral dosing should be performed during site visits. Oral dosing once daily in the morning when at home. See Section4.3.2 of the study protocol for details. At study completion/early withdrawal visit, no study drug will be dispensed and used and unused study drug bottles are to be returned.

[j] Home visits (or site visits if preferred by parent/guardian) may be scheduled as appropriate for drug dispensation to ensure drug supply for the patient, return of unused drug and supplies, and any unscheduled assessments (or scheduled assessments, in exceptional circumstances). At study completion/early withdrawal visit, no study drug will be dispensed and used and unused study drug bottles are to be returned.

[k] The total blood volume to be collected at any timepoint should not exceed 0.8 mL/kg or 2.4 mL/kg over any 4-week period (see Section 4.5.11 of the study protocol for prioritization order for blood samples in case blood volume limit is estimated to be exceeded). Additional PK samples may be taken if required for safety reasons.

[l] Includes SMN protein, SMN mRNA levels and splicing modification of *SMN1*, *SMN2* full-length, and SMNΔ7 mRNA. May also be used for additional exploratory analysis/assay development related to SMA. See Appendix 2 of the study protocol for details.

[m] PK samples obtained on Days 1, 2, and 14 will be shipped immediately for analysis, and on the basis of PK data obtained, the dose for the first infant will be adjusted to reach the targeted exposure range. Should dose adjustment be required, two additional unscheduled PK samples may be collected at a time to be specified by the Sponsor and analyzed immediately (see Section 3.1 of the study protocol). See Appendix 2 of the study protocol for details.

Appendix 2
Schedule of Activities (cont.)

[n] Patients will have a PK sample taken 24 hours after the first dose and prior to receiving the second dose of risdiplam. See Appendix 2 of the study protocol for details.

[o] The ophthalmology assessments include SD-OCT, visual development, red reflex, external ocular examination, pupillary response, cover/uncover (up to Week 52), fix and follow test, ocular examination under magnification, and fundus photography (up to Week 52). See Appendix 3 of the study protocol and Section 4.5.7 of the study protocol for details. *Screening ophthalmology assessments are to be performed between Day –42 and Day 14.*

[p] BSID-III is only designed to evaluate patients up to 42 months of age; thus, this assessment will be stopped at 42 months of age (visit Week 182) for each infant. The Sitting, Standing Walking (Motor Milestones) assessment, Gross and Fine Motor Scales of the BSID-III will be administered at each indicated visit. The Cognitive Scale of the BSID-III will be administered at Day –1; on Weeks 28, 52, 78, and 104; and the OLE visits and study completion/early withdrawal only. *BSID-III is not required at study completion/early withdrawal visits that occur after Week 182.* The Sitting, Standing, Walking (Motor Milestones) assessment and/or Gross Motor Scale can be repeated once within the allowed visit window if the child is uncooperative at the first attempt (See Section 4.5.9.1.1 of the study protocol for details).

[q] HINE is designed to evaluate patients up to 24 months of age. Thus, from Week 104 this assessment will be stopped for each infant once the maximum score is reached at two consecutive visits. *At the earliest, the final HINE-2 evaluation will be at Week 104. It will not be performed at Study Completion/Early Withdrawal Visit if this visit occurs after this assessment's stopping point.*

[r] CHOP INTEND to be discontinued after Week 52, once patient is able to sit independently at two consecutive visits AND has scored at least 60 at the same two consecutive visits. If stopping criteria are met within the first 52 weeks of the study, Week 52 will be the last CHOP-INTEND assessment. If stopping criteria are not met, the CHOP-INTEND will be discontinued once the patient reaches Week 104. Will not be performed at Study Completion/Early withdrawal visit if visits occurs after *Week 104* or stopping criteria have been met (whichever occurs first).

[s] 6MWT to be assessed during OLE visits, starting from Week 182 (Month 42) onwards.

[t] World Health Organisation milestones to be assessed during OLE visits, starting from Week 208 (Month 48) onwards

[u] Includes head-to-chest circumference ratio from anthropometric measurements and nutritional status interview of the parent (or caregiver), including ability to swallow and level of solid food intake. A swallowing assessment will be performed at Day –1 and on Weeks 28, 52, 78, 104; and the OLE visits (see Section 4.5.8 of the study protocol).

[v] This includes SMA related surgeries and procedures.

[w] Only serious adverse events