

Official Title: A TWO PART SEAMLESS, OPEN-LABEL, MULTI-CENTER STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND EFFICACY OF RISDIPLAM (RO7034067) IN INFANTS WITH TYPE 1 SPINAL MUSCULAR ATROPHY

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STATISTICAL ANALYSIS PLAN

TITLE: A TWO-PART SEAMLESS, OPEN-LABEL, MULTI-CENTER STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND EFFICACY OF RO7034067 IN INFANTS WITH TYPE 1 SPINAL MUSCULAR ATROPHY

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STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

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STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) has been amended to incorporate the following changes:

- The sources of natural history data used to derive the performance criteria have been re-evaluated, and the performance criteria defined for the secondary endpoints have been updated ([REDACTED] and Section 4.4.2).
- The interim analysis for efficacy has been removed due to the close proximity of this analysis to the primary analysis (Section 2.4 and Section 4.8).

Additional minor changes have been made to improve clarity and consistency.

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1. **BACKGROUND**

This Statistical Analysis Plan (SAP) documents the statistical methods for summarizing and analyzing efficacy and safety data from the confirmatory (pivotal) Part 2 of Study BP39056 collected from infants with Type 1 spinal muscular atrophy (SMA). The purpose of this document is to describe the data handling rules, derivation rules, and statistical analysis methods.

The global population will include all infants enrolled during the global enrollment phase (including infants enrolled in China during that phase), and the China subpopulation will include all infants enrolled in China (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subpopulation (see Section 5 for information on the China subgroup analyses).

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

2. **STUDY DESIGN**

Study BP39056 is a seamless two-part, open-label, single-arm, multi-center clinical study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of RO7034067 in Type 1 SMA infants. The study will be conducted in two parts and each part will be followed by an open-label extension phase:

Exploratory Part 1: Part 1 is an open-label, dose escalation study in infants with Type 1 SMA aged 1 to 7 months (at time of enrollment). This exploratory part will consist of at least 8 infants and up to 24 infants (if required) to assess the safety, pharmacokinetic (PK), and pharmacodynamic (PD) profile of RO7034067 in infants and determine the dose for Part 2.

An internal monitoring committee (IMC) consisting of selected Sponsor personnel will be responsible for monitoring the safety of infants and selecting the dose for the confirmatory Part 2. The dose selected by the IMC will be confirmed by an external independent Data Monitoring Committee (iDMC).

Confirmatory Part 2: Part 2 is an open-label, single-arm study in 40 infants with Type 1 SMA aged 1 to 7 months (at time of enrollment) to assess the efficacy of RO7034067 at the dose selected in Part 1 over a 24-month treatment period, with the primary analysis performed at 12 months.

The study will progress in an operationally seamless manner from Part 1 into Part 2 after the dose selection decision has been taken. Infants from Part 1 will not be enrolled into Part 2, but all infants will be given the possibility to continue receiving RO7034067 as part of an open-label extension phase. The extension phase will include regular

monitoring of safety, tolerability, PK/PD, and exploratory efficacy of those patients enrolled in Part 1.

The duration of the study for each infant enrolled in Part 2 (not including the open-label extension phase) will be up to 25 months as follows:

- Screening: up to 30 days prior to first dose.
- Treatment period: 24 months from the start of dosing, with the primary analysis after the last infant in the global population reaches 12 months of treatment.
- After each infant completes 24-month treatment, he or she will enter an open-label extension phase.

As in Part 1, the open-label extension phase is planned to run until RO7034067 is commercially available in the country of the infants who participated or until the Sponsor ceases producing or studying RO7034067. If an infant is withdrawn from the clinical study at any time, they will be asked to participate in the follow-up period of the study as described in the Schedule of Assessments (SoA).

The analyses of this study will be structured into two parts: exploratory (Part 1) to select the dose, and confirmatory (Part 2) to evaluate the treatment effect of RO7034067. This analysis plan describes the methods that will be used for the analysis of Part 2.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in [Appendix 1](#). For additional details, see the Schedule of Assessments for Part 2 of the study in [Appendix 2](#).

2.2 OUTCOME MEASURES

2.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of infants sitting without support after 12 months of treatment as assessed by item 22 ('Sits without support for 5 seconds') of the modified Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III).

2.2.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows below. The subset of secondary endpoints that are included within the hierarchical testing approach are specified in Section [4.4.2](#).

Motor Function and Development Milestones

- Proportion of infants who achieve a score of 40 or higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at Month 12 of treatment.
- Proportion of infants who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 8 and Month 12 of treatment.

- Proportion of infants who achieve head control at Month 8, Month 12, and Month 24 of treatment (defined as a score of 3 or higher for item 12 of the CHOP-INTEND).
- Change from baseline in the total raw score of the modified BSID-III gross motor scale at Month 12 and Month 24 of treatment.
- Proportion of infants who achieve the attainment levels of the motor milestones assessed in the Hammersmith Infant Neurological Examination Module 2 (HINE-2)* at Month 8 (subset #), Month 12 and Month 24 of treatment.

*Milestones of: head control#, sitting, voluntary grasp, ability to kick#, rolling#, crawling, standing, and walking.

- Proportion of motor milestone responders as assessed by HINE-2 at Month 12 and Month 24 of treatment.
- Highest motor milestone* achieved by Month 12 and Month 24 of treatment.

*Milestones of: head control (item 9 'Controls head while upright for 15 seconds'), rolling (item 14 'Rolls from side to back'), sitting without support (primary endpoint), crawling (item 30 'Crawls on stomach'), standing (item 40 'Stands alone') and walking (item 42 'Walks alone') as assessed in the modified BSID-III gross motor scale

- Proportion of infants sitting without support for 5 seconds at Month 24 of treatment (defined as per the primary endpoint).
- Proportion of infants sitting without support for 30 seconds (defined as 'Sits without support for 30 seconds' as assessed in item 26 of the modified BSID-III gross motor scale) at Month 24 of treatment.
- Proportion of infants standing at Month 24 of treatment (defined as 'Stands alone' as assessed in item 40 of the modified BSID-III gross motor scale).
- Proportion of infants walking at Month 24 of treatment (defined as 'Walks alone' as assessed in item 42 of the modified BSID-III gross motor scale).

Survival and Ventilation-Free Survival

- Time to death or permanent ventilation (from enrollment). Permanent ventilation is defined as ≥ 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 (from enrollment).
- Proportion of infants who are alive without permanent ventilation at Month 12 and Month 24 of treatment.
- Proportion of infants who are alive at Month 12 and Month 24 of treatment.

Respiratory

- Time to permanent ventilation (from enrollment).
- Proportion of infants who are without permanent ventilation at Month 12 and Month 24 of treatment.

- Proportion of infants who achieve a reduction of at least 30 degrees in their phase angle from baseline, as measured by respiratory plethysmography (RP), at Month 12 of treatment.
- Proportion of infants who do not require invasive or non-invasive respiratory support at Month 12 and Month 24 of treatment.

Nutrition

- Proportion of infants with the ability to feed orally at Month 12 and Month 24 of treatment.

2.2.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints are as follows:

Maintenance of 12-Month Treatment Effect

- Proportion of infants who maintained sitting at Month 24 of treatment (for infants sitting at Month 12), as assessed by item 22 of the modified BSID-III gross motor scale.
- Proportion of infants who maintained (or continued to improve) their phase angle reduction at Month 24 of treatment (for infants with a phase angle reduction of at least 30 degrees from baseline at Month 12), as measured by RP.

Muscle Electrophysiology

- Proportion of infants who achieve an increase of at least 0.3mV from baseline in their compound muscle action potential (CMAP) negative peak amplitude at Month 12 and Month 24 of treatment.

Disease-Related Adverse Events

- Proportion of infants 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.
- Proportion of infants who experience at least one disease-related adverse event resulting in hospitalization by Month 12 and Month 24 of treatment.
- Number of disease-related adverse events resulting in hospitalization per patient-year at Month 12 and Month 24 of treatment.

Healthcare Utilization

- Number of hospitalizations (for any reason) per patient-year and number of nights admitted to hospital per infant at Month 12 and Month 24 of treatment.

Swallowing and Nutrition

- Proportion of infants with the ability to swallow at Month 8, Month 12, and Month 24 of treatment.

Growth Measures

- Ratio between the chest and head circumference at Month 8, Month 12, and Month 24 of treatment.
- Change from baseline in weight percentiles at Month 12 and Month 24.
- Change from baseline in length/height percentiles at Month 12 and Month 24.

Parent/Caregiver Reported Outcomes

- 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.

*Parent-proxy domains of physical abilities, growth and development, bodily pain/discomfort, temperament and moods, behavior, general health perception, parent emotional impact and parent time impact. Single item scores include overall health, change in health and family cohesion.

Clinician Reported Respiratory Function and Swallowing Ability Items

- Proportion of infants with no change or improvement in respiratory function as assessed by the clinician reported Clinical Global Impression of Change (CGI-C) at Month 12.
- Proportion of infants with no change or improvement in the ability to swallow as assessed by the clinician reported CGI-C at Month 12.

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:

- Percent change from baseline in full-length *SMN2* mRNA in blood at each time-point.
- Percent change from baseline in $\Delta 7$ *SMN2* mRNA in blood at each time-point.
- Percent change from baseline in the ratio of full-length to $\Delta 7$ *SMN2* mRNA in blood at each time-point.
- Absolute SMN protein in blood at each time-point.
- Percent 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.
- Anthropometric examination, including weight, height, head circumference and chest circumference.

2.3 DETERMINATION OF SAMPLE SIZE

The purpose of Part 2 of the study is to estimate the proportion of infants who are sitting without support at 12 months of treatment and to test whether this proportion is higher than a performance criterion set at 5%. This 5% threshold was chosen based on the natural history of the disease, typically that Type 1 SMA patients never achieve sitting without support by definition.

The target sample size is 40 infants. This sample size provides at least 90% power to test the null hypothesis $H_0: p \leq 5\%$ versus alternative hypothesis $H_a: p > 5\%$, if the true proportion of infants who would sit on treatment is 20%. 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 is 5 out of 40 for a statistically significant result. If in Part 2, 5 out of 40 infants sit, the lower limit of the two-sided 90% Clopper-Pearson (exact) confidence interval (CI) would be above 5%.

The power and minimum number of infants needed to be observed sitting for a statistically significant result (the critical value) if the number of infants enrolled in Part 2 is less than or greater than 40 are presented below:

| Number of infants enrolled in Part 2 | Critical value | Power (%) |
|--------------------------------------|----------------|-------------|
| 35 | 5 | 85.7 |
| 36 | 5 | 87.3 |
| 37 | 5 | 88.8 |
| 38 | 5 | 90.1 |
| 39 | 5 | 91.3 |
| 40 | 5 | 92.4 |
| 41 | 6 | 85.6 |
| 42 | 6 | 87.1 |
| 43 | 6 | 88.5 |
| 44 | 6 | 89.8 |
| 45 | 6 | 91.0 |

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

Sample Size for the China Extension Period

Part 2 of this study will initially enroll 40 infants across all sites in a global enrollment phase. After completion of the global enrollment phase, additional infants may be enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the

██████████ in an extended China enrollment phase to ensure a total of approximately 10 infants in a China subpopulation. With a sample size of 10 the probability of observing at least 1 infant sitting is 89% if the true proportion of infants who would sit on treatment is 20%.

The global population will include all infants enrolled during the global enrollment phase (including infants enrolled in China during that phase), and the China subpopulation will include all infants enrolled in China (i.e., during both the global enrollment phase and the extended China enrollment phase).

2.4 ANALYSIS TIMING

The primary analysis will be performed after the last infant in the global population has completed 12 months of treatment, or has been withdrawn from the study (and all other infants in the global population have either completed 12 months of treatment or have been withdrawn from the study). 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 infant enrolled into Part 2 during the global enrollment phase has either completed

his or her 12-month assessment or has been withdrawn (and all other infants in the global population have either completed the 12-month assessment or have been withdrawn from the study). 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 infant enrolled in Part 2 of the study during the global enrollment phase. The clinical cutoff date will be the same for all infants, 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 from the global population post Month 12 will be reported. All available safety data from infants enrolled in Part 2 of the study will also be reported.

A database lock for the analyses of the 24-month secondary and exploratory endpoints will occur once the last infant enrolled into Part 2 during the global enrollment phase has either completed his or her 24-month assessment or has been withdrawn (and all other infants in the global population have either completed the 24-month assessment or have been withdrawn from the study). 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 infant enrolled in Part 2 of the study during the global enrollment phase. At the time of the Month 24 analysis, all available interim efficacy data from the global population post Month 24 collected as part of the open-label extension period will be reported. All available safety data will also be reported.

Following the primary analysis, subsequent locks of the database may occur in order to perform safety analyses of the data at further time-points during the study. The final database lock will occur at study end (i.e., last patient, last observation).

In addition, a futility assessment for efficacy will be conducted after the first 14 infants enrolled into the confirmatory Part 2 of the study during the global enrollment phase have reached 12 months of treatment or have been withdrawn.

Analysis Timing for the China Subgroup Analysis

The China subgroup analyses (including infants from both the global enrollment phase and the extended China enrollment phase, if required) will be performed after the last infant in the China subpopulation has completed 12 (or 24) months of treatment, or has been withdrawn from the study (and all other infants in the China subpopulation have either completed 12 [or 24] months of treatment or have been withdrawn from the study), or at the time of the global primary (or Month 24) analysis, respectively, whichever is later.

Once at least 1 infant in the China subpopulation (from either the global enrollment phase or the extended China enrollment phase) has met the primary endpoint of sitting without support at Month 12 (as assessed by the independent central readers), and at least 5 infants in the global population have met the primary endpoint, the objective for the China subpopulation will be considered achieved. All 10 infants in the China

subpopulation will continue to receive 12 months of treatment in order to provide an unbiased estimate of the proportion of infants sitting without support at Month 12.

3. STUDY CONDUCT

3.1 RANDOMIZATION

Part 2 of Study BP39056 is a single arm, open-label study, and all infants will receive RO7034067 at the dose (target exposure level) selected in Part 1.

3.2 INDEPENDENT REVIEW FACILITY

3.2.1 Modified BSID-III Gross Motor Scale

The evaluation of the modified BSID-III gross motor scale, including sitting, 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). The following items of the modified BSID-III gross motor scale will be video recorded:

- Sitting items: items 16, 19, 22, 26, 27, and 28
- Crawling and kneeling items: items 30, 31, 32, and 34
- Standing items: items 29, 33, 35, 36, 40, 51, 52, 60, 61, 69, and 70
- Walking items: items 37, 38, 42, 43, 48, 53, 56, 61, 63, and 71

The two independent central readers will review all recorded items of the modified BSID-III assessment, but will only complete scoring of items 22, 26, 30, 40, and 42. The assessment of 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 other scored items. The role and process of the reading center will be written in a separate charter.

The scores provided by the two independent readers will be evaluated to determine concordance in the five scored items of the gross motor scale. These include: item 22: sitting without support for 5 seconds (primary endpoint, defined as 'Sits without support for 5 seconds'), item 26: sitting without support for 30 seconds ('Sits without support for 30 seconds'), item 30: crawling ('Crawls on stomach'), item 40: standing ('Stands alone'), and item 42: walking ('Walks alone').

For the primary endpoint of sitting without support for 5 seconds and the other items to be classified as confirmed, both independent central readers should classify the milestone (i.e., item) to have been achieved by the infant. If the independent central readers both classify the milestone as not being achieved, 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, then both central readers will be asked to re-score the infant. 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 infant, then the motor milestone will be classified as not confirmed.

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

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

N/A= Not applicable

If ‘Cannot Test (CNT)’ is recorded by one of the independent central readers (and the other central reader provides a score), or if the reasons for ‘CNT’ are discordant, then both central readers will be asked to re-score the infant. 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 upon re-score the two central readers are not in agreement, or if at least one ‘CNT’ is recorded, then the motor milestone will be classified as not confirmed.

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

[REDACTED] 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 will be written 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 infants 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 will be written in a separate charter.

3.3 DATA MONITORING

An external iDMC will be established to monitor patient safety during Part 2 of the study. The iDMC will meet to review data from Part 1 and confirm the dose selection decision of the IMC. The iDMC will provide a recommendation to the Sponsor whether the study can continue as planned (i.e., that the study can move into Part 2 with the selected dose from Part 1 as recommended by the IMC). The final decision based on the iDMC recommendation will be made by the Sponsor. After the dose selection decision, the IMC will hand over responsibility for reviewing patient safety to the iDMC. The iDMC from this time-point on will review the data of all ongoing Part 1 patients (who will continue to be treated in the extension phase) and all Part 2 patients.

The iDMC will meet on a regular basis (approximately every 3 months once the dose selection is confirmed) over the course of Part 2 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 RO7034067.
- 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 an independent Data Coordinating Center (iDCC).

The interim analyses for efficacy and futility during Part 2 of the study will be performed by the Sponsor and 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 RO7034067 in the Type 1 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 Part 1 and Part 2 in order to be able to adjust the dose of individual infants if required, ensuring not to exceed the *mean* exposure cap, and to continue treatment at the targeted exposure level, as infants grow and their body systems mature. The iDMC will be informed of any individual dose adjustments required at the next scheduled iDMC meeting.

The roles, responsibilities, membership, scope of activities, time of meetings, and communication plan for the iDMC were documented in the Charter prior to the initiation of Part 1 of the study. The external iDMC will be chaired by a medically qualified individual with experience with 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 FOR THE GLOBAL POPULATION

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat Population

The intent-to-treat (ITT) population is defined as all infants enrolled in Part 2 of the study, regardless of whether they received treatment or not. The ITT population will be the primary analysis population for all efficacy analyses.

4.1.2 Pharmacokinetic-Evaluable Population

All infants with at least one time-point with a measurable concentration will be included in the PK-evaluable population. Infants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol or if data are unavailable or incomplete which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion.

4.1.3 Safety Population

All infants who receive at least one dose of study medication (RO7034067) will be included in the safety population.

4.2 ANALYSIS OF STUDY CONDUCT

4.2.1 Study Enrollment

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

The number of infants 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 infants with major protocol deviations will be summarized by protocol deviation criterion.

4.2.3 Patient Disposition

The number of infants who were enrolled, discontinued, continuing treatment at the time of the analysis or have completed the study (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 infants entering the open-label extension will also be summarized. The number of infants discontinuing between 0 and 12 months, between 12 and 24 months, and during the open-label extension period, and the reasons for discontinuation, will be summarized.

In addition, the number of infants entering and discontinuing from the safety follow-up period, and the reasons for discontinuation, will be summarized.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Demographic and other baseline characteristics will be summarized for the ITT population using descriptive statistics, means, standard deviations, medians, interquartile ranges (IQRs) and ranges for continuous variables and number and percentages for categorical variables, as appropriate.

Baseline will be defined as the last measurement recorded prior to or on the day of first study drug administration. 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 SMA related 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 (including the number and percentage of infants ≤ 5 months old and > 5 months old), sex, race, ethnicity, country, 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 infants enrolled in each of the following geographical regions: Europe, USA or Canada, 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 an infant's growth over time and to monitor his or her growth in relation to a reference population of healthy children. An infant'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 infant's value deviated from the median of the reference population. Because of the relationship between an infant's z-score and percentile on the growth chart, a standard normal distribution table can be used to obtain an infant'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, and a scatterplot of individual percentiles versus age (at enrollment) will be presented for weight-for-age. The number and percentage of infants in the 3rd, 5th, 10th, 25th, 50th and $> 50^{\text{th}}$ 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.

4.3.2 SMA History and Disease Characteristics

Summary statistics will be presented for the following parameters: *SMN2* copy number, age at onset of symptoms, age at diagnosis, initial SMA symptoms, tracheostomy (yes/no), time between first treatment and onset of symptoms (including the number and percentage of infants with time ≤ 3 months and > 3 months), baseline CHOP-INTEND, modified BSID-III gross motor scale and HINE-2 scores, and baseline CMAP amplitude values (including the number and percentage of infants with values $\leq 1\text{mV}$ and $> 1\text{mV}$).

The current level of motor function, motor functions achieved and maintained (including age function was achieved and age function was lost, if applicable) and highest motor function achieved will also be summarized.

The level of respiratory support required by the infants at baseline will be summarized. The number and percentage of infants who: do not require invasive or non-invasive

pulmonary care, require cough assistance (used daily for therapy or with an illness) or bilevel positive airway pressure (BiPAP) support (< 16 hours per day or \geq 16 hours per day) and have ventilation being provided prophylactically (including type of ventilation: awake assisted ventilation, night-time assisted ventilation, > 16 hours assisted ventilation or airway clearance through cough assistance, if applicable) will be presented. The number and percentage of infants who have been receiving BiPAP support for \geq 16 hours per day for > 21 consecutive days or have been intubated for > 21 consecutive days will also be presented.

The primary food intake type will also be summarized. Food intake type includes solid food, modified oral food intake, nasogastric food intake, 100% gastrostomy tube fed, oral fluid (milk) food intake, or mixed (fluid/puréed food) oral food intake. The number and percentage of infants with the ability to swallow will be presented, and the age the ability to swallow was lost or regained (if applicable) will be summarized. The number and percentage of infants fed orally, via a feeding tube, or via a combination of oral and tube feeding, and the number and percentage of infants who can swallow water, nectar (or similar), rice pudding (or similar), purées, and solid food will also be presented.

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 infants with previous conditions (including conditions with an onset date within 30 days of the screening visit) and conditions concurrent at baseline 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 infants with at least one condition and the total number of conditions will also be presented.

Previous conditions (conditions with an end date before the first dose date) and conditions concurrent at baseline (conditions that start prior to the first dose date and have no end date or an end date after the first dose date) 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 Genentech Drug Thesaurus. All analyses will be performed using these preferred terms and medication classes.

The number and percentage of infants taking each medication will be presented. This includes all medications with a start date within 30 days of the screening visit. Multiple

occurrences of the same medication in an individual patient (i.e., same coded term) will be counted only once. The overall number of infants 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 up to the date of study withdrawal/completion) will be summarized separately. Medications with a start date from 1 day up to 52 weeks after study withdrawal/completion will also be summarized separately.

Treatments given for prophylaxis and 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 infants who had any relevant SMA related surgeries or procedures will be presented. This will include all surgeries or procedures performed within 30 days of the screening visit. Multiple occurrences of the same procedure in an individual patient (i.e., same coded term) will be counted only once. The overall number of infants who have undergone at least one procedure and the total number of procedures reported will also be presented.

Surgeries or procedures performed prior to the first dose date and those performed on or after the first dose date up to the date of study withdrawal/completion will be summarized separately. Surgeries or procedures performed from 1 day up to 52 weeks after study withdrawal/completion will also be summarized separately.

4.4 EFFICACY ANALYSIS

The ITT population will be the primary analysis population for all efficacy analyses. The confirmatory efficacy analyses will only include data from infants enrolled into Part 2 of the study. For consistency with the analysis methods described for the anthropometric measurements in Section 4.6.8, the analyses for weight-for-age and length/height-for-age percentiles will be based on the safety population.

Results from Part 2 will be compared to, and put into context with, natural history data from untreated Type 1 SMA infants. Full details of the available sources to be used as the external control and the benchmarks/performance criteria to be used in the analysis

(e.g., the actual null hypothesis response rate to be tested for secondary endpoints) are provided in [REDACTED]

A time window will be created for each study visit, starting midway between that visit and the previous study visit, and ending midway between that visit and the next study visit (if applicable). Post-baseline efficacy assessments, including assessments performed at an unscheduled visit or early discontinuation visit, will be assigned to a scheduled study visit based on these time windows, even if the assessment is not scheduled to be performed at that visit. 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, except for the growth measures, where the last assessment will be used for summary of the data for consistency with the methods described for the anthropometric measurements in Section 4.6.

4.4.1 Primary Efficacy Endpoint

The primary endpoint for the confirmatory Part 2 of the study is the proportion of infants 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 modified BSID-III gross motor scale. As per the scoring manual, item 22 will not be considered achieved if the infant sits alone for less than 5 seconds before losing balance and falling over, or if the infant uses his or her arms to prop him- or herself up. The assessment of the independent central readers will be used for the primary analysis (as described in Section 3.2). Both central readers should classify the milestone to have been achieved for the endpoint to be confirmed. Infants who do not achieve sitting, or have not maintained sitting achieved earlier, or have been withdrawn, or died, will be classified as non-responders (i.e., non-sitters) for the primary analysis. Infants with a missing assessment at Month 12 will also be classified as non-responders.

The natural history of the disease is well-defined; Type 1 SMA infants never achieve sitting (Cobben et al., 2008; Finkel et al., 2014; [REDACTED]). This natural history can therefore be used to define the performance criterion for success (i.e., a threshold of achievement for the RO7034067-treated infants to be assessed against within this study). The pre-defined performance criterion for the primary endpoint will be 5%.

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

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

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 infants 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 presented.

The results of the primary endpoint will also be compared to results from similar cohorts of untreated Type 1 SMA infants obtained from real world data sources/natural history studies and other clinical trials. The proportion of infants sitting without support in each of these sources will be reported together with the associated 60%, 80%, and 90% CIs (██████████).

4.4.2 Secondary Efficacy Endpoints

All secondary endpoints (except for time-to-event) will be summarized by time-point for the ITT population using descriptive statistics. At Month 12 and Month 24 of treatment, two-sided 90% CIs will also be presented, as appropriate.

The results of the secondary endpoints will be compared to, and put into context with, results of similar cohorts of untreated Type 1 SMA infants constructed from real world data sources/natural history studies and other clinical trials, when data for the endpoint is available. ██████████

██████████ When publicly available real world patient level data exists, summary data was generated from a cohort of patients defined using the study inclusion/exclusion criteria, whenever possible.

The historical control data available to date was used to derive a numerical value to serve as a pre-defined benchmark (i.e., an objective performance criteria or performance goal) against which to assess the efficacy of treatment. If multiple sources of data were available for a secondary endpoint, the cohort with the baseline characteristics most similar to those targeted by the study inclusion and exclusion criteria was used (██████████). The benchmark is based on the associated upper limit of the 90% CI from the historical data. When a pre-defined benchmark could be determined for the secondary endpoint, hypothesis testing will be performed.

The hypothesis to be tested is that the treatment response rate (p) is:

$H_0: p \leq \text{pre-defined benchmark (null)}$ versus $H_a: p > \text{benchmark (alternative)}$.

If the one-sided p-value is $\leq 5\%$ (nominal) then the null hypothesis will be rejected.

To control for multiplicity across the different endpoints, a hierarchical testing approach will be implemented.

The first secondary efficacy endpoint of the proportion of infants who achieve a score of 40 or higher in the CHOP-INTEND at Month 12 will be tested if and only if the primary endpoint has reached the 5% significant level (i.e., $p\text{-value} \leq 0.05$). Other secondary endpoints will be tested at a 5% significance level according to the following hierarchy, as long as the $p\text{-value}$ is ≤ 0.05 for endpoints higher in the hierarchy:

- Proportion of infants who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12.
- Proportion of motor milestone responders as assessed by the HINE-2 at Month 12.
- Proportion of infants who are alive without permanent ventilation at Month 12.
- Proportion of infants sitting without support for 30 seconds (defined as 'Sits without support for 30 seconds' as assessed in item 26 of the modified BSID-III gross motor scale) at Month 24.
- Proportion of infants standing at Month 24 (defined as 'Stands alone' as assessed in item 40 of the modified BSID-III gross motor scale).
- Proportion of infants walking at Month 24 (defined as 'Walks alone' as assessed in item 42 of the modified BSID-III gross motor scale).

Any other endpoints for which hypothesis testing will be performed will be simultaneously tested at the 5% significance level without adjustment for multiplicity, as they are considered to provide supportive information.

The secondary efficacy endpoints in Part 2 are as follows:

4.4.2.1 Motor Function and Development Milestones

4.4.2.1.1 CHOP-INTEND

The number and percentage of infants who achieve a score of 40 or higher in the CHOP-INTEND at Month 12 will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who do not achieve a score of at least 40, or have not maintained an earlier achieved score of at least 40, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing CHOP-INTEND assessment at Month 12 will also be classified as non-responders.

The CHOP-INTEND consists of 16 items scored from 0 to 4, with a higher score indicating better motor skills. Both the left and right sides are scored and 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. If an individual item is missing or 'Cannot Test (CNT)' is recorded, the item score will be set to 0.

[REDACTED]
[REDACTED] An exact binomial test will be performed. The hypothesis to be tested is that the proportion of infants who achieve a score of 40 or higher in the CHOP-INTEND on treatment (p) is:

$H_0: p \leq 17\%$ (null) versus $H_a: p > 17\%$ (alternative).

If the one-sided p -value is $\leq 5\%$, then the null hypothesis will be rejected.

Bar graphs displaying the proportion of infants with each CHOP-INTEND score and change from baseline score at Month 12 and Month 24 will be presented. Each graph will present the proportion of infants who were withdrawn from the study and the proportion of infants who had died by Month 12 and Month 24. A supportive summary table will also be produced.

The number and percentage of infants who achieve a score of 40 or higher at each time-point and corresponding 90% CIs will be presented. The same responder/non-responder definition described above will be used for these analyses.

The CHOP-INTEND score and change from baseline score at each time-point will also be summarized using descriptive statistics. The mean absolute scores and change from baseline scores and corresponding 90% CIs over time will also be presented graphically. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

The number and percentage of infants who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 8 and Month 12 (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who do not achieve an increase of at least 4 points, or have not maintained an earlier increase of at least 4 points, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing CHOP-INTEND assessment at a visit will also be classified as non-responders.

[REDACTED]
[REDACTED] An exact binomial test will be performed.
The hypothesis to be tested is that the proportion of infants who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline on treatment (p) is:

$H_0: p \leq 17\%$ (null) versus $H_a: p > 17\%$ (alternative).

If the one-sided p -value is $\leq 5\%$, then the null hypothesis will be rejected.

Head Control

The number and percentage of infants who achieve head control (defined by a score of 3 or higher for item 12 of the CHOP-INTEND) at Month 8, Month 12, and Month 24 (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who do not achieve a score of at least 3 for item 12, or have not maintained an earlier achieved score of at least 3, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing assessment at a visit will also be classified as non-responders.

4.4.2.1.2 Modified BSID-III Gross Motor Scale

Further Motor Milestones

The number and percentage of infants (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 modified BSID-III gross motor scale), (3) standing (defined as 'Stands alone' as assessed in item 40 of the modified BSID-III gross motor scale), and (4) walking (defined as 'Walks alone' as assessed in item 42 of the modified BSID-III gross motor scale) at Month 24 will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who do not achieve the milestone, or have not maintained this milestone achieved earlier, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing assessment at Month 24 will also be classified as non-responders.

The proportion of infants 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 (Section 4.4.1) testing the same null hypothesis that the proportion of infants who achieve the motor milestone (p) is $\leq 5\%$ (null) versus $p > 5\%$ (alternative). If the one-sided p-value is $\leq 5\%$, then the null hypothesis will be rejected.

The assessment of the independent central readers will be used for the analysis of these further motor milestones (as described in Section 3.2). Both central readers should classify the milestone to have been achieved for the endpoint to be confirmed.

The number and percentage of infants who achieve each of these motor milestones at each time-point and corresponding 90% CIs will be presented. The same responder/non-responder definitions described above will be used for these analyses.

The number and percentage of infants achieving other motor milestones, including items 3 ('Lifts head'), 4 ('Controls head while upright for 3 seconds'), 9 ('Controls head while upright for 15 seconds'), 14 ('Rolls from side to back'), 20 ('Rolls from back to sides'), 25 ('Rolls from back to stomach'), 16 ('Sits with support briefly'), 19 ('Sits with support for 30

seconds') and 30 ('Crawls on stomach'), at each time-point will be presented. The number and percentage of infants with a missing BSID-III assessment at a visit (including withdrawals) and the number and percentage of infants who had died by that visit will also be presented. Percentages will be based on the ITT population.

Highest Motor Milestone

The highest motor milestone achieved by the infant at any visit during the first 12 months (and first 24 months) of treatment will be summarized using numbers and percentages based on the ITT population. This is regardless of the maintenance of effect or subsequent survival status of the infant. Milestones include head control (item 9 'Controls head while upright for 15 seconds'), rolling (item 14 'Rolls from side to back'), sitting without support for 5 seconds (primary endpoint), crawling (item 30 'Crawls on stomach'), standing (item 40 'Stands alone') and walking (item 42 'Walks alone') as assessed in the modified BSID-III gross motor scale.

Total Raw Score

Considering the population of this study, the BSID-III gross motor scale will be administered in a modified way compared to the standard administration described in the original BSID-III manual. Infants' age will not be used as the starting criteria for testing, the order of item administration will be changed, and the discontinuation rule will not be applied. This modified way of administration has been discussed and agreed with the scale developers as acceptable for the study objectives and patient population. As a result, only raw scores will be calculated in this study; scaled (transformed) scores will not be used.

The gross motor scale consists of 72 items scored at 0 (unable to perform the activity) or 1 (criteria for item achieved). The total raw score is calculated by summing the item scores to give a maximum possible score of 72. If an individual item is missing or 'Cannot Test (CNT)' is recorded, the item score will be set to 0.

The total raw score of the modified BSID-III gross motor scale and change from baseline score at Month 12 and Month 24 (and all other time-points) will be summarized using descriptive statistics. These scores will be based on the assessment of the site clinical evaluator. The mean absolute scores and change from baseline scores and corresponding 90% CIs over time will also be presented graphically. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

In addition, bar graphs displaying the proportion of infants with different levels of change in the total raw score from baseline to Month 12 and Month 24 will be presented. Each graph will present the proportion of infants who were withdrawn from the study and the

proportion of infants who had died by Month 12 and Month 24. A supportive summary table will also be produced.

4.4.2.1.3 HINE-2

Motor Milestones

The number and percentage of infants within each attainment response category of the HINE-2 motor milestones at Month 8 (subset # only), Month 12 and Month 24 (and all other time-points) will be presented. 'Cannot test (CNT)' will be included as a separate response category for each milestone. Milestones include head control#, sitting, voluntary grasp, ability to kick#, rolling#, crawling, standing, and walking. The number and percentage of infants with a missing HINE-2 assessment at a visit (including withdrawals) and the number and percentage of infants who had died by that visit will also be presented. Percentages will be based on the ITT population.

Motor Milestone Responders

The number and percentage of motor milestone responders (as assessed by HINE-2) at Month 12 and Month 24 will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. For the responder definition, an improvement in a motor milestone is defined as at least a 2-point increase in ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening is similarly defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing, or walking. Voluntary grasp is excluded from the definition. An infant will be classified as a responder if more motor milestones show improvement than show worsening; infants who die or withdraw will be classified as non-responders. Infants with a totally missing HINE-2 assessment at Month 12 or Month 24 will also be classified as non-responders.

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 development. The total score is calculated by summing the item scores to give a maximum possible score of 26. If an individual item is missing or 'Cannot Test (CNT)' is recorded, the item score will be set to 0.

[REDACTED]

[REDACTED] An exact binomial test will be performed.
The hypothesis to be tested is that the proportion of motor milestone responders on treatment (p) is:

$$H_0: p \leq 12\% \text{ (null) versus } H_a: p > 12\% \text{ (alternative).}$$

If the one-sided p-value is $\leq 5\%$, then the null hypothesis will be rejected.

Bar graphs displaying the proportion of infants with different levels of change in the HINE-2 score from baseline to Month 12 and Month 24 will be presented. Each graph will present the proportion of infants who were withdrawn from the study and the proportion of infants who had died by Month 12 and Month 24. A supportive summary table will also be produced.

The number and percentage of motor milestone responders at each time-point and corresponding 90% CIs will be presented. The same responder/non-responder definition described above will be used for these analyses.

The total score and change from baseline score at each time-point will also be summarized using descriptive statistics. The mean absolute scores and change from baseline scores and corresponding 90% CIs over time will also be presented graphically. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

4.4.2.2 Survival and Ventilation-Free Survival

4.4.2.2.1 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., 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 infant 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 infant 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 electronic case report form (eCRF). Non-invasive ventilation use during the study will be collected via a patient diary.

The median time to ventilation-free survival (and 90% CI) and the proportion of infants who are surviving 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 infants surviving without permanent ventilation at Month 12 and Month 24 will be presented. CIs will be calculated using the complimentary 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. Infants with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be alive and without permanent ventilation. Individual listings will also be presented 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 infant was event-free within that month, in which case the date the infant was last known to be event-free within that month will be used as the event date. If the month is missing, the date the infant was last known to be event-free will be used.

Infants who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. For infants who have been withdrawn from the study and entered safety follow-up, all events reported from the date of enrollment up to the date of withdrawal will be included in the analysis. The patient diary will not be available to provide information about the use of non-invasive ventilation once an infant has been withdrawn from the study and is no longer receiving study drug. If an infant 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 until the outcome of the endpoint is confirmed.

[REDACTED]
[REDACTED] For a fixed time-point, $\log(-\log\{S(t)\})$ is asymptotically normally distributed, so a Z-test will be performed. The hypothesis to be tested is that the proportion of infants who are alive without permanent ventilation on treatment (p) is:

$H_0: p \leq 42\%$ (null) versus $H_a: p > 42\%$ (alternative).

The test statistic $Z = [\log(-\log\{p_0\}) - \log(-\log\{\widehat{S}(t^*)\})] / \text{se}[\log(-\log\{\widehat{S}(t^*)\})]$, where p_0 is the proportion under the null hypothesis (42%), t^* is the time-point of interest (12 months) and $\text{se}[\log(-\log\{\widehat{S}(t^*)\})]$ is the standard error of $\log(-\log\{\widehat{S}(t^*)\})$. If the one-sided p-value is $\leq 5\%$, then the null hypothesis will be rejected.

4.4.2.2.2 Survival

Time-to-death will be presented graphically using Kaplan-Meier curves. The median time to death (and 90% CI) and the proportion of infants 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 infants 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. Infants with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be alive.

Infants who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. For infants who have been withdrawn from the study and entered safety follow-up, all events reported from the date of enrollment up to the date of withdrawal will be included in the analysis.

[REDACTED]
[REDACTED] A Z-test will be performed.
The hypothesis to be tested is that the proportion of infants who are alive on treatment (p) is:

$H_0: p \leq 60\%$ (null) versus $H_a: p > 60\%$ (alternative).

If the one-sided p-value is $\leq 5\%$, then the null hypothesis will be rejected.

4.4.2.3 Respiratory

4.4.2.3.1 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 infants 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 infants 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. Infants with

no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without permanent ventilation.

Infants who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. For infants who have been withdrawn from the study and entered safety follow-up, all events reported from the date of enrollment up to the date of withdrawal will be included in the analysis.

[REDACTED]

[REDACTED] A Z-test will be performed. The hypothesis to be tested is that the proportion of infants who are ventilation-free on treatment (p) is:

$$H_0: p \leq 89\% \text{ (null) versus } H_a: p > 89\% \text{ (alternative).}$$

If the one-sided p-value is $\leq 5\%$, then the null hypothesis will be rejected.

4.4.2.3.2 Respiratory Plethysmography

The number and percentage of infants who achieve a reduction of at least 30 degrees in their phase angle from baseline, as measured by RP, at Month 12 will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who do not achieve a reduction of at least 30 degrees, or have not maintained this level of reduction if achieved earlier, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing assessment at Month 12 will also be classified as non-responders. Two measurements will be taken at baseline to establish test-retest reliability data. The first of these two planned measurements will be used for all analyses. If only one measurement is available at baseline, this measurement will be used.

The number and percentage of infants who achieve a reduction of at least 30 degrees in their phase angle from baseline at each time-point and corresponding 90% CIs will be presented. The same responder/non-responder definition described above will be used for these analyses.

The phase angle and change from baseline values at each time-point will be summarized using descriptive statistics. The rib cage contribution to inspiratory volume, respiratory rate, peak expiratory flow and labored breathing index, and change from baseline values at each time-point will also be summarized. 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. If there are fewer than 8 valid breaths for the first baseline measurement, the second measurement will be used, if available. The mean absolute phase angles and change from baseline phase

angles and corresponding 90% CIs over time will also be presented graphically. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

4.4.2.3.3 Level of Respiratory Support

The number and percentage of infants who do not require invasive or non-invasive respiratory support at Month 12 and Month 24 (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who have not maintained this outcome if achieved earlier, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing assessment at Month 12 or Month 24 will also be classified as non-responders.

The number and percentage of infants 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 have ventilation provided prophylactically (including type of ventilation, if applicable) at each time-point will be presented. The number and percentage of infants with a missing assessment at a visit (including withdrawals) and the number and percentage of infants who had died by that visit will also be presented. Percentages will be based on the ITT population.

4.4.2.4 Nutrition

The number and percentage of infants with the ability to feed orally ('oral' or 'combination of oral and tube feeding') at Month 12 and Month 24 (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who have not maintained the ability to feed orally if achieved earlier, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing assessment at a visit will also be classified as non-responders.

The number and percentage of infants fed orally, via a feeding tube, or via a combination of oral and tube feeding at each time-point will be presented. The number and percentage of infants with a missing assessment at a visit (including withdrawals) and the number and percentage of infants who had died by that visit will also be presented. Percentages will be based on the ITT population. The number and percentage of infants who have experienced coughing/choking during or after eating/drinking will also be presented. For infants fed via a combination of oral and tube feeding, the percentage of feedings delivered through the tube and the change from baseline value will be summarized at each time-point.

4.4.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints in Part 2 are as follows:

4.4.3.1 Maintenance of Treatment Effect

The number and percentage of infants who maintained sitting without support at Month 24 (for infants sitting without support at Month 12, defined as per the primary endpoint) will be presented. Infants who have not maintained sitting, or have been

withdrawn, or died, will be classified as non-responders (i.e., not maintained sitting) for the analysis. Infants with a missing assessment at Month 24 will also be classified as non-responders. The assessment of the independent central readers will be used for this analysis (as described in Section 3.2). Both central readers should classify the milestone to have been achieved for the endpoint to be confirmed.

The number and percentage of infants who maintained (or continued to improve) their phase angle reduction, as measured by RP, at Month 24 (for infants with a phase angle reduction of at least 30 degrees from baseline at Month 12) will also be presented. Infants who have not maintained a reduction of at least 30 degrees, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing RP assessment at Month 24 will also be classified as non-responders.

4.4.3.2 Muscle Electrophysiology

The number and percentage of infants who achieve an increase of at least 0.3mV from baseline in their CMAP negative peak amplitude at Month 12 and Month 24 will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who do not achieve an increase of at least 0.3mV, or have not maintained this improvement if achieved earlier, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing assessment at Month 12 or Month 24 will also be classified as non-responders.

[REDACTED]

An exact binomial test will be performed. The hypothesis to be tested is that the proportion who achieve an increase of at least 0.3mV from baseline in their CMAP negative peak amplitude on treatment (p) is:

$$H_0: p \leq 18\% \text{ (null) versus } H_a: p > 18\% \text{ (alternative).}$$

If the one-sided p -value is $\leq 5\%$, then the null hypothesis will be rejected.

The number and percentage of infants who achieve an increase of at least 0.3mV from baseline in their CMAP negative peak amplitude at each time-point and corresponding 90% CIs will be presented. The same responder/non-responder definition described above will be used for these analyses.

The CMAP negative peak amplitude and area, and change from baseline values at each time-point will also be summarized using descriptive statistics. In addition, the mean absolute CMAP negative peak amplitudes and change from baseline amplitudes and corresponding 90% CIs over time will be presented graphically. Scatterplots of the CMAP negative peak amplitude versus age (at enrollment) and the time between first treatment and onset of symptoms at Month 12 and Month 24 will be presented. All

observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

4.4.3.3 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 terms to the AE dataset. 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. The lowest level terms included in each basket, coded using MedDRA version 20.0, are presented in

██████████ These baskets will be updated twice a year due to MedDRA version upgrades.

Note: the same lowest level 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 infants who experience at least one disease-related AE by Month 12 and Month 24 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 summaries of AE incidences, infants 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 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 {study withdrawal or completion of 12 (or 24) months of treatment}

The number and percentage of infants who experience at least one disease-related AE resulting in hospitalization by Month 12 and Month 24 and corresponding 90% Clopper-Pearson (exact) CIs will be presented overall and by medical concept. The number of disease-related AEs resulting in hospitalization per patient-year at Month 12 and Month 24 and corresponding exact 90% CIs will also be presented overall and by medical concept.

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

4.4.3.4 Healthcare Utilization

The number of hospitalizations (for any reason) per patient-year and corresponding exact 90% CIs, and the total number of hospitalizations at Month 12 and Month 24 will be presented. The number of nights admitted to hospital per infant at Month 12 and Month 24 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) / 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 {study withdrawal or completion of 12 (or 24) months of treatment}

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

4.4.3.5 Swallowing and Nutrition

The number and percentage of infants with the ability to swallow (liquid or any food type) at Month 8, Month 12, and Month 24 (and all other time-points) will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who have not maintained the ability to swallow, or have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing assessment at a visit will also be classified as non-responders.

A shift table comparing the status of each infant at baseline (able to swallow, unable to swallow, missing) to each time-point post baseline (able to swallow, unable to swallow, missing [including deaths]) will be presented.

Time-to-loss of swallowing (for infants with the ability to swallow at baseline) will be presented graphically using Kaplan-Meier curves. The median time to loss of swallowing (and 90% CI) and the proportion of infants with the ability to swallow at Month 12 and Month 24 will be estimated using Kaplan-Meier methodology, when

possible. Ninety percent CIs for the proportion of infants with the ability to swallow at Month 12 and Month 24 will also be presented.

Time-to-loss of swallowing is defined as the time in months from the date of enrollment until the date of loss of swallowing. Infants with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be event-free.

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 infant was able to swallow within that month, in which case the date of the last assessment within that month will be used. If the month is missing, the date the infant was last known to be able to swallow will be used.

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

The primary food intake type at each time-point will be summarized using numbers and percentages. The number and percentage of infants 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.

In each summary table, the number and percentage of infants with a missing assessment at a visit (including withdrawals) and the number and percentage of infants who had died by that visit will be presented. Percentages will be based on the ITT population.

4.4.3.6 Growth Measures

The ratio between the chest and head circumference at Month 8, Month 12, and Month 24 will be summarized. The chest to head circumference ratio and change from baseline ratio at each time-point will also be summarized. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

The change from baseline in the weight-for-age and length/height-for-age percentiles at Month 12 and Month 24 will be summarized. Actual values and change from baseline values at each time-point will also be summarized. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed. For consistency with the analysis methods described for the anthropometric measurements in Section 4.6.8, these analyses will be based on the safety population.

4.4.3.7 Parent/Caregiver Reported Outcomes

The total score and change from baseline score in the ITQOL-SF47 domains and single *item scores* at Month 12 and Month 24 (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.

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 levels (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, scale scores will not be calculated if more than half of the items within a scale are missing. The transformed score is calculated as:

$$\text{Transformed raw score} = \frac{(\text{actual raw score} - \text{lowest possible raw score})}{\text{possible raw score range}} \times 100$$

The 'actual raw score' is the mean of the item responses in a scale (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.

Behavior Scales and Change in Health items are not appropriate for infants younger than 12 months of age, so should not be assessed at the baseline visit (the maximum age at enrollment is 7 months). Only summary scores will be presented for these domains.

In addition, bar graphs displaying the proportion of infants with different levels of change in the ITQOL-SF47 domains from baseline to Month 12 and Month 24 will be presented. Each graph will present the proportion of infants who were withdrawn from the study and the proportion of infants who had died by Month 12 and Month 24. A supportive summary table will also be produced.

4.4.3.8 Parent/Caregiver Reported Motor Milestones

The number and percentage of infants who experience any significant life events (loss or achievement of the following: 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, other) by Month 12 and Month 24 will be presented. This will be based on the report from the parent/caregiver. The number and percentage of infants who were withdrawn from the study and the number and percentage of infants who had died by

Month 12 and Month 24 will be presented. Percentages will be based on the ITT population.

Infants' age at the attainment of a new motor milestone (or at the loss of a motor milestone gained during or before the study) will also 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).

4.4.3.9 Clinician Reported Respiratory Function and Swallowing Ability Items

A range of clinical domain level items will be completed by a clinician in order to capture changes in an infant's respiratory function and ability to swallow at Month 12. The first item is a CGI-C, which is a single item measure of change using 7 response options ranging from "Very much improved" to "Very much worse" (Item 1). The clinician will rate patients on this scale at the Month 12 visit based on their impression of change in the infant's respiratory function or ability to swallow since baseline. Clinicians will also be asked to rate how the infant's change in respiratory function and swallowing ability at Month 12 compare to a similarly aged untreated infant with Type 1 SMA on a 7-point scale ranging from "Very much better" to "Very much worse" (Item 2). Finally, the clinician will be asked to rate the infant's current respiratory function and swallowing ability using a 0-10 numerical response rating scale (Item 3).

Item 1 (CGI-C)

The number and percentage of infants with no change or improvement in respiratory function at Month 12 will be presented with a two-sided 90% Clopper-Pearson (exact) CI for the proportion. Infants who have a worsening in respiratory function, or who have been withdrawn, or died, will be classified as non-responders for the analysis. Infants with a missing assessment at Month 12 will also be classified as non-responders.

The number and percentage of infants in each response category of the CGI-C item will be presented. The number and percentage of infants with a missing assessment at Month 12 (including withdrawals) and the number and percentage of infants who had died by that visit will also be presented. Percentages will be based on the ITT population.

Item 2

The number and percentage of infants in each response category for item 2 will be presented. The number and percentage of infants with a missing assessment at Month 12 (including withdrawals) and the number and percentage of infants who had died by that visit will also be presented. Percentages will be based on the ITT population.

Item 3

The responses for item 3 will be summarized using descriptive statistics. All observed assessments will be included in the analyses; no imputation for missing assessments will be performed.

Similar analyses will be performed for the swallowing items.

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 infants sitting without support for 5 seconds at Month 12, 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 infants sitting without support at Month 12 will be analyzed as described in Section 4.4.1 with sitting defined by the HINE-2 categories of ‘Stable sit’ or ‘Pivots (rotates).’ Infants within either of these response categories for the milestone of sitting at Month 12 will be classified as responders.

[REDACTED]

[REDACTED]

4.4.4.4 Censoring

To assess the impact of early withdrawals on the time-to-death or permanent ventilation, the analyses described in Section 4.4.2.2.1 will be performed with infants who have been withdrawn from the study without entering safety follow-up and have no event reported prior to withdrawal assumed to have an event on the date of withdrawal.

4.4.4.5 Events Reported During Safety Follow-Up

For the secondary efficacy endpoint of time-to-death, the analyses described in Section 4.4.2.2.2 will be performed including all events reported up to 52 weeks after the date of withdrawal (for infants who are withdrawn from the study and enter safety follow-up).

4.4.4.6 Handling of Missing Data

To assess the impact of missing data on the CHOP-INTEND outcomes at Month 12, analyses described in Section 4.4.2.1.1 will be performed using different rules for handling missing data.

If an item of the CHOP-INTEND is missing at baseline or at Month 12, 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 infant belongs. Infants will be classified into the following strata, based on the time between first treatment and onset of symptoms, for the purpose of identifying non-missing data for imputation:
 - Time between first treatment and onset of symptoms ≤ 3 months
 - Time between first treatment and onset of symptoms > 3 months

If there is no data available in that stratum at baseline (i.e., no scores have been recorded), the item score will be set to 0.

- If an item is missing or 'CNT' is recorded at Month 12, and the Month 12 visit is flanked by visits where the item 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 Month 12, and the Month 12 visit is not flanked by visits where the item is available (i.e., Month 12 is the infant'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 infant belongs. If there is no data available in that stratum at Month 12, the item score will be set to 0.

These rules will not be applied for infants who have died or been withdrawn from the study before Month 12, unless the infant has an assessment that falls in the visit window for Month 12.

This imputation will be applied to the proportion of infants who achieve a score of 40 or higher in the CHOP-INTEND at Month 12, the proportion of infants who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12 and the proportion of infants who achieve head control at Month 12 (defined as a score of 3 or higher for item 12 of the CHOP-INTEND). The CHOP-INTEND score and change from baseline score at Month 12 will also be summarized after applying the imputation rules.

4.4.5 Subgroup Analyses

Subgroup analyses will be performed for the primary efficacy endpoint of the proportion of infants sitting without support for 5 seconds at Month 12 and the secondary efficacy endpoint of time-to-death or permanent ventilation. Analyses will be presented for the following subgroups:

- Age at enrollment (≤ 5 months, > 5 months)
- Sex
- Race/ethnicity
- Region (Europe, USA/Canada, rest of world)
- Baseline CHOP-INTEND score (\leq median score, $>$ median score)
- Baseline CMAP amplitude (≤ 1 mV, > 1 mV)
- Time between first treatment and onset of symptoms (≤ 3 months, > 3 months)

The number and percentage of infants sitting without support at Month 12 and corresponding 90% Clopper-Pearson (exact) CIs will be presented for each subgroup using forest plots.

Time-to-death or permanent ventilation will be presented graphically for each subgroup using Kaplan-Meier curves. The median time to ventilation-free survival (and 90% CIs) and the proportion of infants who are surviving ventilation-free at Month 12 and corresponding 90% CIs will be estimated using Kaplan-Meier methodology, when possible.

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 RO7034067 (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 in an exploratory way. Data may be pooled with data from other studies with RO7034067 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. Individual and mean plasma concentrations of RO7034067 (and metabolites as appropriate) versus time data will be tabulated.

Additional PK analyses and exploratory analyses on exposure versus selected safety and efficacy parameters may be conducted as deemed necessary. This may include scatterplots of AUC versus change from baseline in the CHOP-INTEND score, modified BSID-III gross motor scale total raw score, HINE-2 total score and CMAP negative peak amplitude at Month 12 and Month 24; and boxplots of AUC for infants who achieve/do not achieve sitting and head control at Month 12 and Month 24, and infants who

achieve/do not achieve standing and walking at Month 24, as assessed by items 22, 9, 40, and 42 of the modified 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.

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, 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 score, modified BSID-III gross motor scale total raw score, HINE-2 total score and CMAP negative peak amplitude at Month 12 and Month 24; and boxplots of absolute SMN protein level and percent change from baseline in SMN protein level for infants who achieve/do not achieve sitting and head control at Month 12 and Month 24, and infants who achieve/do not achieve standing and walking at Month 24, as assessed by items 22, 9, 40, and 42 of the modified BSID-III gross motor scale, respectively.

4.6 SAFETY ANALYSES

Safety data will be summarized descriptively using the safety population. For Part 2, the safety data will be summarized descriptively for the first 12-month period (i.e., 12-month data for each individual infant) 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. Data collected during the safety follow-up period will be presented separately.

Safety analyses will use the same visit windows defined 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 treatment discontinuation 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 infants 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 volume administered <90% of planned volume administered), number of overdoses (actual

volume administered >110% of planned volume administered), dose intensity, and cumulative dose.

The duration of total treatment intake will be calculated from the infant'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 infants with dose intensity < 80% and ≥ 80% will be presented.

The route of administration of study drug and the number of dose adjustments per infant (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.

AEs will be summarized for the following analysis periods separately:

Treatment period: includes (a) the AEs for which the onset date is on or after the first day of the study drug up to the earliest date of {study withdrawal or completion of 12 (or 24) months of treatment[#]}; or (b) the AEs for which 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.

#Note: for outputs displaying all available interim safety data collected at the time of the analysis, the date of completion of 12 (or 24) months of treatment will be replaced by the clinical cutoff date for the analysis.

All AEs with an onset date on or before the clinical cutoff date will be included in the data cut, regardless of the end date.

All 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 $\geq 5\%$ 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.

AEs resulting in death will be summarized overall and by cause of death (AE as primary cause of death vs progressive disease specified as primary cause of death).

The AE and SAE rate adjusted for patient years (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:

$$\text{AE rate} = (\text{number of AEs observed by Month 12 [or 24]}^{\#} / \text{total patient-years at risk}) * 100$$

where

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

[#]Note: for outputs displaying all available interim AEs collected at the time of the analysis, the date of completion of 12 (or 24) months of treatment will be replaced by the clinical cutoff date for the analysis.

In addition, the overall AE profile summary table, the summary table of all AEs by preferred term and system organ class, and the AE rate tables adjusted for patient-years will be presented for the following subgroups: age at enrollment (≤ 5 months, > 5 months), sex, region and time between first treatment and onset of symptoms (≤ 3 months, > 3 months).

Follow-up period: includes the AEs for which the onset date is from 1 day up to 52 weeks after study withdrawal/completion. All AEs and SAEs will be summarized for the follow-up period. AEs will also be summarized by intensity/severity (NCI-CTCAE grade).

The following AEs of special interest (pre-defined in the protocol) will be summarized separately (for the treatment period and follow-up period):

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

Individual listings will also be generated for AEs, SAEs and AEs leading to withdrawal of study treatment.

In addition, 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

A summary table of patient deaths by death cause (progressive disease vs other causes) will be presented. Patient listings will also be generated containing all details for each infant who died during the protocol-specified AE reporting period (up to 52 weeks after study withdrawal/completion). 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 infants 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. A plot of total bilirubin/ULN versus ALT/ULN and AST/ULN at each time-point will also be presented. The number and percentage of infants with elevated ALT or AST levels at any time-point post-baseline will be presented.

Data collected during safety follow-up will be summarized similarly.

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 infants with values outside the normal ranges. The normal ranges will be based on the age of the infant 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 |

Data collected during safety follow-up will be summarized similarly.

4.6.6 Electrocardiogram

ECG data will be listed for infants with values outside the normal ranges. The normal ranges will be based on the age of the infant 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 infants will be listed.

The following normal ranges will be used:

| Age (months) | PR Duration (ms) | QT Duration (ms) | QRS Duration (ms) | RR Duration (ms) | QTcF (ms) | QTcB (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 infants with PR duration, QRS 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 | ≤ 120 > 120 | |
| >24-≤144 months | ≤ 160 > 160 | |
| QRS duration (ms) | ≤ 90 > 90 | |
| 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 |

Data collected during safety follow-up will be summarized similarly.

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)

circumference-for-age percentiles, and change from baseline percentiles at each time-point will also be summarized.

The number and percentage of infants in the 3rd, 5th, 10th, 25th, 50th, and > 50th percentiles of the WHO growth charts will be presented. Shift tables for each parameter to compare the infant's percentile at baseline ($\leq 3^{\text{rd}}$, $> 3^{\text{rd}}-\leq 5^{\text{th}}$, $> 5^{\text{th}}-\leq 10^{\text{th}}$, $> 10^{\text{th}}-\leq 25^{\text{th}}$ and $> 25^{\text{th}}-\leq 50^{\text{th}}$, $> 50^{\text{th}}$) to each time-point post-baseline will be presented.

Mean percentiles for weight-for-age and length/height-for-age and corresponding 90% CIs will be plotted over time. Scatterplots of individual weight-for-age and length/height-for-age percentiles at Month 12 and Month 24 versus chronological age (age at Month 12 and Month 24) and versus baseline weight-for-age and baseline length/height-for-age percentiles will also be presented.

Individual growth charts will be presented for each infant in the ITT population. One chart will present the weight and length/height of the infant over time, with reference lines for the 3rd, 10th, 25th, 50th, 75th, 90th and 97th percentiles for weight-for-age and length/height-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 weight of the infant over time with reference lines for weight-for-age, plus the following parameters: chest circumference, phase angle, age at onset of any respiratory infection (AEs with a MedDRA high level group term [HLGT] of 'respiratory tract infections'), and age at time of permanent ventilation.

Both charts will also present the age at onset of symptoms, age at diagnosis, age at first dose, age at treatment/study discontinuation and age at death (if applicable).

4.7 MISSING DATA

For responder/non-responder definitions, infants with a missing assessment at a visit (for any reason) will be classified as non-responders.

For the calculation of the CHOP-INTEND score, modified BSID-III gross motor scale total raw score, or HINE-2 total score, if any individual item score contributing to the total score is missing or 'Cannot test (CNT)' is recorded, then that item will be set to 0 if there is at least one non-missing item at the assessment. If all items are missing, then the total score will be set to missing.

No imputation will be performed for missing safety variables.

4.8 INTERIM ANALYSES

A futility assessment for efficacy will be conducted after the first 14 infants enrolled into the confirmatory Part 2 of the study have reached 12 months of treatment or have been withdrawn. If the predictive probability of ‘success’ (defined as observing 5 out of 40 sitting) is less than 10% (corresponding to no infant has met the primary endpoint of sitting without support at Month 12 in the first 14 infants enrolled in Part 2) then the Sponsor may consider stopping the study. The predictive probabilities of success at the primary analysis given the number of infants sitting without support at the futility analysis are presented in [Table 2](#).

Table 2 Predictive Probabilities of Success at Primary Analysis (Month 12) Given Result of Futility Analysis

| Number of infants enrolled in Part 2 sitting without support at futility analysis | Action to be taken | Predictive probability of success at primary analysis (Month 12) (%) |
|---|-------------------------|--|
| 0 | Consider stopping study | 8.8 |
| 1 | Continue | 38.7 |
| 2 | Continue | 75.1 |
| 3 | Continue | 94.9 |
| 4 | Continue | 99.6 |
| 5 | <i>Continue/File</i> | 100.0 |

An interim analysis for futility 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 RO7034067 in the Type 1 SMA population at this earlier time-point. The final decision based on the iDMC recommendation will be made by the Sponsor.

5. CHINA SUBGROUP ANALYSIS

A separate analysis will be performed for the China subpopulation, where data from all infants enrolled in China (i.e., during both the global enrollment phase and the extended China enrollment phase) will be combined and summarized. Data from the China extension cohort will not be included in the primary analysis of the main study. China subgroup analyses will be documented in a separate Clinical Study Report.

All analyses described in this section will include all data from the China subgroup collected up to the clinical cutoff date for the China subgroup analysis as defined in [Section 2.4](#).

The analysis populations will be defined as per [Section 4.1](#), but will only be based on infants who are residents of China, Hong Kong, or Taiwan, and are of Chinese ancestry.

Analyses of study conduct will be performed as described in Section 4.2. Summaries of demographics and baseline characteristics, SMA history and disease characteristics, and medical and treatment history will be produced as described in Section 4.3. Efficacy data for the China subgroup will be analyzed as described in Section 4.4, as appropriate. However, no hypothesis testing will be performed. Safety data for the China subgroup will be analyzed as described in Section 4.6.

6. **REFERENCES**

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Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology.* 2014;83:810-817.

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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.

Appendix 1

Protocol Synopsis

TITLE: A TWO-PART SEAMLESS, OPEN-LABEL, MULTI-CENTER STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND EFFICACY OF RO7034067 IN INFANTS WITH TYPE 1 SPINAL MUSCULAR ATROPHY

PROTOCOL NUMBER: BP39056

VERSION: 5

EUDRACT NUMBER: 2016-000778-40

IND NUMBER: 128972

TEST PRODUCT: RO7034067

PHASE: II

INDICATION: Type 1 spinal muscular atrophy

SPONSOR: F. Hoffmann-La Roche Ltd

OBJECTIVES

Primary Objectives

The primary objectives for the study are as follows:

- Part 1: To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of RO7034067 in infants with Type 1 SMA, and to select the dose for Part 2.
- Part 2: To assess the efficacy of RO7034067 measured as the proportion of infants sitting without support after 12 months of treatment, as assessed in the Gross Motor Scale of the Bayley Scales of Infant and Toddler development – Third Edition (BSID-III) (defined as sitting without support for 5 seconds).

Secondary Objectives

The secondary objectives for Part 2 of this study are as follows:

- To assess the safety and tolerability of oral treatment with RO7034067.
- To assess the pharmacokinetics of RO7034067.
- To assess the pharmacodynamic effects of RO7034067 (*SMN2* mRNA, SMN protein).
- To evaluate at 12 months of treatment with RO7034067 the effect on motor development milestones, such as head control and rolling, as measured in the BSID-III gross motor scale.
- To evaluate at 24 months of treatment with RO7034067 the effect on sitting without support for 5 seconds and further motor development milestones, such as sitting without support for 30 seconds, crawling, standing alone, and walking, as measured in the BSID-III gross motor scale.
- To assess the achievement of motor milestones at 12 and 24 months of treatment with RO7034067, as measured by the Hammersmith Infant Neurological Examination (HINE) Module 2.
- To evaluate the proportion of infants who achieve a score of 40 or higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at 12 months of treatment.

- To evaluate the proportion of infants who achieve an increase of at least 4 points on their CHOP-INTEND score from baseline at 8 and 12 months of treatment.
- To evaluate the proportion of infants who achieve head control at 8, 12, and 24 months of treatment (defined as a score of 3 or higher for item 12 of the CHOP-INTEND).
- To assess the change from baseline in the total raw score of the BSID-III gross motor scale at 12 and 24 months of treatment.
- To assess the proportion of infants who achieve a reduction of at least 30 degrees in phase angle at 12 months of treatment measured by respiratory plethysmography (RP).
- To evaluate the proportion of infants who do not require invasive or non-invasive respiratory support at 12 and 24 months of treatment.
- To assess at 12 and 24 months of treatment the proportion of infants who are alive without permanent ventilation, as defined by ≥ 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.
- To assess the impact of treatment with RO7034067 on time-to-event (death, permanent ventilation).
- To evaluate the proportion of infants with the ability to feed orally at 12 and 24 months of treatment.

Exploratory Objectives

The exploratory objectives for Part 2 of this study are as follows:

- To explore the effect of treatment with RO7034067 on parent/ caregiver-rated infant health status and impact on the parent/ caregiver, as measured by the Infant Toddler Quality of Life Questionnaire at 12 and 24 months.
- To assess at 8, 12, and 24 months of treatment with RO7034067 the ratio between the chest and head circumference.
- To explore the treatment effect on pre-specified disease-related adverse events by 12 and 24 months of treatment.
- To investigate the effect at 12 and 24 months of treatment with RO7034067 on muscle electrophysiology, as assessed by compound muscle action potential (CMAP).
- To explore the effect of treatment with RO7034067 on the number of hospitalizations (for any reason) per patient-year and number of nights admitted to hospital per infant at 12 and 24 months of treatment.
- To evaluate at 24 months the effects of RO7034067 on sustained sitting for those infants sitting at 12 months (defined as sitting without support for 5 seconds).
- To explore at 24 months the maintenance of the effects of RO7034067 on respiratory function for those infants who achieve a reduction of at least 30 degrees in phase angle at 12 months.
- *To explore at 12 months the effect of treatment with RO7034067 on clinician-reported changes in infants' respiratory function and swallowing ability, as measured by the clinical domain level items.*
- *To assess at 12 and 24 months of treatment with RO7034067 the change from baseline in weight and length/height percentiles.*

STUDY DESIGN

Description of Study

This is a seamless open-label, single-arm, multi-center clinical study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of RO7034067 in Type 1 SMA infants. The study will be conducted in two parts and followed by an *open-label* extension phase:

- **Exploratory Part 1:** Part 1 is an open-label, dose escalation study in infants with Type 1 SMA aged 1 to 7 months (at time of enrollment).
 - The first infant will receive a single dose of RO7034067 to assess safety and tolerability, and the pharmacokinetics (PK). If this single dose is safe and well tolerated *in this first infant*, and after the PK has been assessed and evaluated, this infant will continue treatment with RO7034067 and start approximately 2 weeks later the study as per the Schedule of Assessments (SoA) at *the dose level* (Dose Level 1; target $AUC_{0-24h,ss}$ 700 ng • h/mL) *selected based on the PK data obtained from the first single dose*. If the study drug is well tolerated in this first infant for at least one week after reaching approximate steady-state (or a minimum of 2-week treatment), an additional 2 infants will be enrolled (*5 to 7 months of age*) to receive this dose/exposure level.
 - If upon review of safety and tolerability in the first 5 infants for at least 7 days at approximate steady-state (or a minimum of 2-week treatment), this dose/exposure level does not meet any of the dose escalation stopping rules, the dose of the 5th infant will be increased to reach the higher target exposure (Dose Level 2: the exposure with maximum expected SMN protein increase, but below the exposure cap). Assuming dose escalation stopping rules remain unmet after administration of RO7034067 in all 5 enrolled infants (for a minimum of 1 week in the last infant receiving Dose Level 2, and longer treatment duration in all previously enrolled infants at Dose Level 1), 3 additional infants will be enrolled and receive RO7034067 at this higher target exposure. After a minimum treatment duration of 4 weeks at Dose Level 2 (or 2 weeks at the final approximate steady-state exposure) in all 4 infants, all safety, PK, and PD data will be reviewed to select the dose to be evaluated in Part 2.
- **Confirmatory Part 2:** Part 2 is an open-label, single arm study in 40 infants with Type 1 SMA aged 1 to 7 months (at time of enrollment) to assess the efficacy of RO7034067 at the dose selected in Part 1 over a 24-month treatment period, with the primary endpoint analyzed at 12 months of treatment.

On the basis of available data from Part 1, the following dose levels have been selected for Part 2:

- Infants >1 month and below 3 months old at enrollment: 0.04 mg/kg.
- Infants at least 3 months but below 5 months old at enrollment: 0.08 mg/kg.
- Infants 5 months old or older at enrollment: 0.2 mg/kg.

Patients will remain on their initially assigned dose level (i.e., the dose will not change once a patient reaches 3 months and 5 months of age, respectively) unless a change of dose is requested by the Clinical Pharmacologist upon review of the PK data, to ensure that infants are in the targeted exposure range and in compliance with the exposure cap.

After the initial enrollment of 40 infants across all sites in a global enrollment phase, additional infants may be enrolled in an extended China enrollment phase at sites that are recognized [REDACTED] to ensure a total of approximately 10 infants in a China subpopulation.

NUMBER OF PATIENTS

The exploratory Part 1 will consist of at least 8 infants and up to 24 infants (if required) enrolled into two multiple ascending dose cohorts.

In Part 2, 40 infants with Type 1 SMA will be enrolled to receive RO7034067 at the dose (target exposure level) selected in Part 1.

After completion of the global enrollment phase for Part 2, additional infants may be enrolled in an extended China enrollment phase at [REDACTED]-recognized sites to ensure approximately 10 infants in a China subpopulation (including infants enrolled in the global enrollment phase and the extended China enrollment phase).

TARGET POPULATION

This study will include both male and female Type 1 SMA infants aged ≥ 1 month and ≤ 7 months at the time of enrollment.

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:

Infants must meet the following criteria for study entry:

- 1) Males and females aged between 28 days (1 month) of life and 210 days (7 months) (inclusive) at enrollment. For the first 3 infants enrolled in Part 1, age will be between 150 days (5 months) and 210 days (7 months) inclusive and a minimum body weight of 7 kg is required for the first infant only. Enrollment is defined as the moment when infants get their dosing number assigned.
- 2) A legally authorized representative must be able to consent for the patient according to International Conference on Harmonisation (ICH) and local regulations.
- 3) Gestational age of 37 to 42 weeks.
- 4) Confirmed diagnosis of 5q-autosomal recessive SMA, including:
 - a. Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the *SMN1* gene.
 - b. Clinical history, signs or symptoms attributable to Type 1 SMA, i.e., hypotonia, absent deep tendon reflex (DTR) and/or tongue fasciculations with onset after the age of 28 days, but prior to the age of 3 months (inclusive), and inability to sit independently (without support) at the time of screening.
- 5) Patient has two *SMN2* gene copies, as confirmed by central testing.
- 6) Body weight $\geq 3^{\text{rd}}$ percentile for age, using appropriate country-specific guidelines (for the first infant only: > 7 kg).
- 7) Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the Investigator.
- 8) Adequately recovered from any acute illness at the time of screening and considered well-enough to participate in the opinion of the Investigator.
- 9) Medical care meets, in the opinion of the Investigator, local accepted standard of care.
- 10) Able and expected to be able to safely travel to the study site for the whole duration of the study and according to the frequency of required study visits, in the opinion of the Investigator. Air travel is strongly discouraged. The overall condition and situation (including geographical) of the patient should be evaluated and the decision taken by the Investigator prior to enrollment.
- 11) Have a stable home situation with a consistent caregiver.
- 12) Would be able to complete all study procedures, measurements and visits, and the parent or caregiver of the patient, in the opinion of the Investigator, has adequately supportive psychosocial circumstances.
- 13) If not already in place at the time of screening, parent or caregiver of patient is willing to consider nasogastric, naso-jejunal or gastrostomy tube placement during the study to maintain safe hydration, nutrition and treatment delivery, as recommended by the Investigator.
- 14) If not already in place at the time of screening, parent or caregiver of patient is willing to consider the use of non-invasive ventilation during the study, as recommended by the Investigator.

Exclusion criteria:

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

- 1) Inability to meet study requirements.
- 2) Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening or 5 half-lives, whichever is longer.
- 3) Concomitant or previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy either in a clinical study or as part of medical care.
- 4) Any history of cell therapy.
- 5) Hospitalization for pulmonary event within the last 2 months, or planned at the time of screening.
- 6) Unstable gastrointestinal, renal, hepatic, endocrine or cardiovascular system diseases.
- 7) In the opinion of the Investigator, inadequate venous or capillary blood access for the study procedures.
- 8) Patients requiring invasive ventilation or tracheostomy.
- 9) Patients requiring awake non-invasive ventilation or with awake hypoxemia ($\text{SaO}_2 < 95\%$) with or without ventilator support.
- 10) Patients with a history of respiratory failure or severe pneumonia, and have not fully recovered their pulmonary function at the time of screening.
- 11) Multiple or fixed contractures and/or hip subluxation or dislocation at birth.
- 12) Presence of non-SMA-related concurrent syndromes or diseases.
- 13) Confirmed (2 consecutive measurements) systolic blood pressure (SBP) or diastolic blood pressure (DBP) outside the 95th percentile for age; resting heart rate < 70 bpm or > 170 bpm.
- 14) Presence of clinically relevant electrocardiogram (ECG) abnormalities before study drug administration; corrected QT interval using Bazett's method (QTcB) > 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.
- 15) History of malignancy if not considered cured.
- 16) Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration.
- 17) Taking any nutrients known to modulate CYP3A activity (e.g., grapefruit juice; Seville orange) within 2 weeks prior to administration of study drugs.
- 18) The infant (and the mother, if breastfeeding the patient):
 - a. 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.
 - b. 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.
 - c. Any OCT-2 and MATE substrates shall be avoided (including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalixin, cephadrine, fexofenadine).
 - d. Any known FMO1 or FMO3 inhibitors or substrates.

- 19) Clinically significant abnormalities in laboratory test results e.g., Grade > 1 anemia, alanine aminotransferase (ALT) values exceeding $1.5 \times$ the upper limit of normal (ULN) unless the elevated ALT level is considered of muscular origin (i.e., in the absence of other evidence of liver disease which is confirmed by elevated creatine kinase and lactate dehydrogenase [LDH]). 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.
- 20) Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to RO7034067 or to the constituents of its formulation
- 21) Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject in this study.
- 22) Therapeutic use, defined as use for 8 weeks or longer, of the following medications within 90 days prior to enrollment: riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease muscle strength, agents with known or presumed histone deacetylase (HDAC) inhibitory effect, medications known to or suspected of causing retinal toxicity (e.g. deferoxamine, topiramate, latanoprost, niacin, rosiglitazone, tamoxifen, canthaxanthine, sildenafil, and interferon) and medications with known phototoxicity liabilities (e.g., oral retinoids including over-the-counter [OTC] formulations, amiodarone, phenothiazines and use of minocycline). Shorter use of any of these drugs within 90 days prior to enrollment will be reviewed on a case-by-case basis and discussed between the Sponsor and the Investigator, who will jointly make the decision if the patient can be enrolled in the study. (*Infants* who are on inhaled corticosteroids, administered either through a nebulizer or an inhaler, will be allowed in the study).
 - a. *Infants* must not begin treatment with the above medications after initiating study drug.
- 23) Recently initiated treatment (within < 6 weeks prior to enrollment) with **oral** salbutamol or another β 2-adrenergic agonist taken **orally** is not allowed. *Infants* who have been on oral salbutamol (or another β 2-adrenergic agonist) for \geq 6 weeks before screening and have shown good tolerance are allowed. The dose of β 2-adrenergic agonist should remain stable as much as possible for the duration of the study. Use of **inhaled** β 2-adrenergic agonists (e.g., for the treatment of asthma) is allowed.
- 24) Prior use (at any time in the patients' lives) and/or anticipated need for quinolines (chloroquine and hydroxychloroquine), thioridazine, vigabatrin, retigabine, or any other drug known to cause retinal toxicity during the study does not allow participation in the trial. *Infants* exposed to chloroquine, hydroxychloroquine, thioridazine, vigabatrin, retigabine or drugs with known retinal toxicity given to mothers during pregnancy (and lactation) should not be enrolled.
- 25) Recent history (less than 6 months) of ophthalmic diseases (e.g., glaucoma not controlled by treatment, 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 OCT at screening (e.g., retinal layer abnormalities, edema, cystic or atrophic changes) must be discussed with the Investigator, Ophthalmologist, and with the Sponsor, who will jointly make the decision if the patient may be enrolled in the study. *Infants* in whom OCT measurement of sufficient quality cannot be obtained at screening will not be enrolled.

LENGTH OF STUDY

- The duration of the study for each infant enrolled in Part 1 (not including the extension phase) will be divided as follows:
Screening: Up to 30 days prior to first dose.

Treatment Period: minimum of 2 weeks at steady state exposure (as decided by the Internal Monitoring Committee [IMC]).

- The duration of the study for each infant enrolled in Part 2 (not including the extension phase) will be up to 25 months as follows:

Screening: up to 30 days prior to first dose.

Treatment period: 24 months from the start of dosing, with the primary analysis after the last infant reaches a minimum of 12 months of treatment.

After each infant completes 24 months of treatment, he or she will enter an open-label extension.

END OF STUDY

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

The study will continue until RO7034067 is commercially available in the infant's country, or as per local regulation, or per the Sponsor's decision to terminate RO7034067 development.

However, the study will not exceed 4 years (or less as per country specific requirements) after the last infant is enrolled in the study.

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events.
- Incidence and severity of serious adverse events.
- Incidence of treatment discontinuations 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: red reflex, external ocular examination, pupillary examination/response, fix and follow test, corneal light reflex, fundus examination including ophthalmoscopy/slit lamp examination, OCT and fundus photography.
- Physical examination, including detailed examination of the skin, mouth, pharynx and larynx.
- Anthropometric examination, including weight, height, head, and chest circumference.

Adverse events and concomitant medications will be monitored throughout the entire study (screening through follow-up).

PHARMACOKINETIC OUTCOME MEASURES

Blood samples for determination of plasma concentrations of RO7034067, and its metabolite(s) as applicable, will be collected as detailed in the SoA. The following parameters will be calculated (if possible, based on the available data):

- 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}) to assess steady-state.
- Other PK parameters as appropriate

PHARMACODYNAMIC OUTCOME MEASURES

The fluid PD assessments (SMN mRNA and SMN protein in blood) will be performed as detailed in the SoA.

EFFICACY OUTCOME MEASURES

The efficacy outcome measures for this study are as follows:

- Motor milestones achieved as assessed by the Gross Motor Scale of the BSID-III.
- Motor milestones achieved as assessed by Hammersmith Infant Neurological Examination Module 2 (HINE-2).
- CHOP-INTEND.
- RP.
- Disease-related adverse events.
- CMAP.
- Level of respiratory support.
- Ventilation free-survival.
- Ability to swallow and to feed orally.
- *Clinician-reported respiratory function and ability to swallow items.*
- *Change in height and weight.*

PARENT/CAREGIVER-REPORTED OUTCOME MEASURES

The parent/caregiver-reported outcome measure for this study is as follows:

- Parent/caregiver-rated infant health status and impact on the parent/caregiver, as measured by the Infant Toddler Quality of Life (ITQOL) Questionnaire.

BIOMARKER/GENOTYPING SAMPLE COLLECTION

Clinical Genotyping (CG) Samples

A single mandatory whole blood sample will be taken from every patient at screening for DNA extraction. The DNA will be used to determine the number of copies of the *SMN2* gene and to confirm *SMN1* gene mutation or deletion.

A mandatory whole blood sample will be taken for DNA extraction from every patient once enrolled onto the study and may be used for additional confirmatory testing of *SMN1* deletion/*SMN2* copy number.

Samples may be used for exploratory analysis/assay development related to SMA, including, but not limited to, mitochondrial DNA and genes related to SMN function or treatment response.

INVESTIGATIONAL MEDICINAL PRODUCT

Exploratory Part 1:

The Investigational Medicinal Product (IMP) will be supplied in bottles containing 20 mg or 120 mg of RO7034067 drug substance (no excipient). Before administration, the drug substance will be constituted with a solvent, which is prepared by dissolving a provided excipient blend with water for injection. For the first infant(s), a further dilution step is foreseen to enable the administration of a low starting dose.

Confirmatory Part 2:

The IMP will change to a new formulation which is supplied in bottles filled with powder blends containing 20 mg or 60 mg of RO7034067 drug substance as well as all excipients. The drug solution can be directly constituted with purified water in the bottle of the IMP.

RO7034067 should be taken orally once daily. In the case of breastfeeding, the patient should be fed prior to dosing, *winded*, and the study medication administered. Study participants 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.

PROCEDURES

Schedule of assessments tables are provided in Appendices.

STATISTICAL METHODS

The analyses of this study will be structured into two parts; exploratory (Part 1) to select the dose and confirmatory (Part 2) to evaluate the treatment effect of RO7034067.

Following the dose selection for Part 2, data from the exploratory Part 1 of this study (and the Part 1 extension phase) may be locked at intervals in order to analyze and report the safety, PK/PD, and exploratory efficacy of those patients enrolled into Part 1 only.

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 infant enrolled into Part 2 during the global enrollment phase has either completed his/her 12-month assessment or has been withdrawn. At the time of the primary analysis, all available efficacy data post Month 12 will be reported. All available safety data in both parts of the study will be reported. A database lock for the analyses of the 24-month secondary and exploratory endpoints will occur once the last infant enrolled into Part 2 during the global enrollment phase has either completed his/her 24-month assessment or has been withdrawn.

The global population will include all infants enrolled during the global enrollment phase (including infants enrolled at ██████-recognized sites during the global phase), and the China subpopulation will include all infants enrolled at ██████-recognized sites (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the global population and the China subpopulation.

EFFICACY ANALYSES

The intent-to-treat (ITT) population will be the primary analysis population for all efficacy analyses. The ITT population is defined as all enrolled infants, regardless of whether they received treatment or not.

The confirmatory efficacy analyses will only include data from the infants enrolled into Part 2 of the study; it will not include data from the Part 1 infants who will be analyzed to select the dose. Efficacy data of the infants enrolled into Part 1 will be summarized descriptively, using individual patient plots or listings (as appropriate) and presented separately from the confirmatory efficacy analysis of Part 2.

Primary Efficacy Endpoint

The primary endpoint for the confirmatory Part 2 of the study is the proportion of infants who are sitting without support at 12 months of treatment. Infants who do not achieve sitting, or have not maintained sitting achieved earlier, or 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 is 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 $\leq 5\%$ 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.

Secondary Efficacy Endpoints

The secondary efficacy endpoints in Part 2 are as follows:

- **Motor Function and Development Milestones:** Proportion of infants who achieve a score of 40 or higher in the CHOP-INTEND at Month 12; proportion of infants who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 8 and Month 12; proportion of infants who achieve head control at Month 8, Month 12, and Month 24 (defined as a score of 3 or higher for item 12 of the CHOP-INTEND); change from baseline in the total raw score of the BSID-III gross motor scale at Month 12 and Month 24; proportion of infants who achieve the attainment levels of the motor milestones as assessed in the HINE-2 at Month 8 (head control, ability to kick, rolling), Month 12, and Month 24; proportion of motor milestone responders as assessed by HINE-2 at Month 12 and Month 24; highest motor milestone achieved by Month 12 and Month 24; proportion of infants who are alive and sitting without support for 5 seconds at Month 24 (defined as per the primary endpoint); proportion of infants who are alive and sitting without support for 30 seconds at Month 24 (defined as "Sits without support for 30 seconds" as assessed in Item 26 of the BSID-III gross motor scale); proportion of infants who are alive and standing at Month 24 (defined as 'Stands Alone' as assessed in Item 40 of the BSID-III gross motor scale); proportion of infants who are alive and walking at Month 24 (defined as 'Walks Alone' as assessed in Item 42 of the BSID-III gross motor scale).
- **Survival and Ventilation-Free Survival:** Time to death or permanent ventilation (defined as ≥ 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) from enrollment, time to death from enrollment, proportion of infants who are alive without permanent ventilation at Month 12 and Month 24, proportion of infants who are alive at Month 12 and Month 24.
- **Respiratory:** Time to permanent ventilation from enrollment, proportion of infants who are without permanent ventilation at Month 12 and Month 24, proportion of infants who achieve a reduction of at least 30 degrees in their phase angle from baseline, as measured by RP, at Month 12, proportion of infants who do not require invasive or non-invasive respiratory support at Month 12 and Month 24.
- **Nutrition:** Proportion of infants with the ability to feed orally at Month 12 and Month 24.

SAFETY ANALYSES

All infants who receive at least one dose of study medication (RO7034067) will be included in the safety population.

Safety data will be summarized descriptively using the safety population. In Part 1, safety data will be presented in summaries, listings or individual patient plots (as appropriate) by dose/exposure level. For Part 2, the safety data will be summarized descriptively for the first 12-month period (i.e., 12-month data for each individual infant) and for all available safety data collected at the time of the analysis. Similar summaries for the first 24-month period will be presented at the time of the 24-month analysis reporting event.

SAMPLE SIZE JUSTIFICATION

In Part 1, the target sample size is 8 infants, 4 enrolled to each dose level. With 8 infants exposed to RO7034067, there is over an 80% chance to detect an AE in at least one infant, given that the true underlying adverse event rate is 20%. With 4 infants exposed at each dose level, the probability to detect an AE in at least one infant, given that the true underlying adverse event rate is 30%, is 76%.

In Part 2, the target sample size is 40 infants. This sample size provides at least 90% power to test the null hypothesis $H_0: p \leq 5\%$ versus alternative hypothesis $H_a: p > 5\%$, if the true proportion of infants who would sit on treatment is 20%. This is based on an exact binomial test with a onesided 5% significance level. The minimum number of infants needed to be observed sitting is 5 out of 40 for a statistically significant result. *If more than 40 infants are enrolled, the number of babies required to meet the primary endpoint will increase. Further details are provided in the SAP.* If in Part 2, 5 out of 40 infants sit the lower limit of the -twosided- 90% Clopper-Pearson (Exact) confidence interval would be above 5%.

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

Interim Analyses

As this study is open-label, once at least 5 infants enrolled into the confirmatory Part 2 during the global enrollment phase 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 time-point. The study will not be stopped and all 40 infants enrolled within the confirmatory Part 2 will continue to receive 12 months of treatment in order to provide an unbiased estimate of the proportion of infants sitting at Month 12.

In addition, a futility assessment for efficacy will be conducted after the first 14 infants enrolled into the confirmatory Part 2 of the study reach 12 months of treatment or have been withdrawn. If the predictive probability of “success” (defined as observing 5 out of 40 sitting) is less than 10% (corresponding to no infant has met the primary endpoint of sitting without support at Month 12 in the first 14 infants enrolled in Part 2) then the Sponsor may consider stopping the study.

Interim analyses for efficacy and futility 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 RO7034067 in the Type 1 SMA population at this earlier timepoint. The final decision based on the iDMC- recommendation will be made by the Sponsor.

LIST OF PROHIBITED MEDICATIONS

The following medication is explicitly prohibited for the *patients* and the mother if breastfeeding the infant:

- Any inhibitor of CYP3A4, including but not limited to: ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, cimetidine.
- Any inducer of CYP3A4, including but not limited to: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John's wort.
- Any OCT2 and MATE substrates shall be avoided, including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalixin, cephradine, fexofenadine.
- Any known FMO1 or FMO3 inhibitors or substrates.

Use of the following therapies is prohibited for at least 90 days prior to enrollment (unless the Investigator has consulted with the Sponsor during the screening period and both have agreed that the prior use will not constitute a risk to the patient), and during the study:

- **Medications intended for the treatment of SMA:** riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, bortezomib, quercetin, chronic oral or parenteral use of corticosteroids (inhaled corticosteroid use is allowed, see above), agents anticipated to increase or decrease muscle strength or agents with known or presumed HDAC inhibition activity, and any prior use of Spinraza™ or any other SMN2-targeting antisense oligonucleotide, SMN-2 splicing modifier or gene therapy are prohibited.
- **Medications with known phototoxicity and retinal toxicity liabilities:** Oral or topical retinoids, including over-the-counter formulations, amiodarone, phenothiazines, and chronic use of minocycline.
- Patients should not have received *the following drugs at any time in their lives and are prohibited during the study:* quinolines (chloroquine and hydroxychloroquine), thioridazine, vigabatrin and retigabine at any time in their lives

Use of the following therapies is prohibited for the *patients*, and for the mother if breastfeeding the infant during the study and in the preceding 90 days of enrollment: deferoxamine, topiramate, latanoprost, niacin, rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon or any other drugs known to cause retinal toxicity.

Appendix 2 Schedule of Assessments: Part 2

| Week | Screen. | Wk 1 | | | | Wk 2 | | Wk 3 | Wk 4 | | Wk 5 | Wk 6 | Wk 7 | Wk 8 | Wk 9 | Wk 10 |
|---|-----------------------|------------------------|-----------|----------------|----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| | D-30 to Day D-2 | Day -1 ^a | Day 1 | Day 2 | Day 4 | Day 11 | Day 14 | Day 19 | Day 25 | Day 28 | Day 33 | Day 42 | Day 49 | Day 56 | Day 63 | Day 70 |
| Visit Window | | | | | | | ± 1 | | | ± 3 | | | | ± 3 | | ± 3 |
| Assessments | | | | | | | | | | | | | | | | |
| Site Visit | x | x | x | x | | | x | | | x | | | | x | | |
| Home Visit ^d | | | | | | | | | | | | x | | | | x |
| Follow-up call ^e | x | | | | x | x | | x | x | | x | | x | | x | |
| Informed Consent | x | | | | | | | | | | | | | | | |
| Enrollment | | x | | | | | | | | | | | | | | |
| Eligibility | x | x | | | | | | | | | | | | | | |
| Demography | x | | | | | | | | | | | | | | | |
| Medical History | x | | | | | | | | | | | | | | | |
| SMA History | x | | | | | | | | | | | | | | | |
| Physical Examination ^c | x | x | | | | | x | | | x | | | | x | | |
| Significant life events including family | | x | x | | | | | | | | | | | x | | |
| Vital Signs | x | x | x (4h) | | | | x | | | x | | | | x | | |
| ECG-12 lead | x | x | x (4h) | | | | x | | | x | | | | x | | |
| Haematology | x | | | | | | x | | | | | | | x | | |
| Blood Chemistry | x | | | | | | x | | | | | | | x | | |
| Administration of Study Medication | | | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Study medication dispensation/return ^d | | | x | | | | x | | | x | | x | | x | | x |
| Protein binding Sample | x | | | | | | | | | | | | | | | |
| PK Blood Sample ^j | | | 3 | 1 ^k | | | 1 | | | 4 | | | | 4 | | |
| In vivo mRNA | | | x | | | | | | | x (4h) | | | | | | |
| SMN protein | | | x | | | | | | | x | | | | | | |
| Ophthalmology Examination ^g | x | | | | | | | | | | | | | x | | |
| Clinical genotyping | x | | | | | | | | | | | | | | | |
| BSID-gross motor score ^b | | x | | | | | | | | | | | | | | |
| HINE-2 ^b | | x | | | | | | | | | | | | | | |
| CHOP-INTEND ^b | | x | | | | | | | | | | | | x | | |
| Respiratory Plethysmography ^b | | x | | | | | | | | | | | | x | | |
| CMAP ^b | | x | | | | | | | | | | | | | | |
| Level of respiratory support | x | x | | | | | x | | | x | | | | x | | |
| Nutritional check ^m | x | x | | | | | | | | | | | | x | | |
| Diary | | | x | x | | | x | | | x | | x | | x | | x |
| Infant Toddler Quality of Life ^b | | x | | | | | | | | | | | | | | |
| Adverse Events | x ^f | | | | | | | | | | | | | | | |
| Previous and Concomitant Treatments ⁿ | | | | | | | | | | | | | | | | |

Appendix 2 Schedule of Assessments: Part 2 (cont.)

| Week | Wk 11 | Wk 12 | Wks 13-16 | Wk 17 | Wks 18-25 | Wk 26 | Wks 27-34 | Wk 35 | Wks 36-42 | Wk 43 | Wks 44-51 | Wk 52 | Wks 53-60 | Wk 61 | Wks 62-69 | Wk 70 |
|---|--------|--------|-----------|----------------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|-----------|---------|
| Day | Day 77 | Day 84 | | Day 119 | | Day 182 | | Day 245 | | Day 301 | | Day 364 | | Day 427 | | Day 490 |
| Visit Window | | ± 3 | | ± 7 | | ± 7 | | ± 7 | | ± 7 | | ± 7 | | ± 7 | | ± 7 |
| Assessments | | | | | | | | | | | | | | | | |
| Site Visit | | | | x | | x | | x | | x | | x | | x | | x |
| Home Visit ^d | | x | x | | x | | x | | x | | x | | x | | x | |
| Follow-up call ^e | x | | | | | | | | | | | | | | | |
| Informed Consent | | | | | | | | | | | | | | | | |
| Enrollment | | | | | | | | | | | | | | | | |
| Eligibility | | | | | | | | | | | | | | | | |
| Demography | | | | | | | | | | | | | | | | |
| Medical History | | | | | | | | | | | | | | | | |
| SMA History | | | | | | | | | | | | | | | | |
| Physical Examination ^c | | | | x | | x | | x | | x | | x | | x | | x |
| Significant life events including family | | | | x | | x | | x | | x | | x | | x | | x |
| Vital Signs | | | | x | | x | | x | | x | | x | | x | | x |
| ECG-12 lead | | | | x | | x | | x | | x | | x | | x | | x |
| Haematology | | | | x | | | | x | | | | x | | | | x |
| Blood Chemistry | | | | x | | | | x | | | | x | | | | x |
| Administration of Study Medication | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Study medication dispensation/return ^d | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| Protein binding Sample | | | | | | | | | | | | | | | | |
| PK Blood Sample | | | | 1 | | 4 | | 1 | | 4 | | 1 | | 1 | | 1 |
| In vivo mRNA | | | | | | | | x | | | | x | | | | |
| SMN protein | | | | x | | | | x | | | | x | | | | |
| Ophthalmology Examination ^g | | | | x | | x | | x | | x | | x | | x | | x |
| Clinical genotyping | | | | x ^l | | | | | | | | | | | | |
| BSID-gross motor score ^b | | | | x | | | | x | | | | x | | | | x |
| HINE-2 ^b | | | | x | | | | x | | | | x | | | | x |
| CHOP-INTEND ^b | | | | x | | x | | x | | x | | x | | x | | x |
| Respiratory Plethysmography ^b | | | | x | | x | | x | | x | | x | | x | | x |
| CMAP ^b | | | | x | | | | x | | | | x | | | | x |
| Level of respiratory support | | | | x | | x | | x | | x | | x | | x | | x |
| Nutritional check ^m | | | | x | | x | | x | | x | | x | | x | | x |
| Diary | | x | x | x | x | x | x | x | x | x | x | x | x | x | x | x |
| <i>Clinical Domain Global Impression</i> | | | | | | | | | | | | x | | | | |
| Infant Toddler Quality of Life ^b | | | | x | | | | x | | | | x | | | | x |
| Adverse Events | x | | | | | | | | | | | | | | | |
| Previous and Concomitant Treatments ⁿ | x | | | | | | | | | | | | | | | |

Appendix 2 Schedule of Assessments: Part 2 (cont.)

| Week | Wks 71-77 | Wk 78 | Wks 79-86 | Wk 87 | Wks 88-95 | Wk 96 | Wks 97-103 | Wk 104 | Open-Label Extension (OLE) | | | Early withdrawal | Follow Up Visit 1 | Follow Up Visit 2 | Follow Up Visit 3 |
|---|-----------|---------|-----------|---------|-----------|--------------|--------------|------------------------------|----------------------------|-------------|-------------|------------------|-------------------|-------------------|-------------------|
| | Day | Day 546 | Day 609 | Day 672 | Day 728 | Every 13 wks | Every 26 wks | Re-supply Visit ⁱ | EW + 8 ws | EW + 26 wks | EW + 52 wks | ±7 | ±14 | ±14 | |
| Visit Window | | ±7 | | ±7 | | ±7 | | ±7 | ±14 | ±14 | | | ±7 | ±14 | ±14 |
| Assessments | | | | | | | | | | | | | | | |
| Site Visit | | x | | x | | x | | x | x | x | | x | x | x | x |
| Home Visit ^d | x | | x | | x | | x | | | | x | | | | |
| Follow-up call ^e | | | | | | | | | | | | x | | | |
| Informed Consent | | | | | | | | | | | | | | | |
| Enrollment | | | | | | | | | | | | | | | |
| Eligibility | | | | | | | | | | | | | | | |
| Demography | | | | | | | | | | | | | | | |
| Medical History | | | | | | | | | | | | | | | |
| SMA History | | | | | | | | | | | | | | | |
| Physical Examination ^c | | x | | x | | x | | x | x ^h | x | | x | x | | |
| Significant life events including family | | x | | x | | x | | x | | x | | x | x | | |
| Vital Signs | | x | | x | | x | | x | | x | | x | x | | |
| ECG-12 lead | | x | | x | | x | | x | | x | | x | x | | |
| Haematology | | | | x | | | | x | | x | | x | x | | |
| Blood Chemistry | | | | x | | | | x | | x | | x | x | | |
| Administration of Study Medication | x | x | x | x | x | x | x | x | x | x | | | | | |
| Study medication dispensation/return ^d | x | x | x | x | x | x | x | x | x | x | x | x | | | |
| Protein binding Sample | | | | | | | | | | | | | | | |
| PK Blood Sample | | 4 | | 1 | | 4 | | 1 | | 1 | | x | | | |
| In vivo mRNA | | | | x | | | | x | | | | x | | | |
| SMN protein | | | | x | | | | x | | | | x | | | |
| Ophthalmology Examination ^g | | x | | x | | x | | x | x ^j | x | | x | x | x | x |
| Clinical genotyping | | | | | | | | | | | | | | | |
| BSID-gross motor score ^b | | | | x | | | | x | | x | | x | | | |
| HINE-2 ^b | | | | x | | | | x | | x | | x | | | |
| CHOP-INTEND ^b | | x | | x | | x | | x | | x | | x | | | |
| Respiratory Plethysmography ^b | | x | | x | | x | | x | | x | | x | | | |
| CMAP ^b | | | | x | | | | x | | x | | x | | | |
| Level of respiratory support | | x | | x | | x | | x | | x | | x | x | | |
| Nutritional check ^m | | x | | x | | x | | x | | x | | x | | | |
| Diary | x | x | x | x | x | x | x | x | | x | | x | | | |
| Infant Toddler Quality of Life ^b | | | | x | | | | x | | x | | x | | | |
| Adverse Events | | | | | | | | | | x | | | | | |
| Previous and Concomitant Treatments ⁿ | | | | | | | | | | x | | | | | |

Appendix 2

Schedule of Assessments: Part 2 (cont.)

- a Assessments should be performed in the following order, adverse events, previous/concomitant medication, confirmation of eligibility, followed by the order of assessments in Section 4.6.2.2 of protocol, Table 2 in the protocol.
- b See protocol Table 2 (Section 4.6.2.2) for assessments order and blocks of assessments at visits when efficacy measurements are performed
- c Physical examination will include weight, height, head and chest circumference, plus examination of skin, head, ears, nose, mouth and throat (buccal cavity, mucosa and oropharynx), neck and lymph nodes, respiratory, cardiovascular, abdomen, musculoskeletal, neurological and genitourinary systems.
- d Starting at Week 6, home visits may be scheduled for drug dispensation, return of unused drug, and supplies and any required assessments. *Resupply visits (site or home visits) will be performed to ensure the patient has adequate drug and supplies between scheduled site visits as necessary.*
- e The Investigator must agree with the parent/ caregiver when to perform the *mandatory* follow-up phone calls at the most appropriate time (day) between study visits. After Week 12, follow-up phone calls are per Investigator decision. If a patient withdraws from the study and the parent(s)/guardian(s) agrees, follow up phone calls should occur every 2 weeks after the early withdrawal visit until the FollowUp- Visit 1 to collect information on AEs and use of respiratory support.
- f Only SAEs.
- g For the details of the ophthalmology assessments, see Appendix 5 of the protocol.
- h *Only weight is required.*
- i Home *resupply* visits (or site visits if preferred by parent/guardian) after Week 104 *will be performed as necessary to ensure that the patient has adequate drug and supplies between scheduled site visits.*
- j *Additional PK samples may be taken if required for safety reasons.*
- k Patients will have a 24-hour PK sample taken, prior to receiving the second dose of RO7034067.
- l The confirmatory clinical genotyping sample can be collected at this visit or any following visit that includes blood sample collection.
- m A swallowing assessment will be performed at Day -1 and on Weeks 26, 52, 78 and 104 as outlined in Section 4.6.1.9 of the protocol.
- n This includes SMA related surgeries and procedures.