

PROTOCOL

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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MEDICAL MONITOR: [REDACTED], M.D., Ph.D.

SPONSOR: F. Hoffmann-La Roche Ltd

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FINAL PROTOCOL AMENDMENT APPROVAL

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Title
Company Signatory

Approver's Name
[REDACTED]

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PROTOCOL AMENDMENT, VERSION 7: RATIONALE

Protocol BP39056 Version 6 was released but is not effective; this Version 7 represents changes made to Version 5 of the protocol. The protocol has been amended to make the following changes to the study:

- Given the absence of any risdiplam-induced ophthalmological findings to date in 471 patients exposed to risdiplam for up to 3 years, the frequency of ophthalmology assessments has been reduced to every 6 months and color fundus photography will no longer be performed (Section 1.3.2, 4.6.1.8, Appendix 1, Appendix 2, and Appendix 5).
- The length of the open-label extension phase has been defined as 3 years for each patient to allow for a longer safety follow-up period. Continued access to risdiplam will be provided until the end of study, provided that risdiplam is not commercially available in the patient's country. The length of the study has been modified and will not exceed 5 years after the last patient is enrolled in the study (Sections 3.1.1.1, 3.1.1.2, and 3.1.5).
- Cautionary language on the concomitant use of CYP3A4 substrates has been removed, based on the recent results of the clinical drug-drug interaction Study BP41361 and subsequent physiologically-based pharmacokinetic modeling for extrapolation to children and infants. The study showed that coadministration with risdiplam led to only a small increase in exposure of the sensitive CYP3A substrate midazolam, which is not considered to be clinically relevant (Sections 1.2.1.2, 1.2.2, and 4.5.1).
- The safety monitoring period has been modified to extend from screening through the open-label extension, the study completion/early withdrawal visit, and follow-up (phone call). Language related to the study completion/early withdrawal visit and follow-up has been clarified to ensure that all assessments are performed at the last visit for each patient, and that the follow-up should occur 30 days after that visit (Sections 1.3.2, 3.3.1, and 4.5.1; Appendix 1 and Appendix 2).
- Safety monitoring and stopping rules for adverse events affecting the skin, mouth, pharynx, and larynx have been removed to align with current data on potential risks updated in the Risdiplam Investigator's Brochure, Version 7 (Sections 3.3.1, 4.6.1.4, 5.2.1, 5.2.2, 5.2.3, and 5.2.4.1; Table 4, Appendix 1, and Appendix 2).
- The adverse event reporting period has been reduced to 30 days after the study completion/early withdrawal visit (i.e., at least 30 days after the last dose of study drug), to reflect that adverse events are not expected beyond this reporting period; the elimination half-life of risdiplam will not exceed 30 days (Section 5.3.1).

Additional changes to the protocol, along with a rationale for each change, are summarized below:

- Background information on completed and ongoing studies of risdiplam has been updated (Section 1.2.2).

- Dosing instructions have been provided for patients ≥ 2 years of age and with body weight > 20 kg to align with the dosing regimen in Study BP39055 of risdiplam in patients ≥ 2 years old with Type 2 and Type 3 spinal muscular atrophy (Sections 3.1.1.2 and 3.2.1).
- Language regarding ophthalmological assessments has been amended to clarify the requirements for ophthalmological assessors and terminology related to the ophthalmology manual. In addition, the cover/uncover test has been reinstated as an assessment (erroneously omitted in previous protocol versions) and redundant language regarding ophthalmological assessments has been removed (Sections 3.3.1, 4.6.1.8, and 5.2.2; Appendix 5).
- It has been clarified that niacin is permitted if used as a nutritional supplement (Section 4.5.2).
- Language related to home visits has been modified for consistency with the schedules of assessments and for flexibility to allow additional assessments if needed (Section 4.6.1).
- Anthropometric measurement assessments have been revised to reflect appropriate methods for patients as they grow (Section 4.6.1.3).
- Efficacy assessments performed during the open-label extension phase have been reduced to improve patient experience, including removing respiratory plethysmography and compound muscle action potential and reducing the Bayley Scales of Infant and Toddler Development assessments (Section 4.6.1.14, Appendix 1, and Appendix 2).
- Specific details of the compound muscle action potential assessment have been clarified (Section 4.6.1.16).
- The timing of assessments during treatment has been amended to allow flexibility if the patient is uncooperative and to clarify assessments performed up to and including Week 104 and during the open-label extension phase (Section 4.6.2.2).
- A footnote to Table 5 (Adverse Event Severity Grading Scale) that had inadvertently been retained in protocol amendment Version 5 has been removed (Section 5.3.3).
- The statistical analysis description for the exploratory efficacy endpoints, clinician-reported respiratory function and ability to swallow, has been removed (Section 6.6.3).
- The Medical Monitor and applicable contact information has been changed throughout the protocol.
- The study drug name has been updated from RO7034067 to risdiplam throughout the protocol.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

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

PROTOCOL NUMBER: BP39056

VERSION NUMBER: 7

EUDRACT NUMBER: 2016-000778-40

IND NUMBER: 128972

NCT NUMBER: NCT02913482

TEST PRODUCT: Risdiplam (RO7034067)

MEDICAL MONITOR: [REDACTED], M.D., Ph.D.

SPONSOR: F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

Principal Investigator's Name (print)

Principal Investigator's Signature

Date

Please keep the signed original form in your study files, and return a copy to your local Study Monitor.

PROTOCOL SYNOPSIS

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

PROTOCOL NUMBER: BP39056

VERSION: 7

EUDRACT NUMBER: 2016-000778-40

IND NUMBER: 128972

NCT NUMBER: NCT02913482

TEST PRODUCT: Risdiplam (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 risdiplam in infants with Type 1 SMA, and to select the dose for Part 2.
- Part 2: To assess the efficacy of risdiplam 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 risdiplam.
- To assess the pharmacokinetics of risdiplam.
- To assess the pharmacodynamic effects of risdiplam (*SMN2* mRNA, SMN protein).
- To evaluate at 12 months of treatment with risdiplam 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 risdiplam 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 risdiplam, 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 risdiplam 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 risdiplam 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 risdiplam 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 risdiplam on muscle electrophysiology, as assessed by compound muscle action potential (CMAP).
- To explore the effect of treatment with risdiplam 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 risdiplam 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 risdiplam 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 risdiplam 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 risdiplam 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 risdiplam 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 risdiplam 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 risdiplam 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 risdiplam 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 risdiplam 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 *starting* 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 by the [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 risdiplam 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 risdiplam 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. *LPLV is expected to occur at the latest when the last patient enrolled in the study has completed 24 months in the treatment phase and 3 years in the open label extension.*

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

After completion of 24 months of treatment, each patient will enter the open-label extension phase for an additional 3 years. After a patient has completed 3 years in the open-label extension, the patient may continue in the study until EOS, provided that risdiplam is not commercially available in the patient's country.

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 assessments as appropriate for age.
- Physical examination.
- Anthropometric examination, including weight, height, head, and chest circumference.

Adverse events and concomitant medications will be monitored throughout the entire study (screening through *open-label extension or the study completion/early withdrawal visit and follow-up*).

PHARMACOKINETIC OUTCOME MEASURES

Blood samples for determination of plasma concentrations of risdiplam, 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 risdiplam 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 risdiplam drug substance as well as all excipients. The drug solution can be directly constituted with purified water in the bottle of the IMP.

risdiplam should be taken orally once daily. In the case of breastfeeding, the patient should be fed prior to dosing, wined, 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 risdiplam.

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 after 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 (risdiplam) 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 risdiplam, 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 risdiplam 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 retinal toxicity liabilities:** 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: quinolones (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 (*not applicable if used as a nutritional supplement*), rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon or any other drugs known to cause retinal toxicity.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse events
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC _{0-24h}	Area under the curve from time 0 to 24 hours
AUC _{0-24h,ss}	Area under the curve from time 0 to 24 hours at steady state
<i>AUC_{0-last}</i>	<i>Area under curve from time 0 to last measurable concentration</i>
BP	Blood pressure
BSID-III	Bayley scales of infant and toddler development – third edition
CDC	Centers for disease control and prevention
CHOP-INTEND	Children’s hospital of Philadelphia infant test of neuromuscular disorders
CMAP	Compound muscle action potential
C _{max}	Peak plasma concentration
CNS	Central nervous system
CRO	Contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	Concentration at the end of a dosing interval
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DTR	Deep tendon reflex
EC	Ethics Committee
ECG	Electrocardiograms
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EEA	European Economic Area
ERG	Electroretinogram
ESF	Eligibility Screening Form
EU	European Commission
FDA	Food and Drug Administration
FL	Full length

Abbreviation	Definition
FMO	Flavin monooxygenase
GI	Gastrointestinal
HDAC	Histone deacetylase
HINE	Hammersmith infant neurological examination
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	Health-related quality of life
ICH	International Conference on Harmonisation
iDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
IMC	Internal monitoring committee
IMP	Investigational medicinal product
IRB	Institutional Review Board
ITQOL-SF47	Infant/toddler quality of life questionnaire - short form 47 item version
ITT	Intent-to-treat
IxRS	Interactive (voice/web) response system
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDH	Lactate dehydrogenase
LPLV	Last patient, last visit
MATE	Multidrug and toxin extrusion
MDR	Multidrug resistance
NCI	National Cancer Institute
█	█
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NP	Negative peak
OAT	Organic anion transporter
OATP	Organic anion-transporting protein
OCT	Optical coherence tomography
OCT-2	Organic cation transporter-2
OTC	Over-the-counter
PBPK	Physiologically-based pharmacokinetic
PD	Pharmacodynamic
PK	Pharmacokinetic
P-gp	P-glycoprotein
QRS	QRS complex
QT	QT interval

Abbreviation	Definition
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate using the Bazett's correction factor
RBC	Red blood cell
RNA	Ribonucleic acid
RP	Respiratory plethysmography
RR	RR interval
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD-OCT	Spectral domain-optical coherence tomography
SMA	Spinal muscular atrophy
SMN	Survival of motor neuron
<i>SMN1</i>	SMN1 gene
SoA	Schedule of assessments
t_{max}	Time of maximum concentration
ULN	Upper limit of normal
US	United States
WBC	White blood cell

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON DISEASE

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness and profound neuromotor disability beginning in infancy (Crawford et al 1996; Lunn et al 2008). It is the leading genetic cause of mortality in infants and young children, with an incidence of 1 in ~11,000 live births and a carrier frequency estimated at 1 in 50–70 individuals (Sugarman et al 2012).

Clinically, SMA ranges in disease severity. For classification purposes, patients are usually categorized into four main subtypes based on clinical criteria, including achieving (or failing to achieve) physical motor milestones, age of onset and life span (Munsat et al 1992): Type 1 SMA or Werdnig-Hoffmann disease (severe infantile type, onset before 6 months of age, patients never sit without support, with death due to respiratory distress usually within 2 years), Type 2 SMA (intermediate chronic infantile type with onset after the age of 6 months, unable to stand or walk without support), Type 3 SMA or Kugelberg-Welander disease (chronic juvenile type with onset around the age of 18 months, children are able to walk until the disease progresses) and Type 4 SMA (adult onset). A fifth type, denoted as Type 0, has been proposed for extremely severe SMA that manifests during fetal life and results in death within a few weeks after birth (Kolb et al 2011). This clinical trial will enroll Type 1 SMA patients only.

SMA is caused by a homozygous deletion (95% of cases) or mutation of the Survival of Motor Neuron (*SMN*) 1 gene on chromosome 5q (locus 5q13), which encodes SMN, an essential protein expressed in both neuronal and non-neuronal cells (Lefebvre et al 1995). In humans, there are two SMN genes, the *SMN1* gene and its paralog *SMN2*. Species other than human have only one SMN gene, which is equivalent to the human *SMN1* gene. Due to a translationally synonymous C to T mutation at nucleotide 6 in exon 7, the *SMN2* pre-mRNA undergoes alternative splicing, which excludes exon 7 from 85-90% of mature *SMN2* transcripts producing an unstable SMN $\Delta 7$ protein that is rapidly degraded (Lorson et al 1999; Cho et al 2010). Accordingly, full-length *SMN2* mRNA is generated in only 10-15% of splicing events. Since SMA patients only have the *SMN2* gene, their SMN protein levels are significantly decreased (Kolb et al 2011).

In all types of SMA, as the disease progresses, clinical symptoms include hypotonia, symmetrical muscle weakness and atrophy (predominantly of the proximal muscles of the shoulder and pelvic girdle), diminished or absent deep tendon reflexes (DTRs), tremor of fingers and hands, fasciculation of the tongue muscles, and hyporeflexia with orthopedic deformities (contractures, scoliosis). Progressive respiratory failure and frequent pulmonary infections and super-infections are common in Types 1 and 2 SMA. Other common comorbidities include failure to thrive, sleep difficulties, pneumonia, osteopenia and osteoporosis with pathological fractures, poor cough and secretion

clearance, reduced vital capacity, gastroesophageal dysmotility, urinary incontinence, hip dislocation, and joint and muscle pain.

As the medical need in SMA is very high, several drug candidates are currently under investigation in the nonclinical and clinical setting (Lewelt et al 2012; d'Ydewalle et al 2015). The SMN2-targeting antisense oligonucleotide, nusinersen (Spinraza™), has been approved by health authorities in the United States, European Union, Canada, and other jurisdictions for the treatment of SMA in pediatric and adult patients, and marketing applications have been submitted to other regulatory authorities for approval.

Alternative management strategies focus on prevention and treatment of comorbidities, such as failure to thrive, surgical and non-surgical treatment of scoliosis and contractures, pulmonary hygiene, non-invasive ventilation, mobility and seating support, and physical and occupational therapy.

1.2 BACKGROUND ON RISDIPLAM

One of the promising pharmacological strategies currently being pursued is to restore SMN protein levels in SMA patients by modulating *SMN2* splicing to favor the inclusion of exon 7 into the mRNA transcript, thereby increasing expression of stable full-length protein from the *SMN2* gene (Kolb et al 2011; Nurputra et al 2013). One such compound currently being developed is risdiplam, which directly targets the underlying molecular deficiency of the disease and promotes the inclusion of exon 7 to generate full-length *SMN2* mRNA, which increases the production of functional SMN protein. SMN protein increase after treatment with risdiplam has been shown in fibroblasts and motor neurons derived from patients with SMA.

Risdiplam is a follow-up compound to RO6885247, another *SMN2* mRNA splicing modifier which in SMA patients increased levels of full length (FL) *SMN2* mRNA, and reduced levels of *SMN* Δ 7 mRNA. SMN protein in blood increased by up to 2-fold compared to baseline in these patients. The study, BP29420, further showed that the compound RO6885247 was well tolerated in 9 adolescent and adult SMA patients at the 10 mg dose/day for 12-week treatment, with no deaths, serious adverse events (SAEs), or withdrawals due to adverse events (AEs). The main AEs reported were influenza (three patients) and diarrhea (two patients).

See the Risdiplam Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Previous Nonclinical Studies

1.2.1.1 Pharmacology

Risdiplam effectively corrects the dysfunctional splicing of human *SMN2* pre-mRNA in cultured cells by shifting the balance of the alternative splicing reaction completely towards the inclusion of *SMN2* exon 7 and the production of the full-length mRNA and functional SMN protein. In vivo, risdiplam effectively corrects the dysfunctional splicing of the human *SMN2* pre-mRNA in SMA mouse models (the severe SMN Δ 7 model and the

milder C/C-allele model) carrying human *SMN2* transgenes. This correction results in a significant increase in SMN protein levels and a profound prolongation of animal survival, protection of the neuromuscular circuit, and improvement of motor function in the SMN $\Delta 7$ mouse model of severe SMA.

1.2.1.2 Pharmacokinetics

Risdiplam is well-absorbed in rats and monkeys following oral administration. The compound has very low intrinsic clearance in vitro and in vivo, and has free-fraction values of 11, 15, 16, and 10% in human, monkey, rat and mouse plasma, respectively. In human plasma, risdiplam is predominantly bound to serum albumin, with no binding to alpha-1 acid glycoprotein. This results in low systemic clearance in animals and a low predicted systemic clearance in humans. Based on physicochemical properties and in vivo studies in rats, mice and monkeys, risdiplam is predicted to enter the central nervous system (CNS) in humans. Risdiplam is highly bound to melanin in vitro and accumulates into melanin-containing structures of the eye in pigmented rats and monkeys.

Risdiplam is cleared in animals primarily through metabolism with minor contribution from renal clearance. The enzymes involved in human metabolism of risdiplam are flavin monooxygenase (FMO) 1 and 3 and multiple members of the cytochrome P450 superfamily (CYP), especially CYP3A isoenzymes. Risdiplam is not a substrate for human P-glycoprotein (P-gp). The potential for interaction with other drugs that inhibit or induce metabolizing enzymes or active transport proteins cannot be ruled out at this stage of development.

Risdiplam is not an inhibitor of human multidrug resistance protein 1 (MDR1), organic anion-transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1 or OAT3. It is therefore unlikely that co-administration with risdiplam will alter the pharmacokinetics (PK) of other drugs whose disposition is influenced by these transporters. However, risdiplam is an inhibitor of organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE)1 and MATE2-K and the potential for interaction with other drugs that are substrates of those transport proteins cannot be ruled out at this stage. Such drugs are therefore prohibited for patients participating in this study (Section 4.5.2).

1.2.1.3 Toxicology and Safety Pharmacology

A toxicology and safety pharmacology program using risdiplam has been conducted according to the ICH guidelines, with all pivotal studies conducted in compliance with GLP regulations. Pivotal toxicity studies with once daily oral gavage administration of risdiplam of up to 26 weeks in duration were conducted in the juvenile and adult rat and up to 39 weeks in young cynomolgus monkey. In addition, various genotoxicity and safety pharmacology studies have been conducted and, because of the absorption of risdiplam in the UV range, the potential for phototoxicity was also studied in vitro. Mechanistic investigations in vitro and in vivo to elucidate mechanisms of toxicity based

on physicochemical properties and secondary splice target identification were conducted. As risdiplam is being developed to chronically treat SMA, which in its most severe form manifests itself soon after birth, the toxicity testing strategy includes a 39-week toxicity study that was started with young, 2-year old monkeys (with animals still being pre-or peri-pubertal at the end of 39 weeks of treatment and after the 22-week recovery phase), and two repeat-dose GLP juvenile toxicity studies in rats: i) a 13-week rat juvenile study with treatment immediately post-weaning (PND 23-24), and ii) a 4-week rat juvenile study with animals dosed from PND 4 until PND 32. These studies included dedicated assessments of critical developing organ systems according to the available guidelines issued by FDA and CHMP. In addition, a 13/26-week toxicity study in pigmented rats has been conducted to study the onset, if any, and progression of changes in the retina using light/electron microscopy, sdOCT and ERG assessments. In this study, histopathological evaluation of other organs of interest (brain, pancreas and adrenals) was included to compare results of the 26-week chronic toxicity study in albino rats across rat strains.

Safety pharmacology studies in vitro and in vivo conducted with risdiplam did not demonstrate any noteworthy effects.

Findings of toxicological significance for risdiplam were observed in organs with rapid cell turnover in mice, rats, and monkeys and included:

- Micronucleus induction in vitro in mouse cell lines and in rat bone marrow erythroblasts.
- Findings in gastrointestinal (GI) epithelia (increased apoptosis/single cell necrosis) and lamina propria (vacuolation) in mouse, rat, and/or monkey.
- Parakeratosis/hyperplasia/degeneration of the skin, tongue and larynx epithelia with associated inflammation in monkey.
- Degeneration of germ cells in monkey and rat testes.
- Further test item-related findings were observed in hematology (red and white cells) with correlates in small thymus and thymus atrophy in monkeys but without histopathological changes in bone marrow.

Risdiplam-related findings were associated with a clear no-observed-adverse-effect level (NOAEL) and/or a clear statistical threshold using a benchmark dose approach (for micronucleus induction in rat bone marrow).

Evidence suggests that these effects of risdiplam on proliferating cells and tissue are related to alternative splicing effects on secondary targets such as the Forkhead box protein M1 (FoxM1), a major cell cycle regulating factor, and MAP kinase activating death domain (MADD), a gene with various splice variants involved in apoptosis. Further secondary splice targets have been identified but insufficient data are published on the biological impact of changes in splice variant expression.

A further finding of toxicological significance for risdiplam was noted in the retina from the 39-week toxicity study in monkeys. Multifocal peripheral retina degeneration in the photoreceptor layer and microcystic spaces in the inner retinal layers in monkeys was detected by spectral domain-optical coherence tomography (OCT). This was associated with depressed scotopic (rod) B-wave and somewhat less affected photopic (cone) B-wave in the electroretinogram (ERG). These findings were confirmed by histopathology. OCT and ERG are indicative of partial/slow recovery of some parameters in the 22-week recovery phase. The effect on the retina is thought to be connected with evidence of high melanin binding and tissue retention in the retina and impairment of lysosomal function/autophagosomal accumulation in retinal pigmented epithelial cells.

Further noteworthy observations were major differences in tolerability with repeated oral dosing in young (pre- and post-weaning) and adult rats with much higher susceptibility of younger rats to toxic effects of risdiplam than older rats at comparable doses. However, when free exposure to risdiplam is compared between species and ages, no major differences in exposure associated with subacute dose-limiting toxicity are recorded.

In terms of chronic treatment of SMA patients, it is proposed to evaluate doses not exceeding the exposure at the NOAEL/NOEL of the 39-week toxicity study in monkeys with an area under the curve from time 0 to 24 hours (AUC_{0-24h}) of 1870/2060 ng •h/mL in males and females, respectively. Young/very young rats displayed a higher dose-based susceptibility to the subacute, life-threatening toxicity of risdiplam than older rats likely based on a higher free fraction and longer half-life. Thus, in the upcoming clinical studies, careful evaluation of the free fraction of risdiplam in plasma of infants and children is warranted, with specific adaptation of the doses to be tested if differences in plasma protein binding similar to those seen in rats of different ages should be found.

See the Risdiplam Investigator's Brochure for details on nonclinical and clinical studies.

1.2.2 Previous and Ongoing Clinical Studies

As of *March 2020*, risdiplam has been investigated in *five* clinical pharmacology studies: Study BP29840 (SAD, entry-into-human study in healthy male adults); Study NP39625 (a PK study in healthy Japanese adults); Study BP39122 (a mass balance study in healthy male adults); *Study BP41361 (a drug-drug interaction [DDI] study with the CYP3A substrate midazolam, and Study BP40995 (hepatic impairment study)*. All four studies (BP29840, NP39625, BP39122 and BP41361) have been completed; *Study BP40995 is clinically complete but the Clinical Study Report is pending (see the Risdiplam Investigator's Brochure for available data)*.

In Study BP41361, it was observed that administration of risdiplam once daily for 2 weeks in healthy adult subjects slightly increased the exposure of midazolam, a sensitive CYP3A substrate, by 11% for area under curve from time 0 to last measurable concentration (AUC_{0-last}) and 16% for peak plasma concentration (C_{max}). However, the observed magnitude of this effect is not considered clinically relevant. Based on

physiologically-based pharmacokinetic (PBPK) modeling, a similar magnitude of the effect is expected in children and infants as young as 2 months old.

Additionally, there are *four* ongoing studies in patients with SMA: Study BP39054 (an open-label safety and PK/pharmacodynamic (PD) study in non-naïve patients with SMA Type 2 or 3); Study BP39055 (a study to evaluate safety, PK/PD, and efficacy in patients with Type 2 and 3 SMA); Study BN40703 (an open-label study in infants with genetically diagnosed and presymptomatic SMA); and the present study (BP39056).

Current data for ongoing studies is provided in the Risdiplam Investigator's Brochure.

1.2.2.1 Clinical Summary Study BP29840

Study BP29840 consisted of a single ascending dose (SAD) part, including an exploratory investigation of the effect of food, in 25 healthy male subjects of whom 18 received risdiplam at doses ranging from 0.6 mg to 18 mg, and an itraconazole interaction part in 8 subjects.

Risdiplam was rapidly absorbed with a median t_{max} between 2 and 3 hours under fasted conditions. C_{max} and total plasma exposure (area under the curve; AUC) increased in a dose-proportional manner. The elimination half-life was approximately 40 to 50 hours. On average, a small fraction (<10%) of the administered dose was excreted unchanged into urine. Food had no relevant effect on the PK of risdiplam; only the median t_{max} was delayed to 5 hours.

The co-administration of risdiplam with itraconazole resulted in a slight (11%) increase in AUC_{0-120h} and a slight decrease in C_{max} .

Risdiplam had a dose-dependent effect on SMN2 splicing, as shown by a change in the ratio of full-length SMN2 mRNA to SMN Δ 7 mRNA which is interpreted as proof of mechanism in terms of the expected PD effect.

Risdiplam was well-tolerated in this study at all dose levels. There were no deaths, serious adverse events (SAEs) or withdrawals due to adverse events (AEs). No clinically relevant changes in laboratory safety parameters, vital signs, AEs, electrocardiogram (ECG) parameters or ophthalmological assessments were observed.

A total of 27 AEs were reported in the SAD and itraconazole interaction parts. All AEs were of mild intensity and resolved within a short period of time without sequelae. All AEs were considered to be not related to risdiplam by the Investigator with the exception of pollakiuria (placebo) and headache (risdiplam 18 mg).

The most frequently affected System Organ Class was GI disorders (9 AEs) followed by nervous system disorders (4 AEs). The most frequently reported AEs were headache (4 subjects) and diarrhea, abdominal pain and nasopharyngitis (3 subjects each).

There was no dose-related increase in the incidence or severity of reported AEs and no cluster of AEs indicative of a toxic effect of the compound on a given organ system.

More recent and detailed information is provided in the Risdiplam Investigator's Brochure.

1.2.2.2 Clinical Summary Study BP39055 (Part 1)

As of September 2017, 51 patients have been enrolled in Part 1 of Study BP39055, evaluating the safety, tolerability, PK and PD of risdiplam in patients with Type 2 and Type 3 (ambulant or non-ambulant) SMA, with the objective to select the dose for Part 2 of the study.

These 51 patients were enrolled in five cohorts and randomized in a 2:1 ratio to active treatment or placebo. Patients were initially assigned to the following dose levels: 3 mg and 5 mg once daily in patients aged 12–25 years old; and 0.02 mg/kg, 0.05 mg/kg, and 0.25 mg/kg in patients aged 2–11 years old.

An overview of current data can be found in the Risdiplam Investigator's Brochure.

Across these dose levels, risdiplam PK was linear (i.e., there was a corresponding increase in risdiplam plasma concentrations with increase in dose). Steady state was attained after 7–14 days of treatment with risdiplam once daily.

A dose related increase in SMN protein was observed across all dose levels and age groups upon treatment with risdiplam, with a median SMN protein increase of 151% (range 49%–251%) versus baseline at 5 mg in the age group of 12–25 years old, and a 96% (range 17%–150%) increase at 0.25 mg/kg in the age group of 2–11 years old.

A review of all available safety laboratory results, vital signs, ECGs, and ophthalmological assessments did not show any clinically significant adverse findings as compared with baseline or the placebo group.

Risdiplam was well tolerated across all dose levels tested in both age categories and no stopping rules were met. There have been no deaths and no discontinuations from the study for any reason.

Based on these data, a dosing regimen of 5 mg for patients with a body weight ≥ 20 kg and 0.25 mg/kg for patients with a body weight < 20 kg was selected for Part 2 of Study BP39055.

More recent and detailed information is provided in the Risdiplam Investigator's Brochure.

1.2.2.3 Clinical Summary Study BP39056 (Part 1)

The final dose levels selected for Part 2 of this study are 0.08 mg/kg and 0.2 mg/kg, based on the PK data obtained until February 2018 in 16 infants. The mean $AUC_{0-24h,ss}$ was 1700 ng•h/mL with 0.08 mg/kg in infants <5 months old at enrollment, 747 ng•h/mL with 0.08 mg/kg in infants ≥5 months old at enrollment, and 2040 ng•h/mL with 0.2 mg/kg in infants ≥5 months old at enrollment.

Lower clearance and greater exposure was observed in 3 infants <5 months old at the time of enrollment, and therefore the dose in these infants was reduced to 0.08 mg/kg whereas infants ≥5 months old at the time of enrollment received a final dose of 0.2 mg/kg. Per the protocol, the first 3 infants enrolled in the study remained at the dose of 0.08 mg/kg for a target exposure of 700 ng•h/mL.

A median 2-fold increase (range 1.0–5.4) in SMN protein in blood versus baseline was observed for infants with an exposure (AUC_{0-24h}) ≤ 1000 ng•h/mL, and a median 3.2-fold increase (range 1.6–6.5) was obtained in infants with an exposure (AUC_{0-24h}) > 1000 ng•h/mL.

A review of all available safety laboratory results, vital signs, ECGs, and ophthalmological assessments did not show any clinically significant adverse findings as compared with baseline.

Two patients had discontinued from the study due to fatal progression of SMA disease. Events with a fatal outcome reported in these patients were viral respiratory tract infection in 1 patient, and cardiac arrest and respiratory arrest in another patient (all considered to be unrelated to study treatment).

Five additional patients experienced SAEs: pneumonia (2 events in 1 patient), acute respiratory failure, atelectasis, hypoxia, pneumonia aspiration, respiratory distress, neutropenia, influenza, and upper respiratory tract infection. All but one SAE (neutropenia, resolved) were considered as unrelated to study treatment. There have been no AEs leading to modification or permanent withdrawal of study treatment.

Overall, risdiplam was well tolerated across all dose levels tested and no stopping rules were met.

More recent and detailed information is provided in the Risdiplam Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

SMA is the leading genetic cause of death in infants and young children. It is a devastating disease: Type 1 SMA results in almost inevitable mortality within a few years of diagnosis. One drug was recently approved in the United States, European Union,

Canada, and other jurisdictions for the treatment of SMA in pediatric and adult patients (the antisense oligonucleotide nusinersen [Spinraza™]) but, the medical need in SMA is still very high. There is currently no oral treatment for SMA that provides stabilization or improvement of motor function and development, which would be of immense value for patients and parents/ caregivers.

Small molecule *SMN2* splicing modifiers such as risdiplam represent a potential treatment option for patients with SMA, as they increase the amount of SMN protein. Deficiency of SMN protein is the fundamental pathophysiological mechanism of SMA. There is increasing preclinical evidence to suggest that SMN restoration in the CNS results in significant improvements in survival, motor function and disease pathology but is insufficient to fully ameliorate the SMA phenotype (Porensky et al 2012; Passini et al 2011). By restoring SMN protein levels in both the CNS and in peripheral tissue, orally administered *SMN2* splicing modifiers are accordingly hypothesized to provide improved efficacy over compounds currently in development administered to the CNS only (Hua et al 2011).

Risdiplam has demonstrated effective correction of splicing of the human *SMN2* gene. The compound shifts the balance of alternative splicing completely towards inclusion of *SMN2* exon 7 and production of functional SMN protein in human cultured cells and in SMA mouse models (for details, see the Risdiplam Investigator's Brochure). Proof of mechanism for the change in *SMN2* splicing in terms of *SMN2* mRNA was established with risdiplam in a single ascending dose study in healthy subjects. Proof of mechanism in terms of an increase in SMN protein was previously demonstrated with another compound having a similar mechanism of action, RO6885247, with an up to 2-fold increase in SMN protein observed upon treatment with RO6885247.

This study is designed to assess the safety, tolerability, PK and PD of risdiplam in patients with Type 1 SMA aged 1 to 7 months at enrollment, across the exposure range that is expected to provide therapeutic benefit: Part 1, testing two dose/exposure levels of risdiplam in a dose-escalation- manner, and in Part 2, to assess the efficacy and safety of treatment with risdiplam at the dose-level selected from Part 1. The dose-selection approach for Part 2 aims at maximizing efficacy and therapeutic benefit by targeting the maximum SMN protein blood level that can be safely achieved in Type 1 SMA patients, as determined in Part 1 (Section 2 and Section 3.2.2).

As this is the first study with risdiplam in infants with Type 1 SMA, safety and tolerability, PD and PK of risdiplam will be assessed in detail in Part 1, to enable dose-selection for Part 2. Pharmacodynamic effects of risdiplam will be measured in terms of SMN protein and *SMN* mRNA splice forms in blood. Efficacy will be assessed in terms of motor function and motor development milestones with the Gross Motor Scale of the Bayley Scales of Infant and Toddler development – Third Edition (BSID-III; Bayley 2006) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND; Glanzman et al 2010; Glanzman et al 2011). Respiratory function will

be measured by respiratory plethysmography (RP). Other treatment effects will be measured by assessing quality of life and relevant biomarkers (Section 4.6.1.15).

1.3.2 Benefit-Risk Assessment

In the SAD study (BP29840; Section 1.2.2), risdiplam was shown to be safe and well tolerated up to a single dose of 18 mg. This study established proof of mechanism in healthy subjects that, at safe and tolerable doses, risdiplam is able to modulate the splicing of *SMN2* mRNA, leading to an exposure-dependent increase in the amount of full-length *SMN2* (FL-*SMN2*) mRNA and a corresponding decrease in the amount of *SMN2* mRNA lacking exon 7. In Part 1 of Studies BP39055 and BP39056 (see interim data summarized in Section 1.2.2), treatment with risdiplam was safe and well tolerated, and an exposure dependent increase in SMN protein was observed confirming proof of mechanism in patients with SMA. Accordingly, available data to date suggest that risdiplam may provide benefit for patients with SMA.

In view of the adverse findings in the animal toxicology studies, the maximum exposure in the first clinical trial in healthy volunteers (HV) was limited to an individual plasma exposure (AUC_{0-24h}) of 1500 h •ng/mL, to ensure the safety of the participating healthy subjects while assessing safety and tolerability up to a therapeutically relevant exposure level, and to determine essential PK and PD information to support modeling activities and selection of the starting dose for therapeutic trials in infants.

In this study, a slightly higher exposure cap of 2000 h •ng/mL (mean $AUC_{0-24h,ss}$) corresponding to the overall NOAEL of the 39-week toxicology study in cynomolgus- monkey, along with a thorough clinical safety monitoring plan is justified, considering the potential benefit for Type 1 SMA patients enrolled. At the dosing regimen selected for Part 2 of the study, the predicted exposure is a mean $AUC_{0-24h,ss}$ of 1650 ng•h/mL in infants 3–5 months old at enrollment with a dose of 0.08 mg/kg, and a predicted mean $AUC_{0-24h,ss}$ of 2020 ng•h/mL in infants ≥ 5 months old at enrollment with a dose of 0.2 mg/kg. Because this prediction is based on a small number of patients from Part 1, exposure will be monitored in all infants enrolled in Part 2 and the dose adjusted if necessary, to ensure that infants are in the targeted exposure range.

Each dose level to be tested in this study has the potential to provide therapeutic benefit to SMA patients. Available data suggest that a 100% increase in SMN protein levels (the target for the lower dose level tested in Part 1) could turn severe SMA phenotypes into milder forms, while further increase may provide even greater benefit (Section 3.2.1). In Part 1 of the study, a median 2-fold increase (range 1.0–5.4) in SMN protein in blood versus baseline was observed for infants with an exposure (AUC_{0-24h}) ≤ 1000 ng•h/mL, and a median 3.2-fold increase (range 1.6–6.5) was obtained in infants with an exposure (AUC_{0-24h}) > 1000 ng•h/mL.

Safety precautions are provided and a thorough safety monitoring plan focusing on liabilities identified in the nonclinical toxicology studies will be implemented to address

potential safety concerns for the patients enrolled in the trial (Section 5.2). Toxicological findings observed in the nonclinical studies include toxicity involving skin, pharynx/larynx, fertility, potential for genotoxicity based on micronucleus induction and potential irreversible retinal toxicity that could translate into some visual impairment.

With this regard, it is essential to note that the changes found by OCT scanning (and on histopathology) in the peripheral retina in the 39-week monkey study may produce peripheral visual field defects that initially may be asymptomatic. These defects would be similar to those found in early stage peripheral retinal degeneration, and pan-retinal photocoagulation for diabetic retinopathy; initially central visual function is spared in these conditions.

With the extensive ophthalmological monitoring that is included in this study (*and across the risdiplam clinical trial program*) including OCT, possible retinal toxicity in patients should be detected early in a sensitive and timely fashion, conceivably before irreversible functional retinal damage appears. In case of clinically relevant peripheral retinal toxicity, stopping rules will apply (Section 5.2.3), since progression of toxicity and involvement of the macula cannot be ruled out. Based on these elements, the ophthalmological monitoring strategy and stopping rules included in this study appear appropriate to i) minimize the risk of irreversible symptomatic retinal injury, and ii) detect peripheral retinal abnormalities early when peripheral visual field defects would likely be asymptomatic. Implemented ocular monitoring is also addressing functional and structural integrity of central retina and general eye examination.

The key elements of risk management in this study considering nonclinical findings and clinical experience are summarized below:

- Frequent PK assessments (especially in Part 1, Section 1.2.1.3), including the assessment of the free fraction at screening as a precaution to take into account possible differences in plasma protein binding in children compared to adults, to ensure that risdiplam exposure remains below the exposure cap. In Part 2, the PK data will be regularly (every 2 weeks, but may be adjusted on the basis of the data) reviewed by the Clinical Pharmacologist, and on the basis of the PK monitoring, the dose of individual or all infants may be adjusted to ensure that the infants are in the targeted exposure range and in compliance with the exposure cap.
- Safety monitoring throughout the treatment period, *open-label extension, study completion/early withdrawal visit, and follow-up* (Section 5.2.1), including ophthalmology, dermatology and clinical laboratory measures.
- Clear definition of dose-escalation criteria and cohort stopping rules in Part 1 (Section 5.2.4).
- Stopping rules at the individual patient level in Part 1 and Part 2 (Section 5.2.4).
- Inclusion of a guideline for managing specific adverse events (Section 5.2.3).

- Implementation of an IMC (Part 1; Section 3.1.2) and an external independent Data Monitoring Committee (iDMC; Part 2; Section 3.1.3), who will review safety, PK and PD data on a regular and ad-hoc basis throughout the study.
- Appropriate inclusion/exclusion criteria and guidance regarding prohibited therapy (including CYP3A4 inhibitors/inducers, organic cation transporter [OCT]-2 and MATE substrates, FMO inhibitors and substrates, and medications with potential retinal toxicity; Section 4.5).

The strategy and rationale for dose-selection is described in Section 3.2.1. Table 1 gives an overview of the margins versus key toxicities of risdiplam at the starting exposure of this study and at the exposure cap. The safety margins for the targeted exposure in Part 2 are the same as for the exposure cap, because the highest possible dose at the exposure cap has been selected to maximize the increase in SMN protein and subsequently the chance for clinical efficacy in infants with Type 1 SMA.

Based on adverse findings on testes observed i) in both species ii) at exposure matching clinical target exposure, the potential for risdiplam to affect male germ cells and fertility in human is possible. However, from animal studies, there is evidence that the study drug affects the juvenile pachytene spermatocytes with no evidence of targeting the stem cells. Hence, reversibility of the effect would be expected if treatment with risdiplam is discontinued.

Table 1 Overview of the Margins versus Key Toxicities of Risdiplam

Type of Toxicity	Margin at NOAEL vs Starting Exposure of 700 ng • h/mL (AUC _{0-24h})	Margin at NOAEL vs Cap Exposure of 2000 ng • h/mL (AUC _{0-24h})
Micronucleus induction in rat bone marrow	~5	~1.5
Testis toxicity in rats and monkeys	~1	no
Epithelial findings (skin, eyelid, larynx) in monkeys	> 10	>2.5
Hematology changes (RBC and lymphocytes) in monkeys	> 10	>4
Retina changes in monkeys	~3	~1
Overall NOAEL (13 weeks of treatment: juvenile rat)	~10	>3
Overall NOAEL (39 weeks of treatment: monkey)	~3	~1

NOAEL: no-observed-adverse-event level; RBC: red blood cell.

The potential benefit of treatment with risdiplam for Type 1 SMA patients would be an increase in SMN protein levels, in the central nervous system and peripheral tissues, such as muscles and endothelial cells. This pharmacological effect is hypothesized to

translate into an improvement of patients' motor milestones achieved, pulmonary function and overall, a better health status. Following this hypothesis, by the end of the study, major milestones, like sitting without support in some patients and at least stop or slowing of disease progression and its associated co-morbidities, are hypothesized to be achieved. In some patients, beneficial effects in pulmonary function and normalization in motor milestone development are also hypothesized to be seen.

Overall, considering the disease severity of SMA patients and the potential for these patients to benefit from treatment with risdiplam, Roche considers the safety margins in this study appropriate, and data from Part 1 of the study continue to justify the benefit-risk of treatment with risdiplam for 1- to 7-month old patients (at enrollment) with Type 1 SMA.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVES

The primary objectives for the study are as follows:

- **Part 1**

To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in infants with Type 1 SMA, and to select the dose for Part 2.

- **Part 2**

To assess the efficacy of risdiplam 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).

2.2 SECONDARY OBJECTIVES

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

- To assess the safety and tolerability of oral treatment with risdiplam.
- To assess the pharmacokinetics of risdiplam.
- To assess the pharmacodynamic effects of risdiplam (*SMN2* mRNA, SMN protein).
- To evaluate at 12 months of treatment with risdiplam 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 risdiplam 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 risdiplam, 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 risdiplam 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.

2.3 EXPLORATORY OBJECTIVES

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

- To explore the effect of treatment with risdiplam 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 risdiplam 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 risdiplam on muscle electrophysiology, as assessed by compound muscle action potential (CMAP).
- To explore the effect of treatment with risdiplam 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 risdiplam 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 risdiplam 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 risdiplam 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 risdiplam the change from baseline in weight and length/height percentiles.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a seamless open-label, single-arm, multi-center clinical study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of risdiplam 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). This exploratory part will consist of at least 8 infants and up to 24 infants (if required) to assess the safety, PK and PD profile of risdiplam in infants and determine the dose for 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 risdiplam at the dose selected in Part 1 over a 24-month treatment period, with the primary endpoint analyzed at 12 months of treatment.

In both Part 1 and Part 2, after 24 months of treatment patients will enter an open-label extension phase.

In both Part 1 and Part 2, after a patient completes Week 104 it may be possible for the patient to be allocated to another site, following discussion and agreement by the Sponsor. If this occurs, the reallocation will not be considered a new enrollment in the study.

The study will progress in an operationally seamless manner from Part 1 into Part 2 after the dose selection decision has been taken (see Section 3.2.1).

3.1.1.1 Exploratory Part 1

Infants (between the age of 1 and 7 months at enrollment) will be enrolled in a staggered manner in this dose escalation study.

The first infant will receive a single dose of the study drug risdiplam to assess safety and tolerability, and PK (Section 3.2.1). If this single dose of the study drug is safe and well tolerated in this first infant, and after the PK has been assessed and evaluated, this infant will continue treatment with risdiplam 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. PK, safety and tolerability will be assessed prior to enrolling 2 additional patients (1 to 7 months). Safety and tolerability, PK and PD will be closely assessed, and the dose adjusted as required based on actual measured PK versus the predicted target exposure.

In the unlikely case that PK measurements are below the limit of quantification (BLQ) after administration of the first single dose, this first infant will repeat the single dose administration with a higher dose which is predicted to be quantifiable but below the exposure cap.

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 (Section 5.2.4), 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 risdiplam 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 risdiplam 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.

Since Part 1 of the study is exploratory in nature, it may be decided to explore additional or intermediate dose/exposure levels, or to enroll additional infants (up to a maximum total number of 24 infants in Part 1), if required to better characterize the safety and tolerability or PK of risdiplam in infants, and to be able to select the appropriate dose for Part 2.

Once the dose for Part 2 has been selected, upon appropriate safety and tolerability, and without any interruption of treatment, all infants (including the first 4 infants enrolled at Dose Level 1) will be given the possibility to continue receiving risdiplam at the dose selected for Part 2 as part of an extension phase. The open-label extension phase, beginning after 24 months of treatment, will include regular monitoring of safety, tolerability and efficacy will continue *for an additional 3 years for each patient, as outlined below.*

As the infants grow and develop, the dose may need to be adjusted based on body weight, age, or other parameters identified, in order to maintain the exposure level over time in an individual growing infant (i.e., the dose administered may be higher than the dose levels explicitly listed in the protocol, provided the measured and observed PK exposure is in compliance with the exposure cap of a mean $AUC_{0-24h,ss}$ of 2000 ng•h/mL).

The duration of the study for each infant enrolled in Part 1 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]), *followed by treatment for 24 months from the start of dosing*
- *Open-label extension: for an additional 3 years, after completion of 24 months of treatment. After a patient has completed 3 years in the open-label extension, the patient may continue in the study until the end of study (EOS), provided that risdiplam is not commercially available in the patient's country (see Section 3.1.5).*

3.1.1.2 Confirmatory Part 2

A total of 40 infants will be enrolled to receive risdiplam at the dose selected from Part 1. Infants from Part 1 will not be enrolled into Part 2.

On the basis of available data from Part 1, the following *starting* 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. The PK in all infants will be regularly monitored (data review every 2 weeks, but this may be adjusted on the basis of the data) by the Clinical Pharmacologist, and the dose of all or individual infants may be adjusted to ensure that infants are in the targeted exposure range and in compliance with the exposure cap.

As the infants grow and develop, the dose may need to be adjusted based on body weight, age, or other parameters identified, in order to maintain the exposure level over time in an individual growing infant (i.e., the dose administered may be higher than the dose levels listed above, provided the measured and observed PK exposure is in compliance with the exposure cap of a mean $AUC_{0-24h,ss}$ of 2000 ng•h/mL).

Once the final dosing regimen has been selected for this study (0.2 mg/kg for infants <2 years of age), no further dose adjustments are foreseen in any infant in Part 1 or Part 2.

Once a patient reaches 2 years of age, the dose may be adjusted to 0.25 mg/kg, at the request of the Sponsor and upon review of available PK and safety data for each individual infant.

The selected mg/kg dosing regimen (i.e., 0.2 mg/kg for infants <2 years of age, which may be increased to 0.25 mg/kg for infants ≥ 2 years of age upon review of the individual infant's data) will be applied when a patient's body weight is <20 kg. A flat dose of 5 mg will be administered when a patient's body weight is ≥ 20 kg.

The duration of the study for each infant enrolled in Part 2 will be up to 25 months as follows:

- Screening: up to 30 days prior to first dose.
- Treatment period: for 24 months from the start of dosing, with the primary analysis after the last infant reaches 12 months of treatment.
- *Open-label extension: for an additional 3 years, after completion of 24 months of treatment. After a patient has completed 3 years in the open-label extension, the patient may continue in the study until the EOS, provided that risdiplam is not commercially available in the patient's country (see Section 3.1.5).*

Part 2 of this study will initially enroll 40 infants across all sites in a global enrollment phase. Thereafter, additional infants may be enrolled in an extended China enrollment phase at sites in mainland China, Hong Kong, and Taiwan that are recognized by the [REDACTED] to ensure a total of approximately 10 infants in a China subpopulation. The global population will include all infants enrolled during the global enrollment phase (including infants enrolled at [REDACTED]-recognized sites during that phase), and the China subpopulation will include all infants enrolled at [REDACTED]-recognized sites (i.e., during both the global enrollment phase and the extended China enrollment phase).

If an infant discontinues study drug early, they will be asked to participate in a study completion/early withdrawal visit and follow-up as described in the SoA ([Appendix 1](#), [Appendix 2](#)).

3.1.2 Internal Monitoring Committee

The Internal Monitoring Committee (IMC) will consist of selected Roche representatives: Clinical Pharmacologist, Translational Medicine Leader, Safety Science Leader, Statistician, and Statistical Programmer. The IMC will be responsible for monitoring the safety of infants, for selecting the dose for Part 2 and for making the following decisions during Part 1:

- Decision to proceed with daily administration following a single administration in the first patient. Data package reviewed for this decision: all available PK, safety and tolerability data (including AEs, ECGs, vital signs).
- Decisions to proceed with enrollment of further patients at each dose level once the first patient at that dose level has reached steady-state (minimum of 2 weeks), dose-escalation decisions (to a higher dose-level), and associated dose-selection decisions. Data package reviewed for this decision: all PK, available PD (SMN mRNA, SMN protein), safety and tolerability data (including AEs, ECGs, vital signs, clinical laboratory test results, ophthalmology monitoring) in all infants treated for at least 2 weeks (some infants will have longer treatment duration) at the previous dose-level(s).
- The IMC may also decide to increase the number of infants at any of the planned dose levels or to initiate additional dose /exposure levels, up to a maximum of 24 infants in total for Part 1. Data package reviewed for this decision: all PK, available PD (SMN mRNA, SMN protein), safety and tolerability data (including AEs, ECGs, vital signs, clinical laboratory test results, ophthalmology monitoring) in all infants.

The roles, responsibilities, membership, scope of activities, time of meetings and communication plan for the IMC will be documented in an appropriate charter prior to the initiation of the study.

3.1.3 Independent Data Monitoring Committee

An external independent Data Monitoring Committee (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. The iDMC will meet on a regular basis over the course of Part 2 of the study 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, including (but not limited to) continuation, halting or amending the protocol.

Whilst 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 risdiplam 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 2 in order to be able to adjust the dose of individual infants if required, assuring not to exceed the exposure cap, to continue treatment at the targeted exposure level (as infants grow and their body systems mature), and to ensure targeted exposure for newly enrolled patients. Dose adjustments for individual or all patients may occur, as required. The iDMC will be informed of any individual dose changes required at the next scheduled iDMC meeting.

The roles, responsibilities, membership, scope of activities, time of meetings and communication plan for the iDMC will be documented in the Charter prior to the initiation of the study. The external iDMC will be chaired by a medically qualified individual with experience with SMA and will include at least one other 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.

3.1.4 Permanent Ventilation Adjudication Committee

Time to permanent ventilation will be determined by a central, independent Permanent Ventilation Adjudication Committee. This committee will meet periodically to review all pertinent data for infants that may meet the definition of permanent ventilation (≥ 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).

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.
- Leukocytosis.
- Imaging studies demonstrating an active infection.
- Surgical procedure.

The infant will be given a period of 7 days after the event to recover and begin extubation or weaning off ventilation support before the endpoint of permanent ventilation 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 independent Permanent Ventilation Adjudication Committee will determine if this endpoint has been met and provide recommendations to the Sponsor.

The procedures for reviewing and adjudicating events, and the governing and operation of the independent Permanent Ventilation Adjudication Committee will be described in a charter.

3.1.5 End of Study

The EOS is defined as the date when the last patient last visit (LPLV) occurs. *LPLV is expected to occur at the latest when the last patient enrolled in the study has completed 24 months in the treatment phase and 3 years in the open label extension.*

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

After completion of 24 months of treatment, each patient will enter the open-label extension phase for an additional 3 years. After a patient has completed 3 years in the open-label extension, the patient may continue in the study until EOS, provided that risdiplam is not commercially available in the patient's country.

See Section 4.4.4 for conditions regarding post-trial access to risdiplam.

3.2 RATIONALE FOR STUDY DESIGN

This study is designed to assess the efficacy and safety of risdiplam treatment in infants with Type 1 SMA who are aged 1 to 7 months at the time of enrollment.

A single-arm study design is considered justified in the context of the choice of the primary endpoint that is minimally subject to bias and the known natural history of this endpoint within the study population (see below), as defined by the inclusion and exclusion criteria for this study.

The primary endpoint will be the proportion of infants who are sitting after 12-month treatment. This endpoint can be objectively measured, incorporates survival and is a clinically meaningful endpoint. Furthermore, the evaluation of the gross motor scale, including sitting, will be video-recorded in a standardized manner and centrally reviewed by two independent readers, *up to and including the Week 104 assessment*. The assessment of the central readers will be used for the primary analysis.

The natural history of the disease is well-defined i.e., Type 1 SMA infants never achieve sitting without support (Cobben et al 2008; Finkel et al 2014), the primary endpoint in this study. This natural history can therefore be used to define the performance criteria for

success, i.e., a threshold of achievement for the risdiplam-treated infants to be assessed against within this study. The pre-defined performance criteria for the primary endpoint will be 5%.

3.2.1 Rationale for Dosage Selection

Study BP39056 will enroll infants with Type 1 SMA, aged 1 to 7 months at time of enrollment. These Type 1 infants represent the SMA population with the highest unmet medical need who may potentially have the greatest benefit from early initiation of treatment with risdiplam. Given the severity and the high mortality and morbidity in Type 1 infants, all dose levels in this study are aiming to provide therapeutic benefit to infants. In Part 1 of the study, two dose/exposure levels are planned to be assessed in a dose-escalating manner to ensure the safety of all infants. The objectives of Part 1 are to assess safety and tolerability of risdiplam in infants, and PK and PD to identify the most appropriate dose for Part 2 of the study.

Given the limited degree of extrapolation possible from older age, enrollment of infants into this study will not be dependent on the availability of data from older children. Extrapolation from older children with Type 2 and 3 SMA (who are usually older than 2 years of age) would not be adequate due to differences in their physiology, and metabolic pathways for the different age ranges, and the differing profile of co-morbidities in the Type 1 versus the Type 2 and 3 SMA populations.

PBPK modeling has been conducted to predict the PK profile in infants, to help with the selection of the starting dose, and to define the dosing strategy once PK data is available in this age group. A PBPK model was developed using SimCYP version 15 based on physicochemical properties, in vitro, preclinical, and clinical (PK after single dose in healthy subjects, including food effect assessment) study results for risdiplam. Absorption is modeled by a mechanistic approach using the Advanced Dissolution, Absorption and Metabolism (ADAM) model of SimCYP; almost complete absorption (>90%) is predicted. Tissue distribution is described according to tissue to plasma concentration ratios determined in monkeys. Elimination in the PBPK model is assumed mostly by hepatic metabolism (95%) through CYP3A4 and FMO3 enzymes, and minor (5%) renal excretion. This PBPK model adequately described plasma-concentration profiles after single dose of 0.6 to 18 mg in healthy adult subjects in both fasted and fed state, and predicted well the extent of the DDI with itraconazole in healthy male individuals (14% vs 12% increase in AUC_{0-120h} by the prediction and the observation, respectively). This PBPK model was transferred to the SimCYP Pediatric Module to predict PK in infants and children with consideration of growth in body size, organ maturation, ontogeny of metabolic enzymes, and protein binding.

The starting dose for the first infant enrolled was selected based on the most conservative pediatric PBPK model prediction. Nevertheless, there is uncertainty in the prediction and extrapolation, and therefore, Part 1 will start with the administration of a single dose only to a single infant. To ensure the safety of this first enrolled infant, a

safety factor of 10 will be applied to the dose selected based on the most conservative PBPK model scenario. PK will be measured after administration of the single dose, and safety and tolerability will be carefully assessed, and the PBPK model updated with the obtained PK data, in order to select the dose for Dose Level 1 in this first infant (and subsequent infants).

In addition, the free fraction (f_u) of risdiplam will be measured in all infants at screening with an in vitro assay. In case the measured free fraction in infants is different from the free fraction in adults, the starting dose (and subsequent dose levels and the exposure cap) will be adjusted for this difference.

The dose-selection will target in Part 1:

- Starting dose: A single infant will be enrolled initially and will receive a single dose of 0.00106 mg/kg risdiplam (i.e., 0.0074 mg for a 7 kg infant, assuming free fraction = 0.25; the actual dose is to be confirmed with the Sponsor before any drug administration and can be adjusted upon review of all eligibility criteria of the first infant, including free fraction at screening). This dose is predicted to result in an exposure (AUC_{inf}) at least 10-fold below the target exposure of $AUC_{0-24h,ss}$ 700 ng • h/mL (respectively AUC , free fraction 77 ng • h/mL) for Dose Level 1. This dose was selected based on the most conservative PBPK modeling scenario as described above, plus an additionally applied safety factor of 10. This will ensure a safe administration of this compound for the first time to infants, in case the actual observed exposure deviates from the PK profile predicted with the PBPK model.
- Dose Level 1, target exposure of $AUC_{0-24h,ss}$ 700 ng • h/mL: an exposure predicted to result in a doubling of SMN protein levels (i.e., a 100% increase versus the patient's baseline). The actual dose to achieve this target exposure will be calculated based on the PK data obtained in the first infant, and will be likely based on both age and body weight. The PBPK model will be continuously updated with the emerging PK data from all enrolled infants, and the dose adjusted if required. A 100% SMN protein increase is expected to lead to a substantial clinical benefit in SMA patients, turning more severe phenotypes into milder forms, based on SMN protein levels measured in SMA patients (Kolb et al 2006; Sumner et al 2006; Nguyen et al 2008) and on data obtained in animal SMA models regarding efficacy and the associated SMN protein increase (Risdiplam Investigator's Brochure). An AUC_{0-24h} exposure of up to 1470 ng • h/mL was well-tolerated in the SAD study in healthy subjects, without any clinically relevant safety findings. This exposure of $AUC_{0-24h,ss}$ 700 ng • h/mL is a factor of approximately 3 (2.8) below the NOAEL level in the 39-week monkey study (i.e., 2.8-fold below the exposure level at which no adverse findings were observed). Only effects on the testes were observed at those exposure levels in rats. Effects on testes at low exposure and their reversibility could not be assessed in cynomolgus monkey due to sexual immaturity of the animals (see Risdiplam Investigator's Brochure); parents of male subjects will be informed accordingly.

- Dose Level 2: a higher exposure, leading to the maximum possible SMN protein increase (provided all clinical and nonclinical safety data available at the time of the dose escalation decision support this), which is predicted to provide greater benefit based on preclinical data as well as published clinical data with the antisense oligonucleotide nusinersen (Chiriboga et al 2016). Particularly in this lethal disease of Type 1 SMA, it is considered important to strive for maximum possible efficacy. The highest possible increase is currently assumed to be at maximum a 200% SMN protein increase, based on animal and in vitro cell culture data with SMA patient fibroblasts and motor neurons (see Risdiplam Investigator's Brochure). Based on current predictions, this target may be reached at an exposure not exceeding the exposure cap of 2000 ng • h/mL AUC_{0-24h,ss}. Under no circumstances will a dose be selected that leads to an exposure above a mean AUC_{0-24h,ss} of 2000 ng • h/mL or a mean C_{max} of 400 ng/mL (or equivalent free fraction, if the free fraction in infants is different from values in adults).

The dose for Part 2 will be selected by the IMC based on the results obtained from Part 1, and will be a dose that:

- Is judged to be well tolerated and without any known safety signal, based on all available data from Part 1 and as confirmed by the external iDMC.
- Results in an exposure at steady-state below the exposure cap (mean value) of AUC_{0-24h,ss} 2000 ng • h/mL (adjusted for free fraction, if required). To account for changes in PK in different age-groups, a different dose is likely to be selected for the various age groups. The dose will likely be a body weight-adjusted dose, but other criteria, e.g., body surface area (BSA) or age, may be used, depending on the results of the analysis of the PK data obtained in Part 1.
- Results in an SMN protein increase that is expected to be clinically relevant in terms of efficacy.

Overall the approach is to target the highest SMN protein increase that can be safely achieved with risdiplam; however, the shape of the PK/PD curve will be taken into account to determine the most appropriate target exposure (and therefore, dose), considering safety and tolerability data across exposure levels in Part 1, and the above-mentioned exposure cap threshold. Clinical judgment will prevail.

Based on the criteria listed above and currently available data from Part 1, the following *starting* 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. The PK in all infants will be regularly monitored (data review every 2 weeks, but this may be

adjusted on the basis of the data) by the Clinical Pharmacologist, and the dose of all or individual infants may be adjusted to ensure that infants are in the targeted exposure range and in compliance with the exposure cap.

At the dosing regimen selected for Part 2 of the study, the predicted exposure is a mean $AUC_{0-24h,ss}$ of 1650 ng•h/mL in infants 3–5 months old at enrollment with a dose of 0.08 mg/kg, and a predicted mean $AUC_{0-24h,ss}$ of 2020 ng•h/mL in infants ≥ 5 months old at enrollment with a dose of 0.2 mg/kg. The predicted mean $AUC_{0-24h,ss}$ of 2020 ng•h/mL is considered in compliance with the exposure cap of a mean $AUC_{0-24h,ss}$ of 2000 ng•h/mL, since it is only numerically marginally greater and the PK will be monitored in all infants to ensure that the actual observed PK values are in compliance with the cap.

Given the severity of the disease in patients with Type 1 SMA and the observed correlation of SMN protein increase versus individual PK, this target exposure has been selected to maximize the likelihood of clinical benefit while still being compliant with the exposure cap.

The dose of 0.08 mg/kg was chosen for infants 3–5 months old. This dose is predicted to result in a somewhat lower AUC; however, this prediction is currently based on only 4 infants in this age group and therefore associated with some uncertainty. No data is currently available for infants between 28 days (1 month) and 3 months of age; therefore, an additional safety margin has been applied, and a starting dose of 0.04 mg/kg has been selected for Part 2. This dose may be adjusted once PK data in this age group has been obtained.

Available pre-clinical and natural history data suggest that a 100% increase in SMN protein levels could turn severe SMA phenotypes into milder forms, whereas further increase may provide even greater benefit (Section 3.2.1). In Part 1 of the study, a median 2-fold increase (range 1.0–5.4) in SMN protein in blood versus baseline was observed for infants with an exposure (AUC_{0-24h}) ≤ 1000 ng•h/mL, and a median 3.2-fold increase (range 1.6–6.5) was obtained in infants with an exposure (AUC_{0-24h}) > 1000 ng•h/mL. Therefore the selected dose levels for Part 2 are indeed expected to lead to clinically relevant efficacy in patients with Type 1 SMA.

Refer to Section 1.2.2 for the data summary from Part 1 supporting the dose selection for Part 2.

Once the final dosing regimen has been selected for this study (0.2 mg/kg for infants < 2 years of age), no further dose adjustments are foreseen in any infant in Part 1 or Part 2.

Once a patient reaches 2 years of age, the dose may be adjusted to 0.25 mg/kg, at the request of the Sponsor and upon review of available PK and safety data for each

individual infant. The dose of 0.25 mg/kg was identified as the appropriate dose for children ≥ 2 years of age in Study BP39055 in patients with SMA Type 2 and Type 3.

The selected mg/kg dosing regimen (i.e., 0.2 mg/kg for infants < 2 years of age, which may be increased to 0.25 mg/kg for infants ≥ 2 years of age upon review of the individual infant's data) will be applied when a patient's body weight is < 20 kg. A flat dose of 5 mg will be administered when a patient's body weight is ≥ 20 kg. The dose of 5 mg was identified as the appropriate dose for patients aged ≥ 2 years with ≥ 20 kg body weight in Study BP39055 in patients with SMA Type 2 and Type 3.

3.2.2 Rationale for Study Population

Study BP39056 has been designed as the first study in Type 1 SMA infants with risdiplam:

- After risdiplam was shown to be safe and well tolerated after single dose administration in healthy adult volunteers (BP29840), it is essential to study its safety and tolerability profile in the Type 1 target population, especially given the various comorbidities SMA patients present with their age and disease severity.
- The PK profile of risdiplam needs to be specifically evaluated in Type 1 SMA patients of the targeted age-range (infants) since PK will be different in infants compared to older subjects, as well as its PD effects in terms of increase of full-length *SMN2* mRNA and SMN protein levels.
- The risk-benefit of risdiplam in Type 1 SMA patients is considered favorable as it has the potential to address the unmet need in this severely affected population. Therefore, it is important to determine the efficacy and safety of risdiplam, specifically in Type 1 SMA patients.

Type 1 SMA patients have a more severe clinical presentation and reduced survival rate compared to Type 2 and 3 SMA patients. The clinical progression of the disease is more pronounced than in Type 2 and 3 SMA patients and their comorbidities and complications (e.g., swallowing and breathing function) are usually more severe. This population usually has less than three *SMN2* copy numbers and their *SMN* mRNA expression in tissue is considered to be low. Early initiation of treatment in this early onset population with a splicing modifier, as proposed in this study, may lead to a significant increase in SMN protein expression that could rescue partly or completely the chronic SMN protein deficiency during the motor function development phase of these infants. This is expected to lead to a clinically relevant outcome in motor and respiratory function of treated patients, e.g., achievement of sitting milestone after 12 months of continuous treatment. Therefore, targeting patients with Type 1 SMA before the age of 7 months increases the chance to induce beneficial effect in motor-milestones that are developed after the age of 7 months. A very early initiation of an effective treatment is anticipated to counteract the deleterious effects of chronic SMN protein deficiency in the body.

3.2.3 Rationale for Control Group

This is an open-label study. A placebo control group will not be included in this study as it is ethically debatable to treat a Type 1 SMA patient with placebo, considering the rapid decline and short life-expectancy of these patients. The open-label design is considered justified in the context of the choice of the primary endpoint that is minimally subject to bias and the known natural history of this endpoint (and developmental milestones) within the study population, as defined by the inclusion and exclusion criteria for this study.

One drug was recently approved in the United States, European Union, Canada, and other jurisdictions for the treatment of SMA in pediatric and adult patients (the antisense oligonucleotide nusinersen [Spinraza™]) but, the medical need in SMA is still very high. There is currently no oral treatment for SMA that provides stabilization or improvement of motor function and development; accordingly, no active control can be used in this study. However, all patients must receive the local clinical standard of care for SMA patients, as defined by each site Investigator, except for the administration of SMN2-targeting oligonucleotides, which is not allowed.

3.2.4 Rationale for Biomarker Assessments

The putative target tissues for SMA treatment are spinal cord and muscle, tissues that cannot be easily sampled multiple times to evaluate drug effects. As SMA is due to decreased levels of SMN protein, changes in *SMN* mRNA and SMN protein levels (relating to changes in the spinal cord and muscle) will be measured in blood. In addition to the SMN2 copy number analysis done at screening, additional genetic markers which influence the progression and severity of the disease or treatment response may be studied in the patients.

The following blood samples will be collected according to the SoA ([Appendix 1-Appendix 4](#)) for biomarker analyses:

- Clinical genotyping (Section [4.6.1.13](#)).

In addition and as described in Section [4.6.1.13](#), the following blood samples will be collected according to the SoA ([Appendix 1-Appendix 4](#)) to assess the PD effects of risdiplam:

- In vivo splicing modification of *SMN2* mRNA in blood.
- SMN protein levels.

3.3 OUTCOME MEASURES

3.3.1 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 assessments as appropriate for age (*see Section 4.6.1.8 for details*).
- Physical examination
- Anthropometric examination, including weight, height, head, and chest circumference.

A detailed medical history and a complete physical examination will be performed at the time-points indicated in the SoA ([Appendix 1](#), [Appendix 2](#)).

Adverse events and concomitant medications will be monitored throughout the entire study (screening through *open-label extension or the study completion/early withdrawal visit and follow-up*).

3.3.2 Pharmacokinetic (PK) and Pharmacodynamic (PD) Outcome Measures

3.3.2.1 Pharmacokinetic Outcome Measures

Blood samples for determination of plasma concentrations of risdiplam, and its metabolite(s) as applicable, will be collected as detailed in the SoA ([Appendix 1](#), [Appendix 2](#)).

Plasma concentrations of risdiplam and its metabolites as appropriate will be measured by a specific and validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. PK samples may be used for the exploratory identification of metabolites as necessary. Patient exposure to risdiplam will be assessed and the following parameters 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.

3.3.2.2 Pharmacodynamic Outcome Measures

PD assessments will be performed as detailed in the SoA ([Appendix 1](#), [Appendix 2](#)) and will include:

- SMN mRNA in blood.
- SMN protein in blood.

3.3.3 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 (ventilation-free as defined as patient who does not receive permanent ventilation).
- Ability to swallow and to feed orally.
- Clinician-reported respiratory function and ability to swallow items.
- Change in height and weight.

3.3.4 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.

4. MATERIALS AND METHODS

4.1 CENTER

This is a multi-center study to be conducted in multiple countries.

An administrative and contact information list for investigators is provided separately.

4.2 STUDY POPULATION

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

Infants must meet all of the inclusion criteria and none of the exclusion criteria in order to qualify for the study as described below. Unless otherwise stated, inclusion and exclusion criteria refer to the screening period.

For the first 3 infants enrolled into this study, additional inclusion criteria apply.

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), independent from the target sample size of 40 infants that are currently considered for the primary analysis.

4.2.1 Recruitment Procedures

Infants will be recruited primarily from site/country clinical databases, or via referrals from patient groups including those outside the site's country; however, in some cases, potential patients may be identified prior to consenting to take part in this study using prescreening enrollment logs, Independent Ethics Committee/Institutional Review Board (IEC/IRB)-approved newspaper/radio advertisements and mailing lists.

4.2.2 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 patients 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 (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) Infant has two *SMN2* gene copies, as confirmed by central testing.
- 6) Body weight \geq 3rd 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 infant is willing to consider the use of non-invasive ventilation during the study, as recommended by the Investigator.

4.2.3 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) Requiring invasive ventilation or tracheostomy.
- 9) Requiring awake non-invasive ventilation or with awake hypoxemia ($\text{SaO}_2 < 95\%$) with or without ventilator support.
- 10) 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 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 infant):
 - 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 × 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 risdiplam or to the constituents of its formulation (see Risdiplam Investigator's Brochure).
- 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 infant 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 infant may be enrolled in the study. Infants in whom OCT measurement of sufficient quality cannot be obtained at screening will not be enrolled.

4.3 METHOD OF TREATMENT ASSIGNMENT

This is an open-label study and all infants will receive risdiplam.

In Part 1, infants will be enrolled into two multiple-ascending dose cohorts. In Part 2, all infants will be enrolled to receive risdiplam at the dose (target exposure level) selected in Part 1.

An Interactive (voice/web) Response System (IxRS) will be used to manage patient screening, enrollment and drug supply. The patient number will be allocated by IxRS and will be used in the clinical database and for recording data in the electronic case report form (eCRF). Sites should call the IxRS to enter the patient into screening and to register a screen failure. The enrollment call to the IxRS should occur on Day – 1 after the patient's eligibility (i.e., inclusion/ exclusion criteria) has been confirmed.

4.4 STUDY TREATMENT

4.4.1 Formulation, Packaging, and Handling

4.4.1.1 Part 1 Formulation – Risdiplam (Powder and solvent for oral solution, 20 mg and 120 mg)

Risdiplam clinical formulation for Part 1 is a powder and solvent for constitution to an oral solution. Risdiplam drug product is composed of two bottles; one containing 20 mg or 120 mg of risdiplam substance (no excipients) and another with excipients blend (powder for solvent for reconstitution). The excipient blend bottle is constituted with water for injection and entirely transferred to the drug substance bottle to yield an oral solution containing 0.25 mg/mL and 1.5 mg/mL of risdiplam. For the first infant(s), a further dilution step is foreseen to enable the administration of a low starting dose which has been defined as being able to ensure the safety of the first enrolled infant.

The excipient blend used for constitution of the drug substance consists of mannitol, tartaric acid, sodium benzoate, ascorbic acid, polyethylene glycol 6000, disodium edetate dihydrate, sucralose and strawberry flavor. All excipients selected for the powder for oral solution formulation comply with pharmacopeia requirements (United States Pharmacopeia–National Formulary [USP/NF] and/or the European Pharmacopoeia [Ph. Eur] and EU Food regulation).

4.4.1.2 Part 2 Formulation– Risdiplam (Powder for oral solution, 20 mg and 60 mg)

Risdiplam clinical formulation for Part 2 is a powder for constitution to an oral solution. Each bottle contains 20 mg or 60 mg of risdiplam substance with excipients. The powder is constituted with purified water to yield an oral solution containing 0.25 mg/mL or 0.75 mg/mL of risdiplam, respectively.

The excipients used in the Part 2 clinical formulation are the same as for Part 1 formulation (powder and solvent for oral solution), except for isomalt added as diluent.

Infants participating in the Part 1 extension of the study shall continue to use the Part 1 risdiplam clinical formulation until switch to the Part 2 risdiplam clinical formulation upon availability of the new formulation. Infants in Part 2 of the study will receive the Part 2 formulation throughout their participation in the study.

4.4.1.3 Packaging and Handling

The constitution of the study medication will be carried out at the clinical study site authorized pharmacy by qualified pharmaceutical personnel. Further detailed instructions for the constitution procedure will be provided in a separate pharmacy manual. After constitution, the pharmaceutical personnel will insert a press-in-bottle-adaptor into the bottle neck and close with a child-resistant closure. The bottle adaptor allows insertion of oral/enteral dispensers into the bottle for withdrawal of the constituted solution. The bottle that contains the oral solution will be inserted into a labeled carton provided by Roche Clinical Trials Supplies department. The clinical study site will provide oral/enteral dispensers to the parent/caregiver to administer the solution. A diary will be provided to the parent/caregiver with instructions on study drug administration at home.

For each infant and for all occasions of dispensation of study drug, it shall be recorded by the Pharmacist or personnel under their supervision which formulation strength an infant received.

Study drug packaging will be overseen by the Roche Clinical Trial Supplies department and will bear a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labelling of the study medication will be in accordance with Roche standard and local regulations. The qualified individual responsible for dispensing the study drug will prepare the correct drug product according to the individual specific dose allocated to an individual patient.

Upon arrival of investigational products at the site, site personnel should check for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the Monitor upon discovery. All drug supplies should be stored in a secure, temperature-controlled area with limited access. risdiplam investigational product must be stored according to the details on the product label.

For further details, see the Risdiplam Investigator's Brochure and BP39056 Pharmacy Manual.

4.4.2 Dosage, Administration, and Compliance

4.4.2.1 Risdiplam

The qualified individual responsible for dispensing the study drug will prepare the correct dose according to the enrollment schedule. This individual will write the date dispensed and patient number and initials on the study drug vial label and on the Drug

Accountability Record. This individual will also record the MEDNO/study drug batch number received by each patient during the study. Throughout the study, the study medication (risdiplam) should be taken orally once daily. In the case of breastfeeding, the patient should be fed prior to dosing, wined, and the study medication administered. In patients able to swallow, study drug will be administered with a syringe inserted between baby's gum and cheek as described in the study drug administration instructions for use. Thereafter, water (approx. 10–20 mL) should be administered with a baby's bottle to prevent prolonged contact of study drug with buccal mucosa. Similarly, the peribuccal- area of the SMA infant will be washed with water in case of drug drooling or spitting. Breastfeeding should be avoided within one hour after study drug administration. Women breastfeeding will be advised to rinse their breasts with water when breastfeeding occurs shortly after (< 1h) risdiplam administration.

If a parent or caregiver does not administer the dose at the regular time, but realizes prior to 12:00 (noon) local time, they will be instructed to administer the regular dose at that time. If a parent or caregiver realizes a missed administration only after 12:00 (noon) local time, this will be considered a missed dose and parents or caregivers will be instructed to not administer study drug for that day. They should give the regular amount at the next scheduled time on the subsequent day, but not double-up the dose, and report the event in the medication diary.

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. This should be followed by a bolus flush of water through the tube.

The first dose of study medication will be administered at the clinical site on Day 1 after all pre-dose assessments have been conducted.

A subject diary will be required that will capture information related to drug administration for all doses throughout study. All bottles and unused drug and drug supplies will be returned to the site during a study visit or collected during a home visit.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 4.7.

4.4.3 Investigational Medicinal Product Accountability

All IMP (risdiplam) required for completion of this study will be provided by the Sponsor. The investigational site will acknowledge receipt of IMP, to confirm the shipment condition and content. Any damaged shipments will be replaced.

The Investigator is responsible for the control of drugs under investigation. Adequate records of the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. The Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the patient to whom the study drug was dispensed (for example patient initials and date of birth).
- The date(s), quantity of the study drug dispensed to the patient.
- The date(s) and quantity of the study drug returned by the patient.
- All records and drug supplies must be available for inspection by the Roche Monitor [at every monitoring visit].

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used investigational medicinal product for safety reasons. In these cases, it may be acceptable for investigational study site staff to destroy dispensed investigational product before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned, destroyed and provided that adequate storage and integrity of drug has been confirmed.

The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Written documentation of destruction must contain the following:

- Identity of investigational product[s] destroyed.
- Quantity of investigational product[s] destroyed.
- Date of destruction.
- Method of destruction.
- Name and signature of responsible person [or company] who destroyed investigational product[s].

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.4.4 Post-Trial Access to Risdiplam

The Sponsor will offer post-trial access to the study drug (risdiplam) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive study drug after the end of the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued study drug treatment for his or her well-being.
- There are no appropriate alternative treatments available to the patient.
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A patient will not be eligible to receive study drug after the end of the study if any of the following conditions are met:

- The study drug is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or wouldn't otherwise create a financial hardship for the patient).
- The Sponsor has discontinued development of the study drug or data suggest that the study drug is not effective for SMA.
- The Sponsor has reasonable safety concerns regarding the study drug as treatment for SMA.
- Provision of study drug is not permitted under the laws and regulations of the patient's country.

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.5 CONCOMITANT THERAPY AND FOOD

4.5.1 Permitted Therapy

Concomitant therapy includes any medication, e.g., vaccines, prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements and any non-medication interventions (e.g., individual physiotherapy, physical therapy and rehabilitative therapy) used by a patient within 30 days of screening until the *study completion/early withdrawal visit*, unless stated otherwise, see exclusion criteria. All concomitant medications should be reported to the Investigator and recorded on the Previous and Concomitant Treatments eCRF.

Physiotherapy, occupational therapy and other forms of exercise therapy are encouraged but the frequency should remain the same during the clinical study. All concomitant therapy should be reported to the Investigator and recorded on the Previous and Concomitant Treatments eCRF.

All therapy and/or medication administered to manage adverse events should be recorded on the Adverse Event eCRF.

Unless specified differently below, for any chronic treatment, patients should be on stable regimen for 6 weeks prior to screening and should remain on stable regimen throughout the study.

Examples of allowed medications include the following, unless prohibited per Section 4.5.2:

- Inhaled corticosteroids.
- Other inhaled drugs for obstructive airways diseases (e.g., anticholinergics and anti-allergic agents).
- Other systemic drugs for obstructive airways diseases (e.g., leukotriene receptor antagonists).
- Laxatives and other drugs for functional gastrointestinal disorders.
- Occasional use of analgesics, including opioids (e.g., hydromorphone or codeine).
- Any antibiotics.
- Antihistamines.
- Proton pump inhibitors.
- Any vaccine considered as part of the local standard of care for the patient.

4.5.2 Prohibited Therapy

All medications (prescription and OTC) taken within 30 days of study screening will be recorded on the appropriate eCRF.

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

- 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 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.
- 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.
- Any prior use of Spinraza™ or any other SMN2-targeting antisense oligonucleotide, SMN-2 splicing modifier or gene therapy is prohibited.

Medications with known retinal toxicity liabilities

- 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

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 (*not applicable if used as a nutritional supplement*), rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon or any other drugs known to cause retinal toxicity

4.5.3 Prohibited Food

Subjects are to avoid grapefruit juice and Seville orange (juice) starting at least 2 weeks prior to study drug administration.

Breastfeeding of the patient is allowed if the mother is not consuming any prohibited medications (see Section 4.5.2). Breastfeeding is not permitted for one hour after study drug administration in order to avoid direct contact between the mother's skin and the drug product immediately after administration.

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

All examinations listed below will be performed according to the schedule of assessments outlined in [Appendix 1-Appendix 4](#).

Prioritization of blood samples is described in Section 4.6.3.

Follow-up phone calls are planned in this study. Parents (or caregivers of patients, as appropriate) will be called by the Investigator or designee to monitor safety and tolerability when not attending the clinic. Assessments will include adverse events, concomitant medication review, and significant life events ([Appendix 1](#), [Appendix 2](#)).

Home visits are planned in this study (see SoA, [Appendix 1](#), [Appendix 2](#)) to *supply the patient with study medication and check patient diary for compliance. Alternatively, the patients may visit the clinic on the dates scheduled for home visits. If needed, the following assessments could be performed during home visits: blood samples, vital signs, weight, adverse events, concomitant medication review, and significant life event data collection.*

The exact timing of all study assessments (e.g., PK or PD blood sampling) may be shifted depending on emergent data, but the total number of assessments will not change.

4.6.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) or physical/occupational/exercise therapy applied to the patient within 30 days prior to the screening visit.

Demographic data will include age, sex, and parent/ caregiver-reported patient race/ethnicity (collecting this information is essential to be able to evaluate the results of this study, e.g., in case of PK outliers or important between-subjects differences in terms of treatment effect).

4.6.1.2 Spinal Muscular Atrophy History

SMA history will be collected as available in the patient's medical records. The collected parameters will include (list is not exhaustive, please refer to the eCRF):

- Age of onset.
- Previous score on functional motor scale (e.g., CHOP-INTEND, BSID-III).
- Current level of function and highest motor function achieved (i.e., rolling, crawling).

SMA history will be recorded on the eCRF at the time-points specified in the SoA ([Appendix 1](#), [Appendix 2](#)).

4.6.1.3 Anthropometric Measurements

Anthropometric measurements include weight, height, head and chest circumference and will be measured at the time-points specified in the SoAs ([Appendix 1](#), [Appendix 2](#)).

Body Weight

- Body weight will be measured to the nearest 100 g.

Height

- Height (or length) will be measured to the nearest centimeter with the child in lying position using an inflexible length board with fixed headboard and moveable footboard.
- *For all patients who are able to stand, height will be measured while standing using a stadiometer unless they present with scoliosis/contractures.*
- *When a patient's height can no longer be assessed by a fixed board and the patient is unable to stand (e.g., because the patient is longer than the fixed board or due to scoliosis/contractures), the patient's height will be derived from ulna length to the nearest centimeter by the following method:*
 - *Ulnar length (from the tip of the olecranon process to that of the styloid process) will be measured using an anthropometer with the patient in sitting position, the left forearm resting comfortably on a table, elbow bent 90 ° to 110 °, palm facing downwards and fingers extended but together.*
- *Method of height measurement should be kept consistent for as long as possible.*

Head and Chest Circumference

- Head and chest circumference will be measured to the nearest centimeter using an automated flexible, non-stretchable tape device as follows:
 - Head circumference (or occipital-frontal circumference [OFC]) will be measured at the level of the plane passing above the glabella (the most anterior protrusion of the forehead) and over the opisthrocranium- (the most posterior protrusion from glabella on the back of the head), perpendicular to the mid-sagittal plane. The infant's head should be supported away from the table surface. The measuring tape should remain above the ears and fully compress any hair (hair ornaments should be removed and large plaits or braids

loosened). The measurement should be taken to the nearest millimeter and repeated three times with the largest measurement being recorded.

- Chest circumference will be measured with the infant lying on the back, under the axilla and over the nipple line. The measurement should be taken to the nearest millimeter and repeated three times with the largest measurement being recorded.

Head to chest circumference ratio will be derived throughout the study (Section 6.6.3).

4.6.1.4 Physical Examinations

A full physical examination should include an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Full physical examination will be carried out at time-points specified in the SoA ([Appendix 1](#), [Appendix 2](#)). The physical exam will not include pelvic or rectal exams unless deemed necessary by the study site physician.

A neurological examination will be performed during the physical examination. As the motor assessments are performed in the other exams this will focus on mental status, behavior and cognitive assessments. The examination will be performed by asking parents/caregivers about the infant's development, overall behaviour, sleep and mood such as number of tantrums and vocalization. The Investigator will observe and interact with the infant using tasks or paradigms adapted to the infant's age and motor ability, for example observing infant's reaction to a sound, speech development, shifting attention to a newly introduced toy, observing the patient interact with the parent/caregiver.

Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

Changes from baseline abnormalities should be recorded in patient's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.6.1.5 Vital Signs

Blood pressure (BP), pulse rate, respiratory rate and body temperature (oral or tympanic) will be recorded at the time-points specified in SoA ([Appendix 1](#), [Appendix 2](#)).

Measurements should be obtained in a quiet room at a comfortable temperature, with the patient positioned in a semi-supine/supine position with the arms unconstrained by clothing or other material. Measurements should be taken prior to blood draw or at least 10 minutes after the last blood draw and after the patient has been resting for at least 5 minutes.

Throughout the study all blood pressure measurements will be obtained from the same arm (when not possible to measure it from the arm the lower leg may be used) and with the appropriate cuff size, using a well-calibrated automatic instrument with a digital readout (the “ideal” cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference [a length-to-width ratio of 2:1]). Any clothing that covers the location of the cuff placement should be removed.

At screening and at every blood pressure assessment throughout the study, SBP and DBP percentiles for age should be determined using the Centers for Disease Control and Prevention (CDC) tables, which require to first determine patient’s percentile for stature using the CDC growth charts.

Both the CDC blood pressure percentiles tables and growth charts will be provided to the sites prior to study start.

4.6.1.6 Electrocardiograms

At each specified time-point ([Appendix 1](#), [Appendix 2](#)), 12-lead ECG recordings must be obtained in triplicate (i.e., three useful ECGs without artifacts 2-3 minutes apart). The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Whenever possible, the same brand/model of a standard high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements should be used for each patient. The conditions should be as close as possible to pre-dose time-points; this includes but is not limited to food intake, activity level, stressors and room temperature.

To minimize variability, it is important that the infant be in a relaxing position for ≥ 10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. If an ECG is performed after vital sign measurements and blood draws, the patient should be provided with enough time to rest in order to minimize variability. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

For safety monitoring purposes, the Investigator or designee must review, sign, and date all ECG tracings. Paper or electronic copies will be kept as part of the patient’s permanent study file at the site. If considered appropriate by Roche, ECGs may be analyzed retrospectively at a central reader.

ECG characteristics, including heart rate, QRS duration, PR, QT and RR intervals, will be recorded on the eCRF. QTcB (Bazett’s correction; Phan et al 2015), QTcF (Fridericia’s correction) will be calculated by the Sponsor. Both corrections of QTc will be

tabulated and analyzed; although, in children, Bazett's formula appears to provide a better correction of the QT interval. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF, additionally as an AE as appropriate. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

4.6.1.7 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at time-points specified in the SoA ([Appendix 1](#), [Appendix 2](#)).

At any time and as described in Section [4.6.3](#), safety laboratory samples will be given the priority over any other sample, such that the volume of blood taken at any single time-point will not exceed 1.5 mL/kg, and the volume collected over any 8-week period throughout the study will not exceed 4.5 mL/kg.

Additional blood samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient safety. For safety laboratory samples only, use of microcollection method should always be favored in order to limit the amount of blood collected. Where the clinical significance of abnormal lab results is considered uncertain, screening lab tests may be repeated before enrolment to confirm eligibility.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated immediately and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically produced laboratory reports submitted directly from the local or central laboratory.

Samples will be collected for the following analysis:

- Hematology: hemoglobin, hematocrit, erythrocytes (RBC), platelets, leukocytes (WBC), differentials (counts): neutrophils, eosinophils, lymphocytes, monocytes, basophils, reticulocyte.
- Serum chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and conjugated bilirubin, albumin, creatinine, urea nitrogen, sodium, chloride, potassium, glucose.

Based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

4.6.1.8 Ophthalmological Assessments

Ophthalmological assessments will be performed at timepoints specified in the SoAs ([Appendix 1](#), [Appendix 2](#), and [Appendix 5](#)). Examinations will be carried out by a pediatric ophthalmologist, neuroophthalmologist, or pediatric ophthalmology imaging specialist *trained and certified to perform the study-specific ophthalmological assessments*. Ophthalmologic examination and retinal imaging include:

1. Visual Development.
2. Red reflex: Performed with an ophthalmoscope or retinoscope from approximately 30 cm / 1 foot in a semi-darkened room, examination will assess brightness of pupil reflex (color and homogeneity, symmetry of the findings, absence, white, opacified).
3. External Ocular Examination: *including, but not limited to*, eyelids, conjunctiva, sclera.
4. Pupillary Response: Using a bright light, pupillary response of each eye will be assessed for direct and consensual response and when achievable accommodative response will be tested.
5. *Cover/Uncover Test*.
6. Fix and follow test: Failure to fix and follow will be assessed in the context of the patient's medical conditions and age.
7. Ocular examination under magnification (*including* slit lamp / ophthalmoscope of anterior and posterior segments including assessment (with dilation or not) of the retina and optic nerve).
8. OCT imaging will be recorded with the Envisu hand-held device from Bioptigen Inc. (or other hand-held device OCT available approved by the central ophthalmic laboratory), alternative method may include the use of a Spectralis (Heidelberg Engineering) converted to a hand-held system for supine imaging. Every attempt should be made to capture additional images after up, down, left, and right gaze.
9. Color Fundus Photography.

The details of the visual tests will be included in a separate *Central Reading Center* manual.

Whenever feasible, additional ophthalmic assessments such as dark adaptation threshold testing, electro-retinography might be carried out as needed in case of abnormalities or upon recommendation from the site or central Ophthalmologist.

Central Reading

The Central Reading Center will provide sites with the Central Reading Center Manual and training materials for study mandated ocular imaging. Before study images are obtained, site personnel, test images, and systems and software (where applicable) will be certified by the reading center as specified in the Central Reading Center Manual. All ocular images will be obtained only by trained and Central Reading Center-certified personnel at the study sites and forwarded to the Central Reading Center for storage

and for independent analysis, including confirmation of eligibility for defined imaging criteria.

4.6.1.9 Nutritional Check

Nutritional assessment will be performed for all patients at the time-points indicated in the SoA ([Appendix 1](#), [Appendix 2](#)) and will include:

- Head to chest circumference ratio from anthropometric measurements (Section [4.6.1.3](#)).
- Nutritional status interview of the parent/ caregiver including questions about ability to swallow and level of solid food intake.
- A speech language pathologist or other suitably qualified individual will perform a standard swallowing assessment according to local practice at the baseline visit, and then, according to the SoA. This will include assessing the ability of the patient to swallow age appropriate foods.

Based on this assessment, specific nutritional advice may be given individually to the patient's parents/ caregivers by the Investigator or Nutritionist.

4.6.1.10 Plasma Protein Binding

A venous blood sample will be collected from all patients at screening in order to measure plasma protein binding, i.e., to measure the free fraction of the study drug (Section [3.2.1](#)). Results for a patient must be available and checked by the Sponsor before any study drug is administered to this specific patient.

Plasma protein binding (i.e., free fraction, f_u) may also be measured from the PK samples collected during the study.

The plasma protein binding assessment at screening may not be required in Part 2 of this study, depending on the data collected in Part 1.

4.6.1.11 Pharmacokinetic Assessments

Blood for determination of plasma concentrations of risdiplam, and its metabolite(s) as applicable, will be collected as detailed in the SoA ([Appendix 3](#), [Appendix 4](#)).

Additional PK samples may be taken if required for safety reasons, e.g., upon a requested dose change to confirm the new target exposure, or to confirm unusual PK findings before requesting a dose change (see [Appendix 1](#) and [Appendix 2](#)).

Venous blood shall be collected for PK samples. The possibility of capillary blood sampling for PK determination may be assessed during the study by parallel venous and capillary sampling, upon specific request by the Sponsor. Depending on the emerging data from the comparison of venous and capillary blood collection, the Sponsor may give permission for capillary blood collection subsequently.

Plasma concentrations of risdiplam will be measured by a specific validated LC-MS/MS assay. Metabolites may be measured by a specific validated LC-MS/MS assay, or other methods as appropriate, and PK samples may also be used for exploratory metabolite identification.

Actual PK sampling times must be documented in the eCRF. Actual date and time of dosing on the day of PK sampling (and the two preceding dosing occasions if possible) must be documented in the eCRF.

PK samples will be destroyed no later than 5 years after the date of final lock of the clinical database.

4.6.1.12 Fluid Pharmacodynamic Assessments

The following fluid PD assessments will be performed as detailed in the SoA ([Appendix 3](#), [Appendix 4](#)).

However, should the total blood volume to be collected at any time-point according to the Schedule of Assessments exceed 1.5 mL/kg, or the volume collected over any 8-week period throughout the study exceeds 4.5 mL/kg, the blood sample prioritization described in Section [4.6.3](#) should be followed.

- In vivo splicing modification of *SMN2* mRNA in blood

Whole blood samples will be taken from every patient at the time-points specified in the SoA ([Appendix 1](#), [Appendix 2](#)) to measure in vivo splicing modification of *SMN1*, *SMN2* FL, and *SMNΔ7* mRNA during the course of the study. In addition, housekeeping genes for the quantitative analysis of RNA will be measured. Additional mRNA may be used for exploratory analysis/assay development related to SMA including, but not limited to, pathways related to SMN function and treatment response.

- SMN protein levels

Venous blood for SMN protein analysis will be collected from every patient.

Based on continuous analysis of the data in this study and other studies, any sample type not considered to be critical for safety may be stopped at any time if the data from the samples collected does not produce useful information.

These samples will be destroyed no later than 5 years after the date of final lock of the clinical database and may be used for additional exploratory analysis/assay development related to SMA including, but not limited to, pathways related to SMN function or treatment response.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.6.1.13 Clinical Genotyping Samples

A single mandatory whole blood sample will be taken from every patient at screening for DNA extraction ([Appendix 1](#), [Appendix 2](#)). The DNA will be used to determine the number of copies of the *SMN2* gene (see Inclusion criteria in Section [4.2](#)) 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.

The clinical genotyping samples will be destroyed no later than 5 years after the date of final lock of the clinical database. Data arising from clinical genotyping will be subject to the confidentiality standards described in Section [8.4](#).

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.6.1.14 Motor Function and Motor Development Assessments

Assessments of motor function and motor development will be performed as detailed in the SoA ([Appendix 1](#), [Appendix 2](#)).

Bayley Scales of Infant and Toddler Development – Third Edition

The Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) is the current version of the most extensively used measure of infant and toddler development in clinical and research practice. The BSID were first published by Nancy Bayley in *The Bayley Scales of Infant Development* (1969) and have been used extensively worldwide since then to assess the development of infants. Compared to the previous version, the Third Edition of the BSID, published in 2006 (Bayley 2006), was improved by updating normative data, strengthening psychometric qualities and changing some items to make administration and scoring easier and more meaningful.

BSID data reflect the U.S. population in terms of race, ethnicity, infant gender, education level of parents, and demographic location of the infant. The BSID was standardized in 1,700 infants, toddlers, and preschoolers between one and 42 months of age. A supplemental study has also demonstrated strong measurement properties for the BSID-III in 221 infants in the United Kingdom and Ireland. The normed-scores derived from the BSID-III are used in clinical practice to detect infants with developmental delays, as well as to evaluate developmental progress and the impact of therapeutic interventions. In addition, the generated T-scores and percentiles for developmental

achievement allow direct clinical comparison of any stabilization or decline or improvement against normally developing children.

The BSID consists of a core battery of five scales. Three scales (cognitive, motor, language) are administered with child interaction and two scales (social-emotional, adaptive behavior) are conducted with parent questionnaires. The BSID-III also includes a Behavior Observation Inventory, a separate scale for validating examiner and parent perceptions of the child's responses.

In this study, the Gross Motor scale of the BSID-III will be used as an outcome measure to assess attainment of motor milestones; other BSID-III scales will not be used. The test, which is expected to take about 25 minutes to be administered in this population, is assessing the following: static positioning (e.g., head control, sitting), dynamic movement including locomotion (e.g., crawling), quality of movement (e.g., kicking), balance and motor planning.

Considering the population of this study, the test will be administered in a modified way compared to the standard administration of the BSID-III as described in the BSID-III manual, e.g., patient's age will not be used as the starting criteria for testing and the order of item administration may be changed. The standardized instrument kit will be used and the test will be administered by an experienced clinician specifically trained to the test procedures, which will be described in a separate manual. If possible, the same assessor should follow the patient at all visits up to and including Week 104.

All BSID-III assessments performed *up to and including Week 104* will be video-recorded in a standardized manner and centrally reviewed by two independent *central* readers. The assessment of the central readers will be used for the primary analysis. The videos may also be used for training purposes, if the parents provide consent in the Informed Consent Form.

During the open-label extension phase of the study, video recording is optional. The site evaluator will continue to assess the patients on the BSID-III. Video-recording is highly encouraged when a patient achieves new milestones.

During the open-label extension phase of the study, only the following items from the BSID-III full gross motor scale will be assessed:

- *Head control:*
 - *Item 9 – Controls head while upright, 15 seconds*
- *Rolling:*
 - *Item 14 – Rolls from side to back*
 - *Item 20 – Rolls from back to side*

- *Sitting:*
 - *Item 16 – Sits with support briefly*
 - *Item 19 – Sits with support 30 seconds*
 - *Item 22 – Sits without support 5 seconds*
 - *Item 26 – Sits without support 30 seconds*
- *Standing*
 - *Item 33 – Supports weight*
 - *Item 40 – Stands alone*
- *Walking*
 - *Item 37 – Walks with support*
 - *Item 42 – Walks alone*

Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

The CHOP-INTEND is a measure of motor function that was developed from the Test of Infant Motor Performance (TIMP) specifically for weak infants with neuromuscular disease. It includes both active and elicited reflexive movement (16 items in total each scored from 0 to 4), such as spontaneous movement of upper and lower extremity, hand grasping, rolling, head control, and others. A total score is calculated by summing the item scores with lower scores indicating greater severity. The CHOP-INTEND demonstrates good intra- and inter-rater reliability in Type 1 SMA patients (Glanzman et al 2010; Glanzman et al 2011).

The CHOP-INTEND has been used in several studies in Type 1 SMA patients, including both non-drug longitudinal studies, such as the Pediatric Neuromuscular Clinical Research network (PNCR) (Glanzman et al 2010) and the National Institute of Neurological Diseases and Stroke (NINDS) NeuroNext natural history studies in children with Type 1 SMA (Kolb et al 2016), and interventional medicinal product studies, such as the IONIS' study [ClinicalTrials.gov Identifier NCT01839656]. Scores on the CHOP-INTEND are correlated with clinical decline over time, requirement for ventilation and association with *SMN2* copy number (Glanzman et al 2011).

In this study, the CHOP-INTEND will be administered by an experienced and specifically trained clinician. Please refer to the CHOP-INTEND test administration manual for specific instruction regarding administration. The assessment will be video-recorded for quality control purposes as indicated in the Training and Quality assurance methodology manual. If possible, the same assessor should follow the patient at all visits up to and including Week 104. The videos may also be used for training purposes, if the parents provide consent in the Informed Consent Form.

Hammersmith Infant Neurological Examination – Module 2

The Hammersmith Infant Neurological Examination (HINE) is a neurologic examination initially designed to evaluate infants between 2 months and 24 months of age. It is a simple and scorable method that includes 26 items assessing different aspects of neurological examinations such as cranial nerves, posture, movements, tone, and reflexes. The pro forma provides instructions for performing the individual items and diagrams to aid recording. The HINE is easily performed and accessible to all clinicians; it can be completed in 5 to 10 minutes. It has shown good inter-observer reliability, even in inexperienced staff.

In this study, only Module 2 of the HINE, which evaluates 8 development milestones, will be assessed.

4.6.1.15 Respiratory Plethysmography

Respiratory Inductive Plethysmography (RP) will be used to measure the degree of synchrony between diaphragmatic (abdominal) breathing and thoracic cage-driven breathing.

In children with SMA, the weakness of intercostal muscles leads to asynchrony of the thorax with the diaphragm (the motor innervation to the phrenic nerve is relatively spared in SMA) and eventually inefficient and clinically evident paradoxical breathing patterns. The degree of synchrony between the movement of the chest wall and abdomen during the respiratory cycle can be expressed as the phase angle between the two compartments and measured in a non-invasive manner by placing two RP bands around the thorax and abdomen.

In paradoxical breathing, the phase angle (ϕ) is reversed compared to the normal ventilation cycle. In addition to ϕ , RP allows estimation of a number of other clinically significant parameters including tidal volume, work of breathing and episodes of hypopnea or apnea. Improvement in these parameters would indicate treatment-associated improvement in intercostal, subcostal and transverse thoracic muscles, as well as the serratus and paraspinal muscles. These measures would be expected to predict a clinically significant impact in respiratory morbidity and mortality, as well as ameliorating progression of orthopedic deformity (scoliosis, thoracic cage collapse).

In this study, RP will be administered by trained personnel following instructions in the RP manual. The data will be reviewed, processed and analyzed by a central reader and the outcome used for analysis.

4.6.1.16 Compound Muscle Action Potential

Electrophysiological outcome measures obtained through nerve conduction studies, in particular CMAP, provide unique information regarding the function of the motor unit, which is central in the pathophysiological process in SMA.

CMAP, which is the measure of the total output of the motor units that supply a particular muscle, has been extensively used to monitor disease progression in amyotrophic lateral sclerosis (ALS) and SMA; a number of studies have shown that it correlates with disease severity, functional status, *SMN2* copy number, and age (Lewelt et al 2010; Finkel 2013; Kolb et al 2016). Accordingly, CMAP may have potential as a predictive and prognostic biomarker of clinical decline in SMA, and possibly as an early measure of muscle reinnervation in SMA clinical trials.

In Part 1, maximum ulnar CMAP amplitude and area will be obtained by recording from the abductor *digiti minimi* muscle following ulnar nerve stimulation at the wrist. In Part 2, maximum ulnar CMAP amplitude and area will be obtained by stimulating the ulnar nerve at the elbow *or wrist* and recording from the abductor digiti minimi muscle. *The stimulation location for each patient should remain consistent throughout the study.* The laterality of muscle groups studied with CMAP must remain consistent for each subject throughout the study.

Maximum values for both negative peak (NP) amplitude and NP area will be obtained from a total of 3–5 G1 electrode placements, using the supplied disposable surface electrodes.

Infants will be distracted using standard techniques regularly used at the sites for pediatric electromyography studies.

Original CMAP waveforms will be printed and faxed/emailed to the data-coordinating center with the completed clinical research form for independent review. CMAP amplitude and NP area data from all sites will be screened by a single reviewer to ensure strict adherence to protocol and ascertain accuracy of placement of markers for amplitude and area measurements.

CMAP data will be excluded for one or more of the following reasons: 1) <3 technically adequate waveforms associated with unique G1 electrode placement, 2) electrical artifact that precludes accurate amplitude and/or area measurements, and/or 3) initial positive deflection that exceeds one-third of the negative peak amplitude.

CMAP will be performed by an electrophysiologist experienced in the assessment of pediatric patients. As much as possible, the same person should perform all the assessments for each patient throughout the study.

4.6.1.17 Clinician-Reported Respiratory and Swallowing Items

In order to capture changes in an infant's respiratory function and ability to swallow, a range of clinical domain level items will be completed by the Investigator. The first item is a clinical global impression of change (CGI-C), which is a single item measure of change using seven response options: "Very much improved", "Much improved", "Minimally improved", "No change", "Minimally worse", "Much worse", "Very much worse". It is a widely used endpoint in clinical trials across a variety of disease areas. The Investigator will score patients using this scale in Part 2 at the Week 52 visit based on their impression of change in the patient's respiratory function since baseline. The Investigator will also score the individual's swallowing ability in the same manner. Investigators will also be asked to rate how the individual's respiratory function and swallowing ability compare to a similarly aged untreated infant with Type 1 SMA and typically developing infants, on a 7-point scale ranging from "very much better" to "very much worse". Finally, the Investigator will be asked to rate the infant's current respiratory function and swallowing ability using a 0–10 numerical response rating scale.

4.6.1.18 Parent/Caregiver-Reported Outcomes

The infant/toddler quality of life questionnaire - short form 47-item version (ITQOL-SF47) is a parent-completed measure that was developed to assess health status and health-related quality of life (HRQoL) of children between 2 months and 5 years old (Landgraf et al 2013). It also assesses the HRQoL of the parent. It was adapted from the longer 97-item due to concerns about the length of the questionnaire and the subsequent burden on the respondent. Factor analysis, stepwise regression and multitrait item-scaling analysis were conducted to inform item reduction. The conceptual relevance and fit to the conceptual framework were also considered. 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 [2], Temperament and Moods [6], Behavior [12], General Health Perception [5], Parent-Emotional Health [4] and Parent-Time Limitations [4]). Items are scored using a Likert-type scale with five levels (except Parent-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 converted to a 0 (worst health) - 100 (best health) scale.

The ITQOL has been used to assess the parent-reported HRQoL of young children with a variety of conditions, including respiratory diseases, pain, and Type 1 neurofibromatosis (Raaf et al 2007; Mohangoo et al 2012; Oostenbrink et al 2007; Spuijbroek et al 2011). Good evidence of reliability and validity has been demonstrated for the ITQOL-SF47 (using samples of healthy individuals, patients with burn injury, and patients with abdominal pain) (Landgraf et al 2013).

Throughout the study, the same parent/caregiver should complete the ITQOL-SF47. If the parent/caregiver does not speak the language spoken at the site, the ITQOL-SF47 will be translated into the parent/caregiver's language. A translator should not be used to administer the ITQOL-SF47.

4.6.2 Timing of Study Assessments

4.6.2.1 Screening and Pretreatment Assessments

Prior to obtaining patient informed consent for participation into the study, investigational sites will be required to complete and submit to the Sponsor or the contracted Contract Research Organization (CRO) a Screening Notification Form. Based on the availability of screening/enrollment allocations in the current cohort, the Sponsor or CRO will notify the site as to whether the patient screening can or cannot proceed at that current time. This will ensure that the recruitment targets for each cohort are adhered to as per this protocol.

Written informed consent for participation in the study must be obtained (by the parent or legally authorized representative) before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled (screen failures) will be maintained at the study site.

All screening and pre-treatment assessments must be completed and reviewed to confirm that patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure.

In Part 1, an Eligibility Screening Form (ESF) documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator, sent to the Sponsor and kept at the investigational site.

Screening and pre-treatment assessments will be performed within 30 days prior to Day 1. Abbreviated rescreening (written informed consent, medical history, physical examination, body weight, safety laboratory tests, and inclusion/exclusion criteria) may be allowed under circumstances where the patient has passed screening but could not be enrolled within the 30-day screening window due to a study halt, logistical, personal, or technical reasons. At no time should the duration between the original screening visit and the abbreviated rescreening visit exceed 3 months. Abbreviated rescreening will only be permitted in cases where this poses no safety risk to the patient.

Patients cannot commence enrolment procedure until all the entry criteria have been fulfilled. Where the clinical significance of an abnormal screening test result (laboratory or any other tests) is considered uncertain, the test should be repeated to confirm the result.

4.6.2.2 Assessments during Treatment

Under no circumstances will patients who enroll in this study and have completed treatment as specified, be permitted to be allocated a new patient number and re-enroll in the study.

The patient study visits when efficacy assessments are performed (see SoA for time-points; [Appendix 1](#), [Appendix 2](#)) will be the most extensive visits, including all efficacy assessments in addition to pharmacokinetics, pharmacodynamics, full physical examination, and safety assessments. Accordingly, these visits may be conducted either as a one-day visit or over two days, whichever is preferred by the parents or caregiver and possible for the clinical site. For these visits, three blocks of assessments have been identified that should ideally be conducted in the order described in [Table 2](#), flexibility being given to the site to, within each of these blocks, perform the assessments in any order. Should this not be possible, what is critical is that in Blocks 1 and 2, the BSID-III and CHOP-INTEND are always preceded by a break of at least 15 minutes. Additional breaks are recommended at any other time as appropriate for each patient. The breaks can include nursing/feeding of the patient. It is also recommended that for a single patient, assessments are conducted in the same order throughout the trial.

Block 3 may be performed the morning of the day preceding Block 1 or the next day if the Investigator determines that this is required for the patient or is preferred by the parents/caregivers. However, the order of assessments should be maintained for the entirety of the study.

Motor function and motor milestone assessments (BSID-III, CHOP-INTEND, HINE-2) may be delayed to another time or day within the visit window if, in the opinion of the investigator or physiotherapist, the patient is uncooperative.

Table 2 Order and Blocks of Assessments at Visits When Efficacy Measurements Are Performed, up to and Including Week 104^a

Block 1	<ul style="list-style-type: none"> • ECG, vital signs, physical examination (including weight) <p>BREAK</p> <ul style="list-style-type: none"> • BSID-III <p>BREAK</p> <ul style="list-style-type: none"> • CHOP-INTEND • HINE-2 <p>BREAK</p> <ul style="list-style-type: none"> • Blood sample (or insertion of catheter) • Dose administration <p>BREAK</p>
Block 2	<ul style="list-style-type: none"> • RP • Infant Toddler Quality of Life Questionnaire <p>BREAK</p> <ul style="list-style-type: none"> • CMAP <p>BREAK</p>
Block 3	<ul style="list-style-type: none"> • Ophthalmological examination

^a After the Week 104 visit, in the open-label extension phase of the study, RP and CMAP are not performed, and only selected items of the BSID-III are performed. Continue to use the Block 1 order as a recommendation.

When blood samples are scheduled for the same nominal time as other assessments the following order should be followed:

1. 12-lead ECGs
2. blood pressure
3. blood samples.

4.6.2.3 Assessments at Study Completion/Early Withdrawal Visit

Patients who complete the study or discontinue *study drug* early will be asked to return to the clinic for a *study completion/early withdrawal visit* as shown in the SoA ([Appendix 1](#), [Appendix 2](#)).

4.6.2.4 Follow-Up-Assessments

A follow-up phone call should occur 30 days after the study completion/early withdrawal visit to collect information on adverse events and use of respiratory support as outlined in Sections [5.5](#) and [5.6](#) and the SoA ([Appendix 1](#), [Appendix 2](#)).

4.6.3 Prioritization Order for Blood Samples

Time-points for blood samples are indicated in the SoA ([Appendix 1](#), [Appendix 2](#)). However, should the total blood volume to be collected at any time-point according to this SoA exceed 1.5 mL/kg or the volume collected over any 8-week period throughout the study exceed 4.5 mL/kg, the prioritization order indicated in [Table 3](#) below should be followed.

Table 3 Prioritization Order for Blood Samples

1	Any safety laboratory samples (scheduled or unscheduled and performed at the discretion of the Investigator).
2	PK samples, including assessment of free fraction.
3	Samples for SMN protein levels.
4	Samples for in vivo splicing modification of <i>SMN2</i> mRNA.

4.7 PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

The Investigator has the right to discontinue a patient from risdiplam or withdraw a patient from the study at any time. In addition, the parent(s) or caregiver have the right to voluntarily discontinue study drug or withdraw the patient from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- The parent or caregiver's withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the patient.
- Patient non-compliance (including study drug administration as recorded in the patient's diary).

4.7.1.1 Discontinuation from Study Drug

Patient must discontinue study drug if they experience any of the following:

- Ophthalmological or other events as described in [Section 5.2.3](#).
- Unable to continue to comply with study requirements.

For patients who discontinue study drug prematurely, their parents or caregiver will be asked to return with the patient to the clinic for a study completion/early *withdrawal* visit ([Section 4.6.2.3](#)). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF.

Patients who discontinue study drug prematurely will not be replaced in Part 2, but may be replaced in Part 1, if the reason for withdrawal is not related to a safety finding.

If a patient needs to stop administration of study drug (e.g., immediate need for surgery, required treatment with a drug known to or suspected to have an interaction with risdiplam, etc.), the investigator must discuss the situation with the Sponsor to determine whether the patient should withdraw from the study or temporarily discontinue study drug.

4.7.1.2 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

Patients will not be followed for any reason after consent has been withdrawn.

Patients who withdraw from the study for safety reasons will not be replaced. Patients who withdraw from the study for other reasons will not be replaced in Part 2, but may be replaced in Part 1.

When the parents or caregiver voluntarily withdraws the patient from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the parents or caregiver specifically requests for these to be discarded or local laws require their immediate destruction.

4.7.2 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor will notify the Investigator and Health Authorities if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to close down and/or replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice.

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section [5.4](#).

5.1.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section [5.3.5.8](#).
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures, such as biopsies).

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death).
- Life-threatening (i.e., the adverse event, in the view of the Investigator, places the patient at immediate risk of death).

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section [5.3.5.9](#)).

- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, or according to a pre-defined grading criteria (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria; Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.1.3 Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6.
- Suspected transmission of an infectious agent by the study drug, as defined below:
Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2 SAFETY PLAN

The Safety Plan considers observations made in nonclinical investigations, including Good Laboratory Practice (GLP) toxicology studies in rats and cynomolgus monkeys, and the observations made in clinical trials. Hypothetical considerations are included in the interpretation of nonclinical and clinical data. The exposure cap of a mean $AUC_{0-24h,ss}$ 2000 ng •h/mL corresponds to the NOAEL in the 39-week toxicology study in cynomolgus- monkey, i.e., the exposure level at which no adverse events were observed.

Only effects on the testes were observed at those exposure levels in another study in rats (effects on testes could not be assessed in cynomolgus monkey due to sexual immaturity of the animals (Risdiplam Investigator's Brochure); parents of male subjects will be informed accordingly. In humans, the pachytene stage of meiosis is completed towards the end of fetal development. In this study, effects on the oocyte are not expected because premature infants will not be included. In juvenile and adult rat toxicity studies and in monkey toxicity studies, there was no effect on female reproductive organs or female fertility. Any effects on meiosis and oocyte maturation will be further investigated in a pre-postnatal toxicity study in rats (Risdiplam Investigator's Brochure).

The stopping rules detailed in Section 5.2.4 will be applied in case of specific adverse events.

5.2.1 Safety Precautions

Based on observed toxicity in nonclinical studies (see Risdiplam Investigator's Brochure for details), the following safety precautions should be followed for this study:

- Effects on hematology parameters: regular monitoring of hematological parameters will be performed.
- Parents or caregiver will be informed that in case of visual impairments, infants could present with e.g., squint, behavioral changes (e.g., follow faces or fixation losses, not reaching/grabbing objects, rubbing of the eyes).

5.2.2 Safety Monitoring

Based on observed toxicity in nonclinical studies (see Risdiplam Investigator's Brochure for details), the following safety monitoring plan has been compiled:

- Specialty medical doctors (ophthalmologist,) will be identified who will be trained in risdiplam observed nonclinical toxicological findings prior to study start to follow-up quickly in case of any suspicious or actual adverse toxicity event.
- Ophthalmological assessments (*see Section 4.6.1.8 for details*)
- Stopping rules for individual patients have been defined that include criteria for treatment discontinuation in case of ophthalmic events (Section 5.2.4).
- Follow-up phone calls (as per the time-points in the SoA; [Appendix 1](#), [Appendix 2](#)): parents or caregiver will be called by the Investigator or designee to monitor safety and tolerability when not attending the clinic. Assessments will include adverse events, concomitant medication review and significant life events.

5.2.3 Management of Specific Adverse Events

Specific adverse events related to ophthalmological adverse events should be managed as described in [Table 4](#).

Table 4 Guidelines for Managing Specific Adverse Events

Event	Action to take
Ophthalmological event	Consult an Ophthalmologist as quickly as possible for ophthalmic examination and provide a copy of the ICF and contact promptly the study Investigator. If findings are unusual, discontinue study treatment until the study-trained Ophthalmologist at study site and the study Investigator have been consulted and the results of a full ophthalmic examination have been reviewed.

5.2.4 Stopping Rules

5.2.4.1 Individual Patient Stopping Rules

While the Investigators, the Roche *Clinical Science Leader*, the Roche Safety Science Leader, the IMC in Part 1, and the external iDMC in Part 2 (and any other professional considered necessary to consult) will review the benefit-risk profile for the individual patients on an ongoing basis, the following specific safety stopping rules for an individual subject are defined a priori:

- Functional or structural eye abnormalities.
 - Clinically relevant abnormalities on spectral domain (SD)-OCT considered to be related to study drug as assessed by an ophthalmologist, i.e., changes in retinal thickness, presence of edema, cystoid or atrophic changes – in case of equivocal observations retinal imaging can be repeated to confirm or refute the initial results. In case of retinal findings, each individual case will be discussed between the Investigator, the Ophthalmologist examining the patient and the Sponsor to decide discontinuation of study drug administration.
 - Clinically relevant impairment of vision detected by the ophthalmological examination.
- Significant and clinically relevant changes in laboratory parameters, ECG, or vital signs which pose an unacceptable risk for the patient.
- Patients with any elevated ALT of $>3 \times \text{ULN}$, alkaline phosphatase (ALP) $<2 \times \text{ULN}$, and associated with an increase in bilirubin ($\geq 2 \times$ upper limit of normal) (i.e., a suspected “Hy’s law” which indicates risk of severe/serious liver impairment) in the absence of a different explanation.
- Other findings such as a SAE or any other severe AE that, at the joint discretion of Roche *Clinical Science Leader*, Roche Safety Science Leader, and the Investigator, indicate that dosing should be halted.

5.2.4.2 Stopping Rules for a Cohort and Dose-Escalation Criteria Rules in Part 1

Stopping Rules for a Cohort

The IMC will review the safety of the patients at predefined time-points or on an ad-hoc basis (as detailed in the Charter) and can recommend termination of a certain cohort at any time. In addition, a cohort may be terminated at the joint discretion of the Roche Translational Medicine Leader, Clinical Pharmacologist and Safety Science Leader.

Safety Criteria for Dose-Escalation

The dose can be escalated in Part 1 if none of the following circumstances occurs in a cohort of patients at the same dose level (or at the same target exposure level) unless these events are clearly not related to the administration of the study drug:

- Grade ≥ 2 skin or subcutaneous reactions of the same type in more than 2 out of the first 5 infants (or $>40\%$ of all infants at the same exposure level).
- Grade ≥ 2 pharyngeal/laryngeal or mucosal reactions of the same type in more than 2 out of first 5 infants (or $>40\%$ of all infants at the same exposure level).
- Abnormal ophthalmological examination or retinal findings for OCT in more than 2 out of first 5 infants (or $>40\%$ of all infants at the same exposure level, as assessed by a study trained Ophthalmologist).
- Grade ≥ 3 adverse drug reaction (other than those described above) of the same type in more than 2 out of first 5 infants (or $>40\%$ of all infants at the same exposure level).
- Clinically significant laboratory abnormalities of the same type in more than 2 out of first 5 infants (or $>40\%$ of all infants at the same exposure level).
- Clinically significant changes in vital signs of the same type in more than 2 out of first 5 infants (or $>40\%$ of all infants at the same exposure level).
- Clinically significant changes in ECGs of the same type in more than 2 out of first 5 infants (or $>40\%$ of all infants at the same exposure level).

If any of the above circumstances are met, dose-escalation will not proceed but lower or intermediate doses can be tested to select an adequate dose for the confirmatory part of the trial. Dose-escalation can progress with the approval of the IMC when none of the above circumstances are met.

5.2.4.3 Stopping Rules for Part 2

Clinical safety data will be reviewed by the external iDMC, supported by an external statistical group, at predefined time-points or on an ad-hoc basis (as detailed in the Charter) and the iDMC can recommend termination of the study.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all adverse events (see Section 5.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4-5.6.

For each adverse event recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (Section 5.1.2 for seriousness criteria), severity (Section 5.3.3), and causality (Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record. Adverse events will then be reported on the Adverse Event eCRF as follows:

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention should be reported (e.g., serious adverse events related to invasive procedures such as biopsies). Any other adverse event should not be reported.

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until *30 days after the study completion/early withdrawal visit (i.e., at least 30 days after the last dose of study drug)*.

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation time-points. Examples of non-directive questions include the following:

“How has your child felt since its last clinic visit?”

“Has she/he had any new or changed health problems since she/he was last here?”

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.03) will be used to assess adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living ^a .
4	Life-threatening consequences or urgent intervention indicated ^b .
5	Death related to adverse event ^b .

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the NCI CTCAE (v4.03), which can be found at:

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

^a If an event is assessed as a "significant medical event", it must be reported as a serious adverse event (Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

^b Grade 4 and 5 events must be reported as serious adverse events (Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.1.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

- Temporal relationship of event onset to the initiation of study drug.
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study drug, or reintroduction of study drug.
- Known association of the event with the study drug or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Diagnosis versus Signs and Symptoms

For AEs, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.2 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.3 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation time-points. Such events should only be recorded once on the Adverse Event eCRF. The initial severity of the event should be recorded, and the severity should be updated to reflect the most extreme severity any time the event worsens. If the event becomes serious, the Adverse Event eCRF should be updated to reflect this.

A recurrent adverse event is one that resolves between patient evaluation time-points and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

5.3.5.4 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium", as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia".

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.5 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result should be reported as an adverse event if it meets any of the following criteria:

- Accompanied by clinical symptoms.
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation).

- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

It is the Investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3 \times \text{ULN}$) in combination with either an elevated total bilirubin ($>2 \times \text{ULN}$) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with total bilirubin $>2 \times \text{ULN}$
- Treatment-emergent ALT or AST $>3 \times \text{ULN}$ in combination with clinical jaundice.

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or a non-serious adverse event of special interest (Section 5.4.2).

5.3.5.7 Deaths

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, "**unexplained death**" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term "**sudden death**" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of SMA disease and/or associated complications or comorbidities, the Death Attributed to Progressive Disease eCRF should be completed.

5.3.5.8 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

5.3.5.9 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.3.5.9), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care.
- Planned hospitalization required by the protocol (e.g., for study drug administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease.

The patient has not suffered an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.
- Admission to emergency room that does not result in hospitalization will not constitute per se a serious adverse event.
- Hospitalization due solely to the progression of the underlying SMA disease, as particularly in this patient population, hospitalizations are expected and frequently occurring due to the nature of the disease.

5.3.5.10 Overdoses

Risdiplam may have a narrow therapeutic window. Based on exposure in animal studies at the limits of tolerability, there is evidence that acute or short-term toxicity of risdiplam is driven by exposure to free, non-protein-bound risdiplam. Calculations of the free exposure concentrations compared with the exposure associated with the highest dose in this study allow estimating that approximately 10-fold higher free concentrations may be associated with life-threatening signs.

Therefore, the administration of the precise dosage must always be ensured.

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied. An overdose or incorrect administration of study drug is not an adverse event unless it results in untoward medical effects.

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

All adverse events associated with any special situations event as defined above should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.11 Parent/ Caregiver-Reported Outcome Data

Adverse event reports will not be derived from parent/ caregiver-reported outcome data by the Sponsor, and safety analyses will not be performed using these data. Although sites are not expected to review these data, it is possible that an Investigator could become aware of parent/ caregiver-reported outcome data that may be indicative of an AE. Under these circumstances, the Investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF form.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The Investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the Investigator learns of the event. The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.1.2; see Section 5.4.2 for details on reporting requirements)
- Non-serious adverse events of special interest (defined in Section 5.1.3; see Section 5.4.2 for details on reporting requirements)

- Medical device complaints (see Section 5.4.2 and 5.4.3 for details on reporting requirements).

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis.
- Significant new diagnostic test results.
- Change in causality based on new information.
- Change in the event's outcome, including recovery.
- Additional narrative information on the clinical course of the event.

Investigators must also comply with local requirements for reporting serious adverse events to the local Health Authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitors is available 24 hours a day 7 days a week. *Country specific toll-free numbers of the emergency medical call center are filed in the investigator site file.*

5.4.2 Reporting Requirements for Serious Adverse Events and Non-Serious- Adverse Events of Special Interest

For reports of serious adverse events and non-serious adverse events of special interest (see Sections 5.1.2 and 5.1.3), investigators should record all case details that can be gathered on the Serious Adverse Reporting Form and forward this form to the SAE Responsible within 24 hours.

5.4.3 Reporting Requirements for Medical Device Complaints

The Investigator must report all medical device complaints to the Sponsor. The Investigator should document as much information as possible on the Medical Device Complaint including the product batch number and expiration date. If the medical device complaint results in an adverse event, the adverse event must be reported on the Adverse Event eCRF. If the event is serious, the Adverse Event eCRF must be completed and reported to the Sponsor within 24 hours after learning of the event (Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The Investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

5.5.2 Sponsor Follow-Up

For serious adverse events, non-serious adverse events of special interest, the Sponsor or a designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 POST-STUDY ADVERSE EVENTS

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (as defined in Section 5.3.1). If the Investigator becomes aware of any other serious adverse event occurring after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and non-serious adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable Health Authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Risdiplam Investigator's Brochure

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

An IMC and iDMC will monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to Health Authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

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 risdiplam. The confirmatory analyses will only include the infants enrolled into Part 2 of the study; it will not include the Part 1 infants who will be analyzed to select the dose.

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. At the time of the Month 24 analysis, all available efficacy data post Month 24 collected as part of the extension period will also be reported. All available safety data in both parts of the study will 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).

Full details of the statistical methods for the confirmatory part have been pre-specified within the Statistical Analysis Plan (SAP) prior to the first infant enrolled into Part 2.

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 (see Section 6.10 for information on the China subpopulation analyses).

6.1 DETERMINATION OF SAMPLE SIZE

Exploratory Part 1

The target sample size is 8 infants, 4 enrolled to each dose level. With 8 infants exposed to risdiplam, there is over an 80% chance to detect an AE in at least one patient, 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 patient, given that the true underlying adverse event rate is 30%, is 76%.

In order to enable the dose selection for Part 2 (e.g., to take into account and assess variability of PK with different age or body weight of the infants), 16 additional patients may be enrolled in Part 1, for up to a maximum total number of 24 patients.

Confirmatory Part 2

The purpose of this part 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 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 two-sided 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.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of infants who were enrolled, discontinued, continuing treatment at the time of the analysis or have completed the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. Data will be presented for each part of the study separately and summaries for Part 1 will be presented overall and by dose/exposure level.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

All infants who receive at least one dose of study medication (risdiplam) will be included in the safety population. Infants will be grouped according to the dose/exposure level actually received in Part 1.

6.3.2 Pharmacokinetic Analysis Population

All infants with at least one time-point with a measureable concentration will be included in the PK analysis data set. Infants will be excluded from the pharmacokinetic 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 pharmacokinetic analysis. Excluded cases will be documented together with the reason for exclusion.

6.3.3 Efficacy Analysis Population

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.

6.4 SUMMARIES 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 and ranges for continuous variables and number and percentages for categorical variables, as appropriate. Baseline will be defined as the last measurement prior to enrollment unless specified otherwise in the SAP. Data will be presented for each part of the study separately and summaries for Part 1 will also be presented by dose/exposure level.

6.5 SAFETY ANALYSES

The safety endpoints include, but may not be limited to, the following:

- 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 ECG abnormalities.
- Incidence of vital sign abnormalities.
- Incidence of clinically significant findings on ophthalmological examination.
- Anthropometric examination including weight, height, head, and chest circumference.

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.

Analyses required for the IMC or iDMC's data review will be performed as described in the associated IMC or iDMC Charter.

6.5.1 Adverse Events

The original terms recorded on the eCRF by the Investigator for adverse events will be standardized by the Sponsor. Adverse events (AEs) will be summarized by mapped term and appropriate thesaurus level. AEs will also be summarized by severity and relationship to the study drug. Serious AEs and AEs leading to treatment discontinuation will be summarized separately.

6.5.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Patients' listings and summary statistics at each assessment time will be presented using the International System of Units (SI units; *Système International d'Unités*). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory data will be listed for patients with values outside the normal ranges. In addition, shift tables to compare the status at baseline to each time-point post-baseline and overall, will be used, as appropriate.

6.5.3 Vital Signs

Vital signs data will be listed for patients with values outside the normal ranges. In addition, tabular summaries will be used, as appropriate.

6.5.4 Electrocardiogram Data Analysis

ECG data will be listed for patients with values outside the normal ranges. In addition, tabular summaries will be used, as appropriate.

6.5.5 Concomitant Medications

The original terms recorded on the patient's eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by assigning preferred terms. Concomitant medications will be presented in summary tables.

6.6 EFFICACY ANALYSES

The intent-to-treat (ITT) population will be the primary analysis population for all efficacy analyses. 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.

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

6.6.2 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.
Infants who do not achieve a score of at least 40, or have not maintained this score achieved earlier, or have been withdrawn, or died, will be classified as non-responders for the analysis.
- 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.

- Change from baseline in the Total Raw Score of the BSID-III gross motor scale at Month 24.
- Proportion of infants who achieve the attainment levels of the motor milestones as assessed in the HINE-2* at Month 8 (subset #), Month 12 and Month 24.
*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.
- Highest motor milestone* achieved by Month 12 and Month 24.
*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 BSID-III gross motor scale.
- 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).

For the achievement of sitting, standing and walking at Month 24, 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 a non-responder for the analysis.

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.
- Proportion of infants who are alive without permanent ventilation at Month 24.
- Proportion of infants who are alive at Month 12.
- Proportion of infants who are alive at Month 24.

Respiratory

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

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.

- 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.

Analyses of the secondary efficacy endpoints will be performed on all data available in Part 2 at the time of the 12- or 24-month analysis reporting events.

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

The highest motor milestone achieved by the infant at any time during the first 12 months (and first 24 months) of treatment will be summarized using number and percentages based on the ITT population. This is regardless of the maintenance of effect or subsequent survival status of the infant. In addition, the number and percentage of infants within each attainment response category of the HINE-2 motor milestones at Month 12 and Month 24 will be presented. The proportion of motor milestone responders (as assessed by HINE-2) will be summarized at Month 12 and Month 24. 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. An infant is classified as a responder if more motor milestones showed improvement than showed worsening; infants who die or withdraw will be classified as nonresponders.

Time-to-death or permanent ventilation and its individual components will be presented graphically using Kaplan-Meier curves. The median time to ventilation-free survival and the proportion of infants who are surviving ventilation-free at Months 12 and 24 will be estimated using Kaplan-Meier methodology, when possible. 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. Infants with no event reported prior to the analysis cut-off date will be censored at the latest date before the cut-off in which they were known to be alive and ventilation-free. The occurrence of a permanent ventilation event will be determined by the independent Permanent Ventilation Adjudication Committee.

The proportion of infants who at 24 months of treatment are alive and (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 testing the same null hypothesis that the proportion of infants who are alive and have achieved the motor milestone $\leq 5\%$ (null) versus $p > 5\%$ (alternative).

The results of other 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 has been 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 predefined benchmark (i.e., an objective performance criteria or performance goal) (French et al 2010; Wiens et al 2014) 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% confidence interval from the historical data. When a predefined 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:

$H_0: p \leq \text{predefined benchmark}$ (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 hierarchy that has been pre-specified in the SAP as long as the p -value is ≤ 0.05 for endpoints higher in the hierarchy.

Full details of the secondary analysis including the available sources to be used as the external control and the benchmarks/performance criteria to be used in the analysis (including the actual null hypothesis response rates to be tested) have been predefined and justified within the SAP, prior to the first patient enrolled within the confirmatory Part 2.

6.6.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints in Part 2 include, but may not be limited to, the following:

Maintenance of 12-Month Treatment Effect

- Proportion of infants who maintained sitting at Month 24 (for infants sitting at Month 12; defined as per the primary endpoint).
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.
- Proportion of infants who maintained (or continued to improve) their phase angle reduction at Month 24 (for infants with a phase angle reduction of at least 30 degrees from baseline at Month 12).

Muscle Electrophysiology

- Proportion of infants who achieve an increase of at least 0.3 mV from baseline in their CMAP negative peak amplitude at Month 12.
- Proportion of infants who achieve an increase of at least 0.3 mV from baseline in their CMAP negative peak amplitude at Month 24.
Infants who do not achieve an increase of at least 0.3, or have not maintained this improvement if achieved earlier, or have been withdrawn or died, will be classified as non-responders for the analysis.

Disease-Related Adverse Events

- Proportion of infants who experience at least one disease-related adverse event by Month 12 and by Month 24.
- Number of disease-related adverse events per patient-year at Month 12 and 24.
Disease-related adverse events will be collected through the adverse event reporting of the study and events will be identified by applying baskets of Medical Dictionary for Regulatory Activities (MedDRA) lowest level terms to the adverse event dataset. The baskets have been predefined in the SAP and finalized prior to enrollment into Part 2.
- Proportion of infants who experience at least one disease-related adverse event resulting in hospitalization by Month 12 and by Month 24.
- Number of disease-related adverse events resulting in hospitalization per patient-year at Month 12 and 24.

Healthcare Utilization

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

Swallowing and Nutrition

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

Growth Measures

- Ratio between the chest and head circumference at Month 8, Month 12, and Month 24.

Head circumference will be the denominator of the ratio.

- 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 ITQOL-SF47 domains* at Month 12 and Month 24.

* parent-proxy domains of: physical abilities, growth and development, bodily pain, temperament and moods, general health perception; overall health and family cohesion single item scales; and parent emotional impact, parent time impact.

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 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.

Statistical methods, definitions and analyses for all exploratory endpoints have been fully specified in the SAP.

6.6.4 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, United States/Canada, rest of world).
- Baseline CHOP-INTEND score (\leq median score, $>$ median score).
- Baseline CMAP amplitude (≤ 1 mV, > 1 mV).
- Time between onset of symptoms and first treatment (≤ 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 the proportion of infants who are surviving ventilation-free at Month 12 will be estimated using Kaplan-Meier methodology, when possible.

6.7 PHARMACODYNAMIC ANALYSES

All pharmacodynamic parameters will be presented by listings and descriptive summary statistics, as appropriate. In Part 1, data will be presented by dose/exposure level.

6.8 PHARMACOKINETIC ANALYSES

All pharmacokinetic parameters will be presented by listings and descriptive summary statistics. Individual and mean plasma concentrations of risdiplam (and metabolites, as appropriate) versus time data will be tabulated.

Non-linear mixed effects modeling (software NONMEM) will be used to analyze the sparse samples of concentration-time data of risdiplam (and its metabolites if deemed necessary). Population and individual pharmacokinetic parameters will be estimated and the influence of various covariates (such as age, gender and body weight) on these parameters will be investigated in an exploratory way. Data may be pooled with data from other studies with risdiplam in order to improve the parameter estimates from the model. Secondary PK parameters (such as C_{max} and AUC) may be derived from the model for each individual included in the PK analysis and will be presented descriptively. Additionally exploratory analyses on exposure and safety / efficacy relationship may be conducted if deemed necessary. The details of the modeling and exploratory analyses may be reported in a document separate from the clinical study report.

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

Additional PK analyses will be conducted as appropriate.

6.9 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 risdiplam in the Type 1 SMA population at this earlier timepoint. The final decision based on the iDMC recommendation will be made by the Sponsor.

6.10 CHINA SUBPOPULATION ANALYSES

The China subpopulation will include all infants enrolled at [REDACTED]-recognized sites (i.e., during both the global enrollment phase and the extended China enrollment phase). Separate analyses will be performed for the China subpopulation, where data from all infants enrolled at [REDACTED]-recognized sites will be combined and summarized. Results from these analyses will be documented in a separate clinical study report.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the Electronic Data Capture (EDC) system.

A comprehensive validation check program will verify the data. Discrepancies will be generated automatically in the system at the point of entry or added manually for resolution by the Investigator.

The Sponsor will produce a Data Handling Manual and a Data Management Plan that describes the quality checking to be performed on the data. Laboratory data will be sent directly to the Sponsor, using the Sponsor’s standard procedures to handle and process the electronic transfer of these data. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor’s standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

Data for this study will be captured via an on line EDC system. The data collected in the source documents is entered onto the study eCRF. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. For each patient enrolled, an eCRF must be completed and electronically signed by the Principal Investigator or authorized delegate from the study staff. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting adverse event, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the Sponsor/CRO in the eCRFs and in all required reports.

eCRFs will be submitted electronically to the Sponsor/CRO and should be handled in accordance with instructions from the Sponsor/CRO.

At the end of the study, the Investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, parent/ caregiver-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data must be defined in the Trial Monitoring Plan.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The investigational site must also allow inspection by applicable Health Authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigational site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with Health Authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final Clinical Study Report has been completed or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Caregiver's Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study Monitors at any time.

For sites in the United States, each Consent Form may also include patient's legally authorized representative authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local Health Authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with Health Authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local Health Authorities, Sponsor Monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities. Investigators are responsible for providing information on financial interests during the course of the study and for one year after completion of the study (i.e., last patient, last observation).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the Investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

Roche shall also submit an Development Safety Update Report (DSUR) once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study.

In U.S., it is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, will be reviewed and approved by an Institutional Review Board (IRB). This board must operate in accordance with the current Federal Regulations. The Sponsor will be sent a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments /modifications are made to the protocol.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The Investigator will permit national and local Health Authorities, Sponsor Monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The Sponsor of the trial is F. Hoffmann-La Roche Ltd. The Sponsor is responsible for the medical oversight, data management, statistical analysis, and medical writing for the Clinical Study Report.

An IMC will be responsible for reviewing safety, PK and PD data and for dose-escalation decisions in Part 1 and the dose-selection for Part 2. An iDMC will review all available data from Part 1 to confirm the dose-decision taken by the IMC, and will review safety, efficacy, PK and PD for Part 2. The scope and responsibility of these committees will be detailed in a specific Charter.

An IxRS system will be used to register the screening/screening failures, enrollment, drug allocation, withdrawal, discontinuation, and termination of patients.

A CRO will be responsible for study management, monitoring, and in some cases, vendor oversight.

An ophthalmological monitoring vendor will be responsible for central review of ophthalmological assessments, and help support activities associated with training local readers and procuring equipment.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific meetings. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.6 PROTOCOL AMENDMENTS

Any substantial protocol amendments will be prepared by the Sponsor. Substantial protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or any non-substantial changes, as defined by regulatory requirements.

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Appendix 1 Schedule of Assessments: Part 1

Week	Screen.		Wk 1					Wk 2		Wk 3	Wk 4		Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10
Day	D-30 to D-2	Day -1 ^{a,q}	Day 1 ^a	Day 2	Day 4	Day 7	Day 11	Day 14	Day 19	Day 25	Day 28	Day 33	Day 42	Day 49	Day 56	Day 63	Day 70	
Visit Window (in days)								± 1			± 3				± 3		± 3	
Assessments																		
Site Visit	x	x	x	x		x		x			x				x			
Home Visit ^d													x				x	
Follow-up call ^{e,r}					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 ^q				x		x			x				x			
Significant life events including family		x ^q													x			
Vital Signs	x	x ^q	x (4h)			x		x			x				x			
ECG-12 lead	x	x ^q	x (4h)			x		x			x				x			
Hematology	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	x	
Study medication dispensation/return ^d			x			x		x			x		x		x		x	
Protein binding Sample	x																	
PK Blood Sample ^k			3 ^m	1 ^l		2		2			4				2			
In vivo mRNA			x					x			x							
SMN protein			x					x			x							
Ophthalmology Assessments ^h	x														x			
Clinical genotyping	x																	
BSID-gross motor scale ^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				x			
Nutritional check ⁿ	x	x													x			
Diary ^o			x	x		x		x			x		x		x		x	
Infant Toddler Quality of Life ^b		x																
Adverse Events	x ^f																	
Previous and Concomitant Treatments ^s																		

Appendix 1 Schedule of Assessments: Part 1 (cont.)

Week	Wk 11	Wk 12	Wks 13-16 ^d	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	Wks 71-77
Day	Day 77	Day 84		Day 119		Day 182		Day 245		Day 301		Day 364		Day 427		Day 490	
Visit Window (in days)		± 3		± 7		± 7		± 7		± 7		± 7		± 7		± 7	
Assessments																	
Site Visit		x		x		x		x		x		x		x		x	
Home Visit ^d			x		x		x		x		x		x		x		x
Follow-up call ^{e,r}	x																
Informed Consent																	
Enrollment																	
Eligibility																	
Demography																	
Medical History																	
SMA History																	
Physical Examination ^c		x		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	
Hematology				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	x
Study medication dispensation/return ^d		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Protein binding Sample																	
PK Blood Sample		4		2		2		2		2		4		2		2	
In vivo mRNA								x				x					
SMN protein				x				x				x					
Ophthalmology Assessments ^h				x		x		x		x		x					
Clinical genotyping				x ^p													
BSID-gross motor scale ^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		x	
Nutritional check ⁿ				x		x		x		x		x		x		x	
Diary ^o		x	x	x	x	x	x	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 ^s	x																

Appendix 1 Schedule of Assessments: Part 1 (cont.)

	Week	Wk 78	Wks 79-86	Wk 87	Wks 88-95	Wk 96	Wks 97-103	Wk 104	Open-Label Extension (OLE)			Study Completion ^v or Early Withdrawal	
	Day	Day 546		Day 609		Day 672		Day 728	Every 13 wks ^k	Every 26 wks	Re-supply Visit ^j	Visit	Follow-Up (30 days after visit)
Visit Window (in days)		± 7		± 7		± 7		± 7	± 14	± 14		± 14	
Assessments													
Site Visit		x		x		x		x	x	x		x	
Home Visit ^d			x		x		x				x		
Follow-up call ^{e,r}													x
Informed Consent													
Enrollment													
Eligibility													
Demography													
Medical History													
SMA History													
Physical Examination ^c		x		x		x		x	x ⁱ	x		x	
Significant life events including family		x		x		x		x		x		x	
Vital Signs		x		x		x		x		x		x	
ECG-12 lead		x		x		x		x		x		x	
Hematology				x				x		x		x	
Blood Chemistry				x				x		x		x	
Administration of Study Medication		x	x	x	x	x	x	x	x	x		x ^w	
Study medication dispensation/return ^d		x	x	x	x	x	x	x	x	x	x	x ^d	
Protein binding Sample													
PK Blood Sample		4		2		2				1		1	
In vivo mRNA				x				x				x	
SMN protein				x				x				x	
Ophthalmology Assessments ^h		x						x		x		x ^u	
Clinical genotyping													
BSID-gross motor scale ^b				x				x		x		x	
HINE-2 ^b				x		x		x		x		x	
CHOP-INTEND ^b		x		x		x		x		x		x	
Respiratory Plethysmography ^b		x		x		x		x				x ^t	
CMAP ^b				x				x				x ^t	
Level of respiratory support		x		x		x		x		x		x	x
Nutritional check ⁿ		x		x		x		x		x		x	
Diary ^o		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 ^s		x											

Appendix 1

Schedule of Assessments: Part 1 (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, 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 head, ears, nose, 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 and any required assessments, as described in Section 4.6.1. Resupply visits (site or home visits) will be performed to ensure the patient has adequate drug and supplies between scheduled site visits as necessary. *At study completion/early withdrawal visit, no study drug will be dispensed and used and unused study drug bottles are to be returned.*
- 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, a follow-up phone call should occur 30 days after the *study completion/early withdrawal visit* to collect information on AEs and use of respiratory support.
- f Only SAEs.
- g The first patient will initially receive a single dose only, i.e., all procedures from Screening until Day 2 (except study drug administration on Day 2 and collection of SMN protein and in vivo mRNA on Day 1) are to be completed. This first patient will approximately 2 weeks later return to the site to start treatment at the adjusted dose and complete all procedures per SoA starting with Day -1 (see footnote q).
- h For the details of the ophthalmology assessments, see Appendix 5.
- i Only weight is required.
- j After Week 104, *study drug resupply at home* will be performed as necessary to ensure that the patient has adequate drug and supplies between scheduled site visits. *Alternatively, the resupply visit can be on site if preferred by parent/guardian.*
- k Additional PK samples may be taken if required for safety reasons.
- l Patients will have a 24-hour PK sample taken, prior to receiving the second dose of risdiplam.
- m Only the first patient will require an additional PK sample on the Day 1 visit when they return to begin daily administration i.e., the visit approximately 2 weeks after the single risdiplam dose. See PK/PD Blood Draw Appendix 3.
- n *In addition, a full swallowing assessment will be performed at Day -1 and on Weeks 26, 52, 78 and 104 as outlined in Section 4.6.1.9.*
- o The time of drug administration will be entered into the diary daily. The diary will be examined at each site and home visit for completeness.
- p The confirmatory clinical genotyping sample can be collected at this visit or any following visit that includes blood sample collection.
- q The first patient will complete only these assessments on Day -1 when he/she returns to the clinic site after approximately 2 weeks to start treatment at the adjusted dose (see footnote g).
- r The first patient will have weekly phone calls until they return to the clinic site after approximately 2 weeks to start treatment at the adjusted dose.
- s This includes SMA related surgeries and procedures.
- t *Not required if the patient withdraws after the Week 104 visit.*

Appendix 1

Schedule of Assessments: Part 1 (cont.)

- u Not required if previous ophthalmology assessment occurred within 4 weeks prior to the study completion/early withdrawal visit.*
- v If an OLE every 26-week visit was completed within 4 weeks of the study completion/early withdrawal visit, only the following assessments need to be repeated at the study completion/early withdrawal visit: study drug return, diary return, adverse event, and concomitant medication.*
- w Final dose of study drug to be administered on day of study completion visit. At the investigator's discretion and if appropriate, study drug may be administered on the day of early withdrawal visit.*

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
Day	D-30 to 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 (<i>in days</i>)							± 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		
Hematology	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 ^l			3	1 ^l			1			4				4		
In vivo mRNA			x							x (4h)						
SMN protein			x							x						
Ophthalmology Assessments ^g	x													x		
Clinical genotyping	x															
BSID-gross motor <i>scale</i> ^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	x														
Previous and Concomitant Treatments ⁿ		x														

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 (in days)		± 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
Hematology				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 Assessments ^g				x		x		x		x		x				
Clinical genotyping				x ^l												
BSID-gross motor scale ^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
Clinical Domain Global Impression												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)			Study Completion ^k or Early Withdrawal	
Day		Day 546		Day 609		Day 672		Day 728	Every 13 wks ⁱ	Every 26 wks	Re-supply Visit ^l	Visit	Follow-Up (30 days after visit)
Visit Window (in days)		±7		±7		±7		±7	±14	±14		±14	
Assessments													
Site Visit		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	
Significant life events including family		x		x		x		x		x		x	
Vital Signs		x		x		x		x		x		x	
ECG-12 lead		x		x		x		x		x		x	
Hematology				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 ^r	
Study medication dispensation/return ^d	x	x	x	x	x	x	x	x	x	x	x	x ^d	
Protein binding Sample													
PK Blood Sample		4		1		4		1		1		1	
In vivo mRNA				x				x				x	
SMN protein				x				x				x	
Ophthalmology Assessments ^g		x						x		x		x ^q	
Clinical genotyping													
BSID-gross motor scale ^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 ^p	
CMAP ^b				x				x				x ^p	
Level of respiratory support		x		x		x		x		x		x	x
Nutritional check ⁿ		x		x		x		x		x		x	
Diary	x	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 ^o	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, [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 head, ears, nose, 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 and any required assessments, *as described in Section 4.6.1*. Resupply visits (site or home visits) will be performed to ensure the patient has adequate drug and supplies between scheduled site visits as necessary. *At study completion/early withdrawal visit, no study drug will be dispensed and used and unused study drug bottles are to be returned.*
- 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, a follow-up phone call should occur 30 days after the *study completion/early withdrawal visit* to collect information on AEs and use of respiratory support.
- f Only SAEs.
- g For the details of the ophthalmology assessments, see [Appendix 5](#).
- h Only weight is required.
- i After Week 104, *study drug resupply at home* will be performed as necessary to ensure that the patient has adequate drug and supplies between scheduled site visits. *Alternatively, the resupply visit can be on site if preferred by parent/guardian.*
- j Additional PK samples may be taken if required for safety reasons.
- k *If an OLE every 26-week visit was completed within 4 weeks of the study completion/early withdrawal visit, only the following assessments need to be repeated at the study completion/early withdrawal visit: study drug return, diary return, adverse event, and concomitant medication.*
- l Patients will have a 24-hour PK sample taken, prior to receiving the second dose of risdiplam.
- m The confirmatory clinical genotyping sample can be collected at this visit or any following visit that includes blood sample collection.
- n *In addition, 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.*
- o This includes SMA related surgeries and procedures.
- p *Not required if the patient withdraws after the Week 104 visit.*
- q *Not required if previous ophthalmology assessment occurred within 4 weeks prior to the study completion/early withdrawal visit.*
- r *Final dose of study drug to be administered on day of study completion visit. At the investigator's discretion and if appropriate, study drug may be administered on the day of early withdrawal visit.*

Appendix 3 PK/PD Blood Draws: Part 1

Week/ Visit	Day	Scheduled Time (H)	PK Blood Sample ^b	SMN Protein ^c	In vivo mRNA ^d	Clinical Genotyping
Screening	30-2					x
Week 1	Day 1 ^a	Predose	x ^e	x	x	
		2H	x			
		4H	x			
		6H	x			
	Day 2	24 H	x			
	Day 7	Predose	x			
		4H	x			
Week 2	Day 14	Predose	x	x		
		4H	x		x	
Week 4	Day 28	Predose	x	x		
		2H	x			
		4H	x		x	
		6H	x			
Week 8	Day 56	Predose	x			
		4H	x			
Week 12	Day 84	Predose	x			
		2H	x			
		4H	x			
		6H	x			
Week 17	Day 119	Predose	x	x		x ^f
		4H	x			
Week 52	Day 364	Predose	x	x		
		2H	x			
		4H	x		x	
		6H	x			
Week 78	Day 546	Predose	x			
		2H	x			
		4H	x			
		6H	x			
Week 104	Day 728	Predose	x	x		
		2H	x			
		4H	x		x	
		6H	x			
Week X ^b		Predose	x	x ^c		
		4H	x		x ^d	
OLE		Predose	x			
<i>Study Completion/Early Withdrawal</i>			x	x	x	

- a The first patient will initially receive a single dose only and all post-dose PK samples are to be collected on Day 1 and Day 2 as per the SoA (SMN protein and in-Vivo RNA not collected). This first patient will, approximately 2 weeks later, return to the site to start treatment at the adjusted dose and will have all Day 1 samples collected as per the SoA.
- b Week X: PK blood draws at Predose and 4 hours also at Weeks 26, 35, 43, 61, 70, 87 and 96.
- c Week X: SMN protein is collected at Predose at Weeks 35 and 87.
- d Week X: In vivo mRNA is collected at 4 hours at Weeks 35 and 87.
- e Only the first patient will require a predose PK sample on the Day 1 visit when they return to begin daily administration i.e., the visit approximately 2 weeks after the single risdiplam dose.
- f The confirmatory clinical genotyping sample can be collected at this visit or any following visit that includes blood sample collection.

Appendix 4 PK/PD Blood Draws: Part 2

Week/ Visit	Day	Scheduled Time (H)	PK Blood Sample ^a	SMN Protein ^b	In vivo mRNA ^c	Clinical Genotyping
Screening						x
Week 1	Day 1	Predose		x	x	
		2H	x			
		4H	x			
		6H	x			
	Day 2	24 H	x			
Week 2	Day 14	Predose	x			
Week 4	Day 28	Predose	x	x		
		2H	x			
		4H	x		x	
		6H	x			
Week 8	Day 56	Predose	x			
		2H	x			
		4H	x			
		6H	x			
Week 17	Day 119	Predose	x	x		x ^d
Week 26	Day 182	Predose	x			
		2H	x			
		4H	x			
		6H	x			
Week 43	Day 301	Predose	x			
		2H	x			
		4H	x			
		6H	x			
Week 78	Day 546	Predose	x			
		2H	x			
		4H	x			
		6H	x			
Week 96	Day 672	Predose	x			
		2H	x			
		4H	x			
		6H	x			
Week X		Predose	x ^a	x ^b	x ^c	
OLE		Predose	x			
<i>Study Completion/Early Withdrawal</i>			x	x	x	

- a Week X: PK blood Draws at Predose at Weeks 35, 52, 61, 70, 87, 104 and additional visits.
- b Week X: SMN protein samples collected predose at Weeks 35, 52, 87 and 104.
- c Week X: In vivo mRNA samples collected at 4 hours on Week 4, and at predose on Weeks 35, 52, 87 and 104.
- d The confirmatory clinical genotyping sample can be collected at this visit or any following visit that includes blood sample collection.

Appendix 5 Ophthalmology Examination: Parts 1 and 2

Week	screening	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	OLE		Study Completion/ Early Withdrawal
		8	17	26	35	43	52	61	70	78	87	96	104	Every 13 wks ^a	Every 26 wks	
Day		Day 56	Day 119	Day 182	Day 245	Day 301	Day 364	Day 427	Day 490	Day 546	Day 609	Day 672	Day 728			
Examination ^b	x	x	x	x	x	x	x			x			x		x	x ^e
SD-OCT ^c	x	x	x	x	x	x	x			x			x		x	x ^e
Color Fundus photography ^d	x			x			x									

a In the case of early withdrawal of the patient, the examination, and SD-OCT will be performed as scheduled in [Appendix 1](#) and [Appendix 2](#).

b The ophthalmology examination includes, as appropriate for age: visual development, red reflex, external ocular examination, pupillary examination/response, cover/uncover test, fundus examination including ophthalmology/slit lamp examination, fix and follow test and ocular examination under magnification.

c Every attempt should be made to capture additional images after up, down, left and right gaze.

d Fundus photography should be attempted at least once at each visit indicated. If unsuccessful, an image of the fundus may be captured during funduscopy.

e Not required if previous ophthalmology assessment occurred within 4 weeks prior to the study completion/early withdrawal visit.