Official Title: An Open-Label Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy

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PROTOCOL

TITLE:	**AN OPEN-LABEL STUDY OF RISDIPLAM IN INFANTS WITH GENETICALLY DIAGNOSED AND PRESYMPTOMATIC SPINAL MUSCULAR ATROPHY**
PROTOCOL NUMBER:	BN40703
VERSION NUMBER:	4
EUDRACT NUMBER:	2018-002087-12
IND NUMBER:	128972
TEST PRODUCT:	Risdiplam (RO7034067)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
30-Mar-2021 20:51:05	Company Signatory	[redacted]

PROTOCOL HISTORY

Version	Date Final
4	See electronic date stamp on title page
3	18 September 2020
2	26 February 2019
1	13 July 2018

PROTOCOL AMENDMENT, VERSION 4: RATIONALE

Protocol BN40703 has been amended primarily to reduce the overall number of ophthalmological assessments, including revision of the ophthalmological assessment requirements at baseline, and to modify the conditions for closure of recruitment. These changes were based on ophthalmological results from Study BP39056 (FIREFISH) and the overall risdiplam clinical development program. Changes to the protocol, along with the rationale for key changes, are summarized below:

- Ophthalmological monitoring conducted in 461 patients has not revealed any ophthalmological safety concerns. This dataset includes 62 patients from Study BP39056 (FIREFISH) aged 2.2 months to 6.9 months at enrollment, thus establishing retinal safety in infants older than 2 months. Moreover, ophthalmological follow-up has been conducted for at least 1 year in 3 patients in the present study without any risdiplam-induced findings. Therefore, in order to reduce burden on patients and their families and caregivers, ophthalmological assessments will be conducted at the following visits: screening, Weeks 8, 28, and 52, and yearly thereafter (Section 1.3.2 and Appendix 3).
- A high number of repeat optical coherence tomography (OCT) images may be required to gain optimal OCT quality and in order not to delay the start of treatment in presymptomatic SMA infants, the time window for obtaining high quality screening ophthalmologic assessments is expanded from Day −42 to Day 14. In the event that an OCT of sufficient quality cannot be obtained prior to enrollment, one must be obtained by Day 14 (Section 4.1.2, Appendix 1and Appendix 3).
- The conditions for the closure of recruitment have been updated in order to facilitate completion of the study in a reasonable timeframe. Recruitment has been challenging because patients having other treatment options, particularly those patients who have two copies of the *SMN2* gene as they are the most likely candidates for alternative therapies. Previously, recruitment would have closed when a minimum of 10 patients who meet criteria for the primary efficacy population had been enrolled (two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude $\geq$ 1.5 mV). This has been updated so that recruitment will now close when either at least 25 patients, including a minimum of 5 patients who meet the criteria for the primary efficacy population (Section 6.3.3) are enrolled, OR when a total of 10 patients who meet the criteria for the primary efficacy population are enrolled (Sections 3.1, 3.3 and 4.1).

Additional changes include the following:

- Safety data for Study BN40703 have been updated (Section 1.2.2.4)
- The timing of the primary analysis has been updated to account for the possibility that recruitment may be completed prior to 10 primary efficacy population patients being enrolled. Instead of the primary analysis occurring when the last patient with two *SMN2* copies and a baseline CMAP amplitude $\geq$ 1.5 mV reaches

Month 12 of treatment, it will occur when the last patient enrolled overall reaches Month 12 of treatment (Sections 3.1 and 6).

- The description of the sample size has been updated to include the requirements for a statistically significant result in the event that recruitment stops prior to enrolling 10 patients with two *SMN2* copies and a baseline CMAP amplitude $\geq$ 1.5 mV (Sections 6.1 and 6.5.1).

- At the request of the Belgian Health Authority (FAMHP), language regarding the monitoring of potential toxicities of co-administered CYP3A substrates removed with protocol version 3 has been restored (Section 4.4.1).

- At the request of the FAMHP, language prohibiting grapefruit or Seville orange juice, which was removed with protocol version 3, has been restored because during the study, patients will reach the age where drinking these products may become possible (Section 4.4.3).

- It has been clarified that home nursing will only be used in exceptional circumstances that prevent a patient from attending the study visit at the site (Section 4.5).

- Language has been added to clarify that, regarding the stopping of the Hammersmith Infant Neurological Examination (HINE-2), the earliest final HINE-2 evaluation will be at Week 104 . Previously, it was stated that from Week 104, this assessment will be stopped for each infant once the maximum score is reached at two consecutive visits, however, it was not clear at which visit this could first be achieved (Section 4.5.9.2 and Appendix 1).

- It has been clarified that the Hammersmith Functional Motor Scale Expanded (HFMSE) may be video recorded for quality control purposes (Section 4.5.9.4).

- It has been clarified that Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) is not required at study completion/early withdrawal visits that occur after Week 182 (Appendix 1).

Additional minor changes and corrections 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:	**AN OPEN-LABEL STUDY OF RISDIPLAM IN INFANTS WITH GENETICALLY DIAGNOSED AND PRESYMPTOMATIC SPINAL MUSCULAR ATROPHY**
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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 retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

PROTOCOL SYNOPSIS

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

Objectives and Endpoints

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

Efficacy Objectives

Primary Efficacy Objective

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

Secondary Efficacy Objectives

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

To evaluate the efficacy of risdiplam on the development of clinically manifested SMA on the basis of the following endpoints:

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

To evaluate the efficacy of risdiplam on survival and permanent ventilation on the basis of the following endpoints

- Time to death
- Time to permanent ventilation
- Time to death or permanent ventilation
- Proportion of patients alive without permanent ventilation (at Month 12 and Month 24 of treatment)
- Proportion of patients alive (at Month 12 and Month 24 of treatment)

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

- Proportion of patients who achieve the attainment levels of the motor milestones assessed in the HINE-2 (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) (at Month 12 and Month 24 of treatment)
- Proportion of patients with two copies of the *SMN2* gene sitting without support (at Month 12 of treatment [as assessed in Item 22 of BSID-III Gross Motor Scale]) for 5 seconds (independent of the CMAP value at baseline)
- Proportion of patients sitting without support (at Month 24 of treatment [as assessed in Item 22 of BSID-III Gross Motor Scale] for 5 second
- Proportion of patients sitting without support (at Month 12 and Month 24 of treatment [as assessed in Item 26 of BSID-III Gross Motor Scale]) for 30 seconds
- Proportion of patients standing (at Month 24 [defined as “Stands Alone” for at least 3 seconds as assessed in Item 40 of the BSID-III Gross Motor Scale])
- Proportion of infants walking (at Month 24 [defined as “Walks Alone” takes at least 3 steps as assessed in Item 42 of the BSID-III Gross Motor Scale])
- Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of the chronological reference standard (at Months 24 and 42 [as assessed through the use of the BSID–III Gross Motor Scale])

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

- Change from baseline in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale (at Month 12 and Month 24 of treatment)
- Proportion of patients who achieve a score of 40 or higher, 50 or higher, and 60 or higher in the CHOP INTEND motor function scale (at Month 12 of treatment)
- Proportion of patients who meet CHOP INTEND stopping criteria at any point up to Month 24 of treatment
- Change from baseline (Month 24) in the Hammersmith Functional Motor Scale Expanded (HFMSE) (at Month 60 of treatment).

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

- Number and proportion of patients within 3rd percentile of normal range for weight-for-age, length/height-for-age and weight-for-length/height (at Months 12, 24, 36, 48, and 60 of treatment based on the WHO Child Growth Standards) (WHO 2019)
- Number and proportion of patients within 3rd percentile of normal range for head circumference-for-age (at Month 12 and Month 24 of treatment, based on the WHO Child Growth Standards) (WHO 2019)
- Change from baseline percentiles for weight-for-age, length/height-for-age and weight-for-length/height (at Months 12, 24, 36, 48 and 60 of treatment)
- Change from baseline percentiles for head circumference-for-age (at Month 12 and Month 24 of treatment)
- Change from baseline in chest circumference (at Month 12 and Month 24 of treatment)
- Ratio between chest and head circumferences (at Month 12 and Month 24 of treatment)

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

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

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

- Change from baseline in CMAP amplitude (at Month 12 and 24 of treatment)

To evaluate the pharmacodynamic (PD) effects of risdiplam on the basis of the following endpoints:

SMN mRNA levels in blood

SMN protein levels in blood

Exploratory Efficacy Objectives

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

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

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

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

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

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

Proportion of patients who attain motor milestones as assessed by WHO criteria (at Months 48 and 60 of treatment)

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

Total Walk Distance in the six-minute walk test (6MWT; ambulant patients only) (at Month 60 of treatment)

To explore the treatment effect on speech development on the basis of the following endpoint:

Speech development as assessed during the neurological examination (at Months 12, 24, 36, 48, and 60 of treatment).

- To explore the effect of treatment with risdiplam on the number of hospitalizations on the basis of the following endpoints:

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

Proportion of patients with no hospitalizations (at 12, 24, 36, 48, and 60 months of treatment).

To explore the treatment effect on pre-specified disease-related adverse events on basis on the following endpoint:

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

Safety Objectives

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

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

Incidence and severity of serious adverse events

Incidence of treatment discontinuation due to adverse events

Incidence of abnormal laboratory values

Incidence of abnormal ECG values

Vital signs abnormalities, including body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate

Ophthalmological examination as appropriate for age (e.g., red reflex, external ocular examination, pupillary examination/response, cover/uncover, fix and follow test, corneal light reflex, fundus examination including ophthalmoscopy/slit lamp examination, SD-OCT, and fundus photography)

Physical examination, including detailed examination of the skin and mouth

Pharmacokinetic Objective

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

Plasma concentration of risdiplam and its metabolite(s), as appropriate, at specified timepoints

Area under the concentration–time curve (AUC)

Concentration at the end of a dosing interval to assess steady-state

Other PK parameters as appropriate

Biomarker Objective

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

Relationship between exploratory biomarkers in blood and efficacy, safety, PK, or other biomarker endpoints

Relationship of genetic, epigenetic, or genomic markers with efficacy, safety, PK, or other biomarker endpoints related to SMA

Health Status Utility Objective

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

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

Study Design

Description of Study

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

There will be a screening, treatment, open-label extension (OLE) phase, and a follow-up. Screening will be up to 42 days prior to first dose, bearing in mind the maximum age of the patient at first dose of study drug is 42 days. Screening assessments may be repeated before enrollment to confirm eligibility. Patients will be enrolled in the study regardless of *SMN2* copy number. Recruitment will be global (e.g., at sites in United States, European Union, Russia, Brazil, Australia, Taiwan, Saudi Arabia and National Medical Products Administration recognized sites in China). All patients will receive risdiplam orally once daily for 2 years at a dose selected to achieve the targeted exposure range of close to 2000 ng • hr/mL (the dose may be adapted as patients grow and mature), followed by an OLE phase of at least 36 months

and a follow-up, for a total treatment duration of at least 5 years for each infant enrolled.
Enrollment will be closed when one of the following conditions have been met:
At least 25 patients, including a minimum of 5 patients who meet the criteria for the primary efficacy population are enrolled,
OR
A total of 10 patients who meet the criteria for the primary efficacy population are enrolled.

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

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

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

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

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

Target Population
Inclusion Criteria
Patients must meet the following criteria for study entry:
Signed Informed Consent Form by a legally authorized representative for the patient in accordance to International Council on Harmonisation (ICH) and local regulations

Males and females aged from birth (1 day) to 6 weeks (42 days) of age at the time of first dose (Day 1); a minimum age of 7 days at first dose is required for the first infant to be enrolled

Gestational age of 37–42 weeks for singleton births; gestational age of 34–42 weeks for twins

Body weight $\geq 3^{rd}$ percentile for age, using appropriate country-specific guidelines

Genetic diagnosis of 5q-autosomal recessive SMA, including confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the *SMN1* gene

Absence of clinical signs or symptoms at screening (Day –42 to Day –2) or at baseline (Day –1) that are, in the opinion of the investigator, strongly suggestive of SMA

Receiving adequate nutrition and hydration at the time of screening, in the opinion of the investigator

Adequately recovered from any acute illness at baseline and considered well enough to participate in the study, in the opinion of the investigator

Able and expected to be able to safely travel to the study site for the entire duration of the study and in accordance to the frequency of required study visits, in the opinion of the investigator

Able to complete all study procedures, measurements, and visits, and the parent (or caregiver), in the opinion of the investigator, has adequately supportive psychosocial circumstances

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

Parent (or caregiver) is willing to consider the use of non-invasive ventilation during the study, if recommended by the investigator

Exclusion Criteria

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

Concomitant or previous participation in any investigational drug or device study at any time

Concomitant or previous administration of an SMN2-targeting antisense oligonucleotide, SMN2-splicing modifier, or gene therapy either in a clinical study or as part of medical care

Presence of significant concurrent syndromes or diseases

In the opinion of the investigator, inadequate venous or capillary blood access for the study procedures

Requiring invasive ventilation or tracheostomy

Requiring awake non-invasive ventilation

Awake hypoxemia (SaO2 $<$ 95%) with or without ventilator support

Multiple or fixed contractures and/or hip subluxation or dislocation at birth

Systolic blood pressure or diastolic blood pressure or heart rate considered to be clinically significant by the investigator

Presence of clinically relevant ECG abnormalities before study drug administration; corrected QT interval using Bazett's method $>$ 460 ms; personal or family history (first degree relatives) of congenital long QT syndrome indicating a safety risk for patients as determined by the investigator. First-degree atrioventricular block or isolated right bundle branch block are allowed.

The infant (and the mother, if breastfeeding the infant) taking any of the following:

- Any inhibitor of CYP3A4 taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing, including but not limited to: ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, cimetidine
- Any inducer of CYP3A4 taken within 4 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing, including but not limited to: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John's wort
- Use of any OCT 2 and MATE substrates within 2 weeks prior to dosing (including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine)
- Use of any known FMO1 or FMO3 inhibitors or substrates

Clinically significant abnormalities in laboratory test results (e.g., Grade $>$ 1 anemia, ALT values exceeding 1.5 $\times$ the upper limit of normal unless the elevated ALT level is considered of muscular origin [i.e., in the absence of other evidence of liver disease that is confirmed by elevated creatine kinase and lactate dehydrogenase]). Out of range creatine kinase levels should be reviewed in light of the underlying SMA pathology of the patient; elevated levels per se do not disqualify the patient from the study. In the case of uncertain or questionable results, tests performed during screening may be repeated before enrollment to confirm eligibility.

Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to risdiplam or to the constituents of its formulation (see the Risdiplam Investigator's Brochure)

Treatment with oral salbutamol or another β2 adrenergic agonist taken orally for SMA is not allowed. Use of inhaled β2 adrenergic agonists (e.g., for the treatment of asthma) is allowed.

Anticipated need for thioridazine, vigabatrin, retigabine, or any other drug known to cause retinal toxicity during the study. Infants exposed to thioridazine, vigabatrin, retigabine, or drugs with known retinal toxicity given to mothers during pregnancy (and lactation) should not be enrolled.

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

End of Study

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

Length of Study

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

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

Investigational Medicinal Products

Test Product (Investigational Drug)

The investigational medicinal product for this study is risdiplam.

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

Statistical Methods

Primary Analysis

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

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

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

If the one-sided p-value is $\leq$ 5% (Type 1 error rate), then the null hypothesis will be rejected. If the lower limit of the two-sided 90% confidence interval is above the 5% threshold, the primary objective of the study will be considered achieved. The number and percentage of infants sitting at each timepoint will also be presented, using the same responder/non-responder definition described above.

As this is an open-label study, once at least 3 out of 10 infants *(if 10 patients in the primary analysis population are enrolled)* have met the primary endpoint of sitting without support at Month 12 (as assessed by the independent central readers), the minimum number of infants needed for a statistically significant result will have been achieved and the primary objective of

the study will be considered achieved at this earlier timepoint. *The primary analysis will be conducted once the last patient enrolled (irrespective of SMN2 copy number) has reached 12 months of treatment, in order to assess the primary endpoint, and to allow the assessment of the 12 month secondary and exploratory endpoints in all patients*. The study will not be stopped early if the primary objective has been reached, and all infants enrolled will continue to receive 12 months of treatment to provide an unbiased estimate of the proportion of infants sitting at Month 12.

Determination of Sample Size

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

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

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

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

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

Interim Analyses

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

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

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

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	six-minute walk test
AUC	area under the concentration–time curve
AUC_{0-24}	area under the concentration–time curve from time 0 to 24 hours
$AUC_{0-24,ss}$	area under the concentration–time curve from time 0 to 24 hours at steady state
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}	maximum plasma concentration observed
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
DAP	Data Analysis Plan
DDI	drug–drug interaction
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EOS	end of study
FDA	Food and Drug Administration
FMO	flavin-containing monooxygenase
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE	Hammersmith Infant Neurological Examination
HIPAA	Health Insurance Portability and Accountability Act
HRQoL	health-related quality of life
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ITQOL	Infant Toddler Quality of Life Questionnaire™
ITQOL-SF47	Infant Toddler Quality of Life Questionnaire™– 47-item short-form version
ITT	intent-to-treat (population)
IxRS	interactive voice or web-based response system
LPLV	last patient, last visit

Abbreviation	Definition
MATE	multidrug and toxin extrusion
MN	mobile nursing
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
OCT 2	organic cation transporter 2
OLE	open-label extension
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetic
PRO	patient-reported outcome
QTc	corrected QT interval
QTcF	QT interval corrected through use of Fridericia's formula
SD-OCT	spectral-domain optical coherence tomography
SMA	spinal muscular atrophy
SMN	survival motor neuron (protein)
SMN	*survival motor neuron* (gene)
ULN	upper limit of normal
WHO	World Health Organisation

1. BACKGROUND

1.1 BACKGROUND ON SPINAL MUSCULAR ATROPHY

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 and Pardo 1996; Lunn and Wang 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 and Davies 1992): Type 1 SMA or Werdnig-Hoffmann disease (severe infantile type with onset before 6 months of age; infants 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, children 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 able to walk until the disease progresses), and Type 4 SMA (adult onset).

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 SMNΔ 7 protein that is rapidly degraded (Lorson et al. 1999; Cho and Dreyfuss 2010). Accordingly, full-length *SMN2* mRNA is generated in only 10%−15% of splicing events. Because patients with SMA only have the *SMN2* gene, their SMN protein levels are significantly decreased (Kolb and Kissel 2011).

Consistent with this mechanism, several studies have reported a phenotype-genotype relationship among patients with SMA, showing that an increased *SMN2* copy number is correlated with improved survival outcomes and maintenance of motor function (Feldkotter et al. 2002; Mailman et al. 2002): The majority of patients with Type 1 SMA have two *SMN2* copies, though some have three and even four or five copies; patients with Type 2 SMA usually have three *SMN2* copies; patients with Type 3 SMA have three or four *SMN2* copies; and patients with Type 4 SMA have four or more *SMN2* copies (Crawford et al. 2012). Considering the number of studies that have confirmed a positive correlation between *SMN2* copy number and a milder phenotype,

SMN2 copy number is currently regarded as a determinant of SMA disease severity (yet it is not the only phenotype modifier; see Prior et al. 2009 for example).

Although the exact mechanism by which SMN protein deficiency leads to motor neuron loss as observed in patients with SMA is currently unclear (Nurputra et al. 2013), the elucidation of the molecular basis of SMA suggests several therapeutic approaches based on the general principle of increasing SMN protein expression (Kolb and Kissel 2011). In fact, considering that SMN protein levels in patients with SMA Type 1, Type 2, and Type 3 are ~30%–40%, ~50%–60% and ~60%–80%, respectively, of the normal level (i.e., level in *SMN1*± carrier individuals) (Kolb et al. 2006; Sumner et al. 2006; Nguyen et al. 2008), even moderate changes in SMN protein levels are expected to have a substantial clinical benefit in patients with SMA, turning more severe phenotypes into milder forms. In addition, nonclinical data suggest that greater than 100% SMN protein increase is likely to result in better efficacy in patients with SMA.

The timing of therapeutic intervention is crucial since most of the degeneration in motor neurons occurs in the first months of life in patients with Type 1 SMA. It has been demonstrated that infants with Type 1 SMA undergo a rapid loss of motor units in the first 3 months of life. Results from recent clinical trials in presymptomatic patients have shown a more rapid achievement of motor milestones and diminished disease severity when therapy was administered at an early age and earlier in the disease course (Hwu et al. 2017).

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, 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 superinfections 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.

Nusinersen (Spinraza™) is currently licensed for the treatment of SMA. This intrathecally administered antisense oligonucleotide acts by binding downstream of exon 7 in the *SMN2* pre-mRNA, allowing for its inclusion in the mRNA message, thus enhancing translation into fully functional *SMN2* encoded protein (Hua et al. 2010). However, the medical need in SMA is still high, and there is currently no approved oral treatment for SMA that provides stabilization or improvement of motor function. Several drug candidates are currently under investigation in the clinical setting (Kariyawasam et al. 2018).

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.

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

1.2 BACKGROUND ON RISDIPLAM

One of the promising pharmacological strategies currently being pursued is to restore functional SMN protein levels in patients with SMA 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 and Kissel 2011; Nurputra et al. 2013). This approach is supported by the recent approval of nusinersen, an antisense oligonucleotide promoting inclusion of exon 7 in *SMN2* pre-mRNA, thereby increasing the amount of full-length SMN protein expressed by the *SMN2* gene. Risdiplam (formerly known as RO7034067) is an orally bioavailable small-molecule compound, which directly targets the underlying molecular deficiency of the disease, promoting the inclusion of exon 7 to generate full-length *SMN2* mRNA and thereby increasing the production of the functional SMN protein. The specificity for *SMN2* over other transcripts was elucidated in a study with *SMN2* splicing modifier tool molecules of the same chemical series and closely related to risdiplam (Sivaramakrishnan et al. 2017). These data demonstrate that risdiplam modifies alternative splicing rather than gene expression with high specificity.

Risdiplam has been investigated in five clinical pharmacology studies in healthy subjects and in three ongoing studies in patients with SMA. To date, treatment with risdiplam has been safe and well tolerated in all studies, and an exposure-dependent increase in SMN protein was observed in patients with SMA, confirming proof of mechanism. Risdiplam has been approved in the USA for patients 2 months of age and older.

Findings from nonclinical studies and clinical study data relevant to this study are summarized below.

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

1.2.1 Nonclinical Studies

1.2.1.1 Pharmacokinetics

For a detailed summary of preclinical data, please refer to the Risdiplam Investigator's Brochure.

Risdiplam is cleared in animals and humans primarily through metabolism with minor contribution from renal clearance. The metabolizing enzymes involved are

flavin-containing monooxygenase (FMO) 1 and 3 and members of the CYP superfamily, especially CYP3A. Risdiplam is an inhibitor of organic cation transporter 2 (OCT 2), 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. Such drugs are therefore prohibited for patients participating in this study.

Risdiplam is a weak inhibitor of CYP3A. A small, but clinically not relevant, interaction was observed in adult subjects (increase in AUC 11% and C_{max} 16%). 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. Caution should be applied for co-administration of risdiplam and CYP3A substrates in infants <2 months of age.

1.2.1.2 Toxicology

For a detailed summary of the toxicology data, please refer to the Risdiplam Investigator's Brochure.

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

A further finding of significance was noted in the retina from the 39-week toxicology 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 (SD-OCT). This was associated with depressed scotopic (rod) B-wave and somewhat less affected photopic (cone) B-wave in the electroretinogram. These findings were confirmed by histopathology. Experimental evidence suggests that the effect on the retina is not directly associated with effects on tissue proliferation but is related to in vitro evidence of high melanin binding and tissue retention in the retina. Despite high tissue accumulation and tissue retention of risdiplam in monkey and pigmented rat retinal pigment epithelium/retina, no evidence for any retinal effects was present after 26 weeks of treatment in pigmented rats, at which time retinal changes were clearly seen in monkeys. Thus, melanin-bound risdiplam in the retina does not confer toxicity per se.

The doses for the clinical studies in patients with SMA were selected to result in a mean exposure (area under the concentration–time curve from time 0 to 24 hours at steady state [$AUC_{0\text{-}24,ss}$]) of $\leq$2000 ng • hr/mL. This corresponds to the mean exposure at the no-observed-adverse-effect level (NOAEL)/no-observed-effect level (NOEL) of the 39-week toxicity study in monkeys with an area under the concentration–time curve from time 0 to 24 hours ($AUC_{0\text{-}24}$) of 1870/2060 ng • hr/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, careful evaluation of the free fraction of risdiplam in plasma of

infants 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.

In rats, risdiplam resulted in embryo-fetal toxicity with retarded fetal development, evidenced by lower fetal weights and minor differences in skeletal ossification. There was no evidence of embryo-fetal death or fetal dysmorphology (teratogenicity) in rats. The NOAEL for rats was 3 mg/kg/day, corresponding to C_{max} 319 ng/mL and AUC_{0-24h} 4630 ng•h/mL on gestational day (GD) 15. In rabbits, risdiplam administered from Days 6 to 19 of gestation resulted in maternal toxicity and embryo-fetal death and malformations (hydrocephaly). The NOAEL for rabbits was 4 mg/kg/day for risdiplam (C_{max}1500 ng/mL, AUC_{0-24h} 7990 ng•h/mL on GD 15).

1.2.2 Clinical Studies

Risdiplam has been investigated in five clinical pharmacology studies; all five studies (BP29840, BP39122, NP39625, BP41361, and BP40995) have been completed (see the Risdiplam Investigator's Brochure for available data):

- Study BP29840 (single ascending dose, entry-into-human study in healthy male adults)
- Study BP39122 (a mass-balance study in healthy male adults)
- Study NP39625 (a pharmacokinetic [PK] study in healthy Japanese adults)
- Study BP41361 (a drug-drug interaction [DDI] study with the CYP3A substrate midazolam)
- Study BP40995 (a hepatic impairment study)

Additionally, there are three ongoing studies in patients with SMA:

- Study BP39054 (an open-label study to evaluate safety, pharmacokinetics, and pharmacodynamics in non-naive patients with Type 1, 2, or 3 SMA)
- Study BP39055 (a study to evaluate safety, pharmacokinetics, pharmacodynamics, and efficacy in patients with Type 2 or 3 SMA)
- Study BP39056 (a study to evaluate safety, pharmacokinetics, pharmacodynamics, and efficacy in patients with Type 1 SMA)

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

1.2.2.1 Pharmacokinetics

In the completed single ascending dose study in healthy adults (BP29840), risdiplam was rapidly absorbed with a median time of maximum concentration between 2–3 hours under fasted conditions. Food had no relevant effect on the pharmacokinetics. Maximum plasma concentration (C_{max}) and total plasma exposure (area under the concentration–time curve [AUC]) increased in a dose-proportional manner. The elimination half-life was approximately 41–64 hours. On average, a small fraction ($<$ 10%) of the administered dose was excreted unchanged into urine. Itraconazole

(CYP3A4 inhibitor) had only a minor effect on the pharmacokinetics. A mass-balance study (BP39122) showed that the major pathway of elimination was fecal excretion with on average 53.2% of the dose administered; urinary excretion of [14C]-radioactivity accounted for on average 28.2% of the dose administered. Study NP39625 showed that there was no difference in plasma or urine PK parameters, or the pharmacodynamic (PD) effects of risdiplam on SMN mRNA and SMN protein, between Japanese and Caucasian healthy subjects.

In Part 1 of Study BP39055 in patients with Type 2 or 3 SMA, pharmacokinetics was linear (i.e., there was a corresponding increase in risdiplam plasma concentrations with increase in dose). The median $AUC_{0\text{-}24,ss}$ at the highest evaluated dose of 5 mg was 1610 ng • hr/mL (range: 1140–1950 ng • hr/mL) in the 12–25-year-old group. In the group of patients with SMA aged 2–11 years, the highest evaluated dose of 0.25 mg/kg led to a median $AUC_{0\text{-}24,ss}$ of 1450 ng • hr/mL (range: 1230–2090 ng • hr/mL). There was no indication of nonlinear pharmacokinetics versus dose or a change in pharmacokinetics with time after multiple-dose administration. Steady state was attained after 7–14 days of treatment with risdiplam once daily.

In Study BP39056 in infants with Type 1 SMA, the final dose level selected was 0.2 mg/kg for all infants <2 years old. The mean $AUC_{0\text{-}24,ss}$ at 0.2 mg/kg was 1930 ng • hr/mL (range: 1230–3300) at the Month 12 visit.

Please see Section 3.3.1 for details on dose selection.

1.2.2.2 Pharmacodynamics

In healthy adults (Studies BP29840 and NP39625), risdiplam had a dose-dependent effect on *SMN2* splicing, as shown by a change in the ratio of full-length *SMN2* mRNA to SMNΔ7 mRNA.

In Part 1 of Study BP39055 in patients with Type 2 or 3 SMA, a median SMN protein increase of 151% (range: 49%–251%) versus baseline was observed for the highest evaluated dose of 5 mg in patients 12–25 years old, and a 96% (range: 17%–150%) increase in SMN protein was noted for the highest tested dose of 0.25 mg/kg in the 2–11 year age group.

In Part 1 of Study BP39056 in infants with Type 1 SMA, a 2-fold increase (median; range 1.0–5.4) in SMN protein versus baseline was observed for infants with an exposure ($AUC_{0\text{-}24}$) ≤ 1000 ng • hr/mL and a 3.2-fold increase (median; range 1.6–6.5) in infants with an exposure ($AUC_{0\text{-}24}$) > 1000 ng • hr/mL.

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

1.2.2.3 Efficacy

The objectives for Study BP39056 Part 1 were to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in infants with Type 1 SMA and to select the dose for Part 2. As of 2 May 2018, preliminary review of efficacy data from Part 1 indicates benefits of treatment.

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

1.2.2.4 Safety

In healthy adults, single doses of risdiplam have been well tolerated at all dose levels (Studies BP29840, NP39625, and BP39122) and in combination with itraconazole (Study BP29840, Part 3). There were no deaths, withdrawals due to adverse events, or any severe adverse events. One serious adverse event of pneumonia was reported in Study BP39122, which resolved upon supportive treatment and was assessed as unrelated to study treatment by the investigator. No clinically relevant changes in laboratory safety parameters, vital signs, adverse events, ECG parameters, or ophthalmological assessments related to risdiplam were observed in any study.

In Part 1 of Study BP39055 as of 2 May 2018, risdiplam was well tolerated in patients with Types 2 and 3 SMA across all dose levels tested. Adverse events reported during active treatment in Part 1 were mostly mild in intensity and resolved without any change to study treatment. In Part 1, eight serious adverse events were reported during active treatment in 5 patients; all were reported as unrelated to study drug. No deaths have been reported, and 1 patient discontinued due to withdrawal of consent, but not due to adverse events.

In Part 1 of Study BP39056, the dose finding part of the study, risdiplam has been well tolerated in all 21 patients with Type 1 SMA across all dose levels tested. The pivotal Part 2 of the study has started. As of 2 May 2018, adverse events reported for all 21 patients in Part 1 were mostly mild or moderate in intensity and resolved without change in study treatment. Nine patients experienced at least one serious adverse event; 2 of the 9 patients had a serious adverse event with a fatal outcome. The two fatal events reported were viral respiratory tract infection in 1 patient, and cardiac arrest and respiratory failure in the other patient; both were considered to be unrelated to study treatment. Seven additional patients experienced serious adverse events: pneumonia (two events) and neutropenia and influenza; acute respiratory failure; hypoxia and aspiration pneumonia and respiratory distress; respiratory distress and atelectasis; upper respiratory tract infection; pneumonia and rash and pneumothorax; failure to thrive. All serious adverse events were reported as unrelated to study medication with the exception of neutropenia that occurred in the context of pneumonia and resolved 3 days after onset despite ongoing treatment with risdiplam. There have been no adverse events leading to modification or permanent withdrawal of study treatment.

No clinically significant adverse findings related to study medication have been observed in safety laboratory results, vital signs, and ECG. Ophthalmological assessments available to date from Part 1 and the ongoing Part 2 of Studies BP39055 and BP39056 did not show drug-related toxicity.

No individual or cohort stopping rules have been met in any of the studies to date.

Part 1 patients are now in the extension treatment periods of the respective studies.

In this study, BN40703, as of 21 January 2021 after 12 patients have been enrolled and treated for median duration of 6.4 months (range: 0.1–14.9), risdiplam was well tolerated. Adverse events were mostly mild in intensity. There were no adverse events leading to discontinuation of study drug. 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.

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 caused by a lack of functional SMN protein, resulting in almost inevitable mortality for patients with Type 1 SMA within the first 2 years of life. Among the different strategies that are currently being pursued to restore SMN protein levels in patients with SMA, modulation of *SMN2* splicing to favor inclusion of exon 7 into the mRNA transcript, thereby increasing expression of stable full-length protein from *SMN2*, is one of the most promising (Kolb and Kissel 2011; Nurputra et al. 2013). This approach is supported by nusinersen, currently the only licensed treatment for SMA. Nusinersen is an intrathecally administered antisense oligonucleotide that promotes inclusion of exon 7 in *SMN2* pre-mRNA and thereby increases the amount of full-length SMN protein expressed by the *SMN2* gene. However, there is currently no approved oral treatment for SMA that restores SMN protein levels in both the CNS and in peripheral tissue. Thus the medical need for SMA is still high.

The timing of therapeutic intervention is crucial since most of the degeneration in motor neurons occurs in the first months of life in patients with Type 1 SMA. It has been demonstrated that infants with Type 1 SMA undergo a rapid loss of motor units in the first 3 months of life, with more than 95% of motor units lost within 6 months of age (Swoboda et al. 2005; Kolb et al. 2017; Govoni et al. 2018). Moreover, a recent clinical trial in patients with presymptomatic SMA who, without any treatment, would develop a phenotype of Type 1 SMA, have shown a more rapid achievement of motor milestones

and diminished disease severity when therapy was administered at an early age and earlier in the disease course (Hwu et al. 2017).

Small molecule *SMN2* splicing modifiers such as risdiplam represent a potential treatment option for patients with SMA, as they increase the level of SMN protein. Deficiency of SMN protein is the fundamental pathophysiological mechanism of SMA. There is increasing nonclinical 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 (Passini et al. 2011; Porensky et al. 2012). By restoring SMN protein levels in both the CNS and in peripheral tissue, orally administered *SMN2* splicing modifiers are hypothesized to provide improved efficacy over compounds administered intrathecally (i.e., to the CNS only; Hua et al. 2011).

The study is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants aged from birth to 6 weeks who have been (at first dose) genetically diagnosed with SMA (*SMN1* deletion and any *SMN2* copies) but are not yet presenting with symptoms.

Efficacy in terms of development milestones will be assessed with the Bayley Scales of Infant and Toddler Development®, Third Edition (BSID-III), including the Gross Motor Scale, the Hammersmith Infant Neurological Examination (HINE) and the World Health Organisation (WHO) milestones. Efficacy in terms of motor function will be assessed with the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), the Hammersmith Functional Motor Scale Expanded (HFMSE), and the six-minute walk test (6MWT). Other treatment effects will be measured by assessing quality of life and relevant biomarkers (see Section 4.5.12).

1.3.2 Benefit–Risk Assessment

The benefit–risk evaluation of risdiplam is based on nonclinical pharmacology and toxicology studies in rats and cynomolgus monkeys, as well as the clinical experience to date with risdiplam in healthy subjects and in patients with SMA. In healthy adults, single doses of risdiplam have been well tolerated at all dose levels (Studies BP29840, NP39625, and BP39122), and risdiplam had a dose-dependent effect on *SMN2* splicing in healthy adults, as shown by a change in the ratio of full-length *SMN2* mRNA to SMNΔ7 mRNA. In Part 1 of the ongoing Studies BP39055 and BP39056, treatment with risdiplam was safe and well tolerated at all dose levels, and an exposure-dependent increase in SMN protein (median 2 to 3 fold) was observed, confirming proof of mechanism in patients with SMA. The increase in SMN protein levels observed in Part 1 of Studies BP39055 and BP39056 is expected to have a substantial clinical benefit in patients with SMA, turning more severe phenotypes into milder forms. No clinically relevant changes in laboratory safety parameters, vital signs, adverse events, ECG parameters, or ophthalmological assessments related to risdiplam were observed in any study, and no individual or cohort stopping rules have been met. Accordingly, available data to date suggest that risdiplam may provide benefit for patients with SMA.

The doses selected for patients with SMA for the current study and for other ongoing studies (BP39054, BP39055, and BP39056) aim for a mean exposure at steady state of $AUC_{0\text{-}24,ss} \leq 2000$ ng • hr/mL. This corresponds to the mean exposure at the NOAEL/NOEL (multifocal peripheral retina degeneration) of the 39-week toxicity study in monkeys with an $AUC_{0\text{-}24}$ of 1870/2060 ng • hr/mL in males and females, respectively. This exposure cap has been selected to maximize the increase in SMN protein and subsequently the chance for clinical efficacy in patients with SMA, while still providing a safety margin versus the ophthalmology findings in the animal study. The individual pharmacokinetics in all patients will be monitored closely and regularly, and the dose will be adjusted as required to maximize the likelihood of clinical benefit, while still being compliant with the exposure cap.

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. Toxicological findings observed in the nonclinical studies include toxicity involving skin, pharynx/larynx, and fertility; potential for genotoxicity based on micronucleus induction; and potential irreversible retinal toxicity that could translate into some visual impairment (e.g., night tunnel vision).

With this regard, it is essential to note that the changes found by SD-OCT scan (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 and would normally not affect visually oriented behavior and quality of life. As of the clinical cutoff date of *21 January 2021*, ophthalmological assessments did not show any retinal toxicity in any patient exposed to risdiplam at any dose.

Ophthalmological monitoring in this study *includes SD-OCT at three post-baseline visits during* the first year and every *year* thereafter until the end of the study in case of clinically relevant peripheral retinal toxicity, stopping rules will apply (see Section 5.1.3). On the basis of these elements, the ophthalmological monitoring strategy and stopping rules included in this study appear appropriate to minimize the risk of irreversible symptomatic retinal injury and to detect peripheral retinal abnormalities early when peripheral visual field defects would likely be asymptomatic.

The key elements of risk management in this study, taking into consideration the nonclinical findings and clinical experience so far, are summarized below:

- Frequent PK assessments, including assessment of free fraction from a sample taken at screening as a precaution to take into account possible age-related differences in plasma protein binding, to ensure that risdiplam exposure remains in compliance with the exposure cap. 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 patients may be adjusted to ensure that the patients are in the targeted exposure range and in compliance with the exposure cap.

- Safety monitoring throughout the study including ophthalmology, dermatology, and clinical laboratory measures (see Section 5.1.4)
- Stopping rules at the individual patient level (see Section 5.1.3)
- Guidelines for managing specific adverse events (see Section 5.2.3)
- Implementation of an external independent Data Monitoring Committee (iDMC), who will review safety on a regular and ad-hoc basis at least until the last patient enrolled in this study has completed 12 months of treatment together with data from other ongoing studies (see Section 3.1.1)
- Appropriate inclusion/exclusion criteria and guidance regarding prohibited therapy (including CYP3A4 inhibitors/inducers/substrates, OCT 2 and MATE substrates, FMO inhibitors and substrates, and medications with potential retinal toxicity; see Section 4.1)

The potential benefit of early treatment with risdiplam for patients with SMA would be an increase in functional SMN protein levels in the CNS and peripheral tissues, such as muscles and endothelial cells. This early pharmacological effect is hypothesized to translate into an improvement or even normalization of developmental milestone acquisitions, including major motor milestones such as sitting without support, standing, and possibly walking.

The study population is expected to predominantly include presymptomatic infants who, without any treatment, would develop a phenotype of Type 1 SMA. Given the potential for these patients to benefit from treatment with risdiplam, the safety margins in this study are considered appropriate. Data from ongoing SMA studies with risdiplam justify the benefit–risk of treatment with risdiplam in infants aged from birth to 6 weeks of age (at first dose) who have been genetically diagnosed with SMA but are not yet presenting with symptoms.

2. OBJECTIVES AND ENDPOINTS

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

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

In line with the study population expected to predominantly include presymptomatic infants who, without any treatment, would develop a phenotype of Type 1 SMA, the primary efficacy objective for this study is to evaluate the efficacy of risdiplam in patients

with two copies of the *SMN2* gene (excluding the known *SMN2* gene modifier mutation c.859G>C) and baseline compound muscle action potential (CMAP) amplitude ≥1.5 mV, as determined by the proportion of patients who are sitting without support after 12 months of treatment. Sitting is defined as "sits without support for 5 seconds" as assessed in Item 22 of the BSID-III Gross Motor Scale.

2.1.2 Secondary Efficacy Objectives

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

- To evaluate the efficacy of risdiplam on the development of clinically manifested SMA on the basis of the following endpoints:
  - Proportion of patients developing clinically manifested SMA (at Month 12 and Month 24 of treatment)
- To evaluate the efficacy of risdiplam on survival and permanent ventilation on the basis of the following endpoints:
  - Time to death
  - Time to permanent ventilation
  - Time to death or permanent ventilation
  - Proportion of patients alive without permanent ventilation (at Month 12 and Month 24 of treatment)
  - Proportion of patients alive (at Month 12 and Month 24 of treatment)
- To evaluate the efficacy of risdiplam on the achievement of motor milestones defined in the BSID-III and by the HINE-2 on the basis of the following endpoints:
  - Proportion of patients who achieve the attainment levels of the motor milestones assessed in the HINE-2 (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) (at Month 12 and Month 24 of treatment)
  - Proportion of patients sitting without support (at Month 24 of treatment [as assessed in Item 22 of BSID-III Gross Motor Scale]) for 5 seconds
  - Proportion of patients with two copies of the *SMN2* gene sitting without support (at Month 12 of treatment [as assessed in Item 22 of BSID-III Gross Motor Scale]) for 5 seconds (independent of the CMAP value at baseline)
  - Proportion of patients sitting without support (at Month 12 and Month 24 of treatment [as assessed in Item 26 of BSID-III Gross Motor Scale]) for 30 seconds
  - Proportion of patients standing (at Month 24 of treatment [defined as "Stands Alone" for at least 3 seconds as assessed in Item 40 of the BSID-III Gross Motor Scale])
  - Proportion of patients walking (at Month 24 of treatment [defined as "Walks Alone" takes at least 3 steps as assessed in Item 42 of the BSID-III Gross Motor Scale])
  - Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of the chronological reference standard (at Months 24

and 42 of treatment [as assessed through the use of the BSID–III Gross Motor Scale])

- To evaluate the efficacy of risdiplam on motor function on the basis of the following endpoints:
  - Change from baseline in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) motor function scale (at Month 12 of treatment)
  - Proportion of patients who achieve a score of 40 or higher, 50 or higher, and 60 or higher in the CHOP INTEND motor function scale (at Month 12 of treatment)
  - Proportion of patients who meet CHOP INTEND stopping criteria at any point up to Month 24 of treatment
  - Change from baseline (Month 24) in the Hammersmith Functional Motor Scale Expanded (HFMSE) (at Month 60 of treatment).
- To evaluate the efficacy of risdiplam on growth measures on the basis of the following endpoints:
  - Number and proportion of patients within 3rd percentile of normal range for weight-for-age, length/height-for-age and weight-for-length/height (at Months 12, 24, 36, 48, and 60 of treatment based on the WHO Child Growth Standards) (WHO 2019)
  - Number and proportion of patients within 3rd percentile of normal range for head circumference-for-age (at Month 12 and Month 24 of treatment, based on the WHO Child Growth Standards) (WHO 2019)
  - Change from baseline percentiles for weight-for-age, length/height-for-age and weight-for-length/height (at Months 12, 24, 36, 48 and 60 of treatment)
  - Change from baseline percentiles for head circumference-for-age (at Month 12 and Month 24 of treatment)
  - Change from baseline in chest circumference (at Month 12 and Month 24 of treatment)
  - Ratio between chest and head circumferences (at Month 12 and Month 24 of treatment)
- To evaluate the efficacy of risdiplam on the nutritional status of the patients on the basis of the following endpoint:
  - Ability to swallow and to feed orally (at Months 12, 24, 36, 48, and 60 of treatment)
- To evaluate the efficacy of risdiplam on the degree of innervation on the basis of the following endpoint:
  - Change from baseline in CMAP amplitude (at Month 12 and 24 of treatment)
- To evaluate the PD effects of risdiplam on the basis of the following endpoints:
  - SMN mRNA levels in blood

- SMN protein levels in blood

2.1.3 Exploratory Efficacy Objective

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

- To evaluate the efficacy of risdiplam to achieve other developmental milestones as defined by BSID-III and WHO milestones on the basis of the following endpoints:
  - Cognition assessed through the use of the BSID-III Cognitive Scale (at Months 12, 24, and 42 of treatment)
  - Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of chronological reference standard (at Months 24 and 42 of treatment [as assessed through the use of the BSID–III Cognitive Scale])
  - Fine motor function assessed through the use of the BSID–III Fine Motor Scale (at Months 12, 24, and 42 of treatment)
  - Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of chronological reference standard (at Months 24 and 42 of treatment [as assessed through the use of the BSID–III Fine Motor Scale])
  - Proportion of patients who attain motor milestones as assessed by WHO criteria (at Months 48 and 60 of treatment)
- To evaluate the efficacy of risdiplam on motor function on the basis of the following endpoint:
  - Total Walk Distance in the six-minute walk test (6MWT; ambulant patients only) (at Month 60 of treatment)
- To explore the treatment effect on speech development on the basis of the following endpoint:

  Speech development as assessed during the neurological examination (at Months 12, 24, 36, 48, and 60 of treatment).
- To explore the effect of treatment with risdiplam on the number of hospitalizations on the basis of the following endpoints:
  - Number of hospitalizations (for any reason, except if for study purpose only [e.g., to facilitate study assessments]) per patient-year and number of nights admitted to hospital per patient (at 12, 24, 36, 48, and 60 months of treatment).
  - Proportion of patients with no hospitalizations (at 12, 24, 36, 48, and 60 months of treatment).
- To explore the treatment effect on pre-specified disease-related adverse events on the basis of the following endpoint:
  - Pre-specified disease-related adverse events by 12 and 24 months of treatment

2.2 SAFETY OBJECTIVES

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

- Incidence and severity of adverse events, with severity determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5 (NCI CTCAE v5)
- Incidence and severity of serious adverse events
- Incidence of treatment discontinuation due to adverse events
- Incidence of abnormal laboratory values
- Incidence of abnormal ECG values
- Vital signs abnormalities, including body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate
- Ophthalmological examination as appropriate for age (e.g., red reflex, external ocular examination, pupillary examination/response, cover/uncover, fix and follow test, corneal light reflex, fundus examination including ophthalmoscopy/slit lamp examination, SD-OCT, and fundus photography)
- Physical examination, including detailed examination of the skin and mouth

2.3 PHARMACOKINETIC OBJECTIVE

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

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

2.4 BIOMARKER OBJECTIVE

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

- Relationship between exploratory biomarkers in blood (listed in Section 4.5.11.5) and efficacy, safety, PK, or other biomarker endpoints
- Relationship of genetic, epigenetic, or genomic markers with efficacy, safety, PK, or other biomarker endpoints related to SMA

2.5 HEALTH STATUS UTILITY OBJECTIVE

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

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

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

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

There will be a screening, treatment, open-label extension (OLE) phase, and a follow-up. Screening will be up to 42 days prior to first dose, bearing in mind the maximum age of the patient at first dose of study drug is 42 days. Screening assessments may be repeated before enrollment to confirm eligibility. *Patients will be enrolled in the study regardless of SMN2 copy number.* Recruitment will be global (e.g., at sites in United States, European Union, Russia, Brazil, Australia, Taiwan, Saudi Arabia and National Medical Products Administration recognized sites in China). All patients will receive risdiplam orally once daily for 2 years at a dose selected to achieve the targeted exposure range of close to 2000 ng •hr/mL (the dose may be adapted as patients grow and mature), followed by an OLE phase of at least 36 months and a follow-up, for a total treatment duration of at least 5 years for each infant enrolled. *Enrollment will be closed when one of the following conditions have been met:*

1. *At least 25 patients, including a minimum of 5 patients who meet the criteria for the primary efficacy population (Section 6.3.3) are enrolled,*

   OR

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

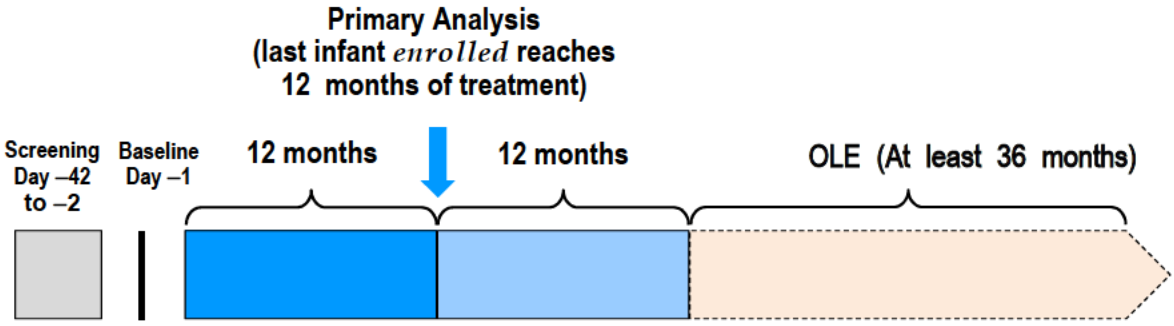
The OLE phase (Month 24 up to Month 60) will continue as per the main study in regards to dosing and will include regular monitoring of safety, tolerability, pharmacokinetics, and efficacy. Details of the assessments and their frequency are given in Appendix 1. Thereafter, the patient may continue until end of study, provided that risdiplam is not commercially available in the country of the site or until the Sponsor ceases producing or studying risdiplam (see Section 3.2). However, the overall study will not exceed a total of 5 years after the last patient is enrolled in the study.

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

The primary endpoint is defined as the proportion of patients sitting without support after 12 months of treatment, as assessed in the BSID-III Gross Motor Scale (defined as sitting without support for 5 seconds). *The primary efficacy population is defined in Section 6.3.3.* Additional secondary endpoints will include longer-term (after 24 months) evaluation of motor milestone achievements and other developmental milestones.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1, Appendix 2, and Appendix 3. Data will be reviewed on an ongoing basis by the Sponsor and an iDMC (see Section 3.1.1).

Figure 1 Study Schema



OLE = open-label extension.

3.1.1 Independent Data Monitoring Committee

An external iDMC has been established to monitor patient safety within all the clinical patient studies during the confirmatory phase of the risdiplam clinical development program. In addition to regular review of all data emerging from this open-label study by the Sponsor, the external iDMC will monitor patient safety during this period of the study. The iDMC will meet on a regular basis (approximately every 3 months) 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.

Following the first regulatory approval in either the U.S. or E.U., the iDMC will continue to meet and review patient safety until 12 months after the last patient is enrolled in this study or the Part 2 database of Study BP39056 (FIREFISH) has been locked for the 24-month analysis, whichever occurs later.

A Sponsor clinical pharmacologist (who is not a member of the iDMC) will regularly review the PK data to adjust the dose of individual patients if required, to ensure not to exceed the exposure cap, to continue treatment at the targeted exposure level (as the patients grow and 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 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 iDMC charter. 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.

3.1.2 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 patients that may meet the definition of permanent ventilation ($\geq$16 hours of non-invasive ventilation per day or intubation for $>$21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy).

An acute reversible event will include any of the following events that occur between 7 days prior and 7 days after the onset of $\geq$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 $\geq$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.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of study (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 2 years in the treatment phase and 3 years in the OLE phase.

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

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

3.3 RATIONALE FOR STUDY DESIGN

This study is designed to assess the efficacy and safety of risdiplam treatment in infants aged from birth to 6 weeks of age (at first dose) genetically diagnosed with SMA but not yet presenting with symptoms.

The target population for the primary efficacy analysis is patients who have two copies of the *SMN2* gene *and a baseline CMAP amplitude of ≥1.5mV, reflective of* a Type 1 population. Nevertheless, infants with copy number 1, 3, or 4 will not be excluded and enrollment of infants into the study will continue until *at least 25 patients, including a minimum of 5 patients who meet the criteria for the primary efficacy population are enrolled, OR when 10 patients who meet the criteria for the primary efficacy population are enrolled.* All infants enrolled regardless of copy number (i.e., full population) will be used as the primary population for safety, while those infants with SMN2 copy number 2 and baseline CMAP amplitude ≥1.5mV will form the primary efficacy population for the study.

In line with the study population expected to predominantly include presymptomatic infants who, without any treatment, would develop a phenotype of Type 1 SMA, the primary endpoint will be the achievement of a motor milestone that a Type 1 infant would not normally achieve according to natural history data (sitting without support). According to the WHO windows of achievement for motor milestones in healthy infants, sitting without support is expected to be achieved by 9 months of age and walking alone by 18 months of age; hence, a 24-month treatment period with the primary analysis and reporting after 12 months of treatment is planned.

Similar to the single-arm design of Study BP39056 in symptomatic Type 1 infants, a performance criteria approach for the primary analysis will be used (i.e., a threshold of achievement for the presymptomatic risdiplam-treated infants to be assessed against within this study). The predefined performance criterion for the primary endpoint will be 5%, based on the assumption that there is a 97% chance that a presymptomatic infant

with two *SMN2* copies develops SMA Type 1 (Feldkotter et al. 2002). If the lower limit of the two-sided 90% (exact) confidence interval is above this 5% threshold, the primary objective of the study will be considered achieved.

The primary endpoint can be objectively measured, incorporates survival, and is clinically meaningful. The evaluation of the primary endpoint will be video recorded in a standardized manner and centrally reviewed by two independent readers to confirm the investigators' assessments. To reduce the risk of bias in the assessment of the endpoint, the central readers' assessment will be used for the primary analysis.

3.3.1 Rationale for Risdiplam Dose and Schedule

The target exposure is an $AUC_{0\text{-}24,ss}$ of close to 2000 ng • hr/mL, with the average exposure of all patients not predicted to exceed 2000 ng • hr/mL. This target AUC has been selected to maximize the likelihood of clinical benefit while maintaining a safety margin versus the findings in the animal toxicology studies (except effects on testes). This target exposure has been assessed and was well tolerated in all SMA patients in the ongoing clinical studies, including infants as young as 2.2 months (status: 14 November 2019) at the start of treatment.

In Study BP39056 Part 1 (infants with Type 1 SMA), a median 2-fold increase (range: 1.0–5.4) in SMN protein in blood versus baseline was observed for infants with an exposure ($AUC_{0\text{-}24}$) ≤ 1000 ng • hr/mL, and a median 3.2-fold increase (range: 1.6–6.5) was obtained in infants with an exposure ($AUC_{0\text{-}24}$) ≥ 1000 ng • hr/mL. Thus, this exposure is predicted to provide clinical benefit to patients with SMA treated with risdiplam.

The mean AUC for all infants in Study BP39056 was 1930 ng • hr/mL (range 1230–3300) at the Month 12 visit at the 0.2 mg/kg dose.

The first patient enrolled into this study must be at least 7 days old at time of first dose.

The first patient enrolled aged between 4 and 6 weeks (29 and 42 days) of age at first dosing will receive a once daily oral dose of 0.04 mg/kg of risdiplam to assess safety, tolerability, and pharmacokinetics.

The first patient enrolled aged between 7 days and 28 days of age at the time of first dose will receive a once daily oral dose of 0.004 mg/kg. A ten-fold safety factor has been applied to account for uncertainty of the metabolism and excretion of risdiplam in this young age range. However, during the course of this study, emerging PK data from the first patients enrolled in this study indicated that the very low dose of 0.004 mg/kg would not be required.

The starting dose for all patients may be adjusted to the most appropriate dose based on the latest available data from the currently ongoing Study BP39056 in infants 1–7 months and based on emerging PK data from this study BN40703.

Pharmacokinetics will be assessed at Days 1, 2, and 14 in the first infant (while the patient continues to receive once daily treatment), and at subsequent timepoints as detailed in the schedule of activities (Appendix 1). PK samples obtained on each of Days 1, 2, and 14 will be shipped immediately for analysis, and on the basis of the PK data obtained, the dose for the first patient will be adjusted to reach the targeted exposure range. Should the initial starting dose be too low to provide reliable PK measurements, the dose will be adjusted and two additional unscheduled PK samples may be taken (in addition to those specified in Appendix 1) to confirm pharmacokinetics at the adjusted dose.

Provided risdiplam is well tolerated in the first patient for at least 1 week and the pharmacokinetics have been reliably assessed, further patients in the respective age category may be enrolled. The dose to be administered to the subsequently enrolled patients will be based on the PK data obtained from the first infant (and all other PK and safety data available from all other studies with risdiplam at that time) and will be in compliance with the specified exposure cap of an $AUC_{0\text{-}24,ss}$ 2000 ng • hr/mL (mean).

Pharmacokinetics will be regularly assessed in all patients, and the dose will be adjusted based on the observed PK data to achieve the targeted exposure range and to be in compliance with the exposure cap.

Dose adjustments between the scheduled visits based on weight change are allowed (e.g., if weight change is >10% according to parent/caregiver). The change in weight may be discussed during the follow-up phone calls with the parent/caregiver. The weight used to perform dose calculations between visits should be taken at site (e.g., by bringing the patient in for an unscheduled visit). However, if the patient is unable to come to site for a scheduled or unscheduled visit, due to exceptional circumstances, the weight can be taken at an alternative location, provided suitable scales are used, as determined by the Sponsor. During OLE, as visits are 26 weeks apart, unscheduled visits to assess weight may be expected. If patients are attending site for any other reason during OLE, it is advisable to also take the opportunity to measure weight. Any dose adjustment has to be performed by the site and cannot be made by the parent/caregiver themselves.

The fu of risdiplam will be measured in all patients from a sample taken at screening with an in vitro assay. If the measured free fraction in patients is different from the free fraction observed in infants and adults in other ongoing studies, the dose will be adjusted for this difference.

As the patients grow and develop, the dose may be adjusted for an individual or all patients, to maintain the exposure level over time in an individual growing patient, and to match individual exposure versus the target exposure (see Section 3.1).

3.3.2 Rationale for Patient Population

Patients with Type 1 SMA have a more severe clinical presentation and reduced survival rate compared with patients with Types 2 and 3 SMA. The clinical progression of the disease is more pronounced in patients with Type 1 SMA than those with Types 2 and 3 SMA, and their comorbidities and complications (e.g., swallowing and breathing function) are usually more severe. The number of *SMN2* copies and the presence of its c.859G>C variant still remain as the major modifiers of SMA disease (Prior et al. 2009; Bernal et al. 2010). Distribution of the positive modifier of SMA phenotype, *SMN2* c.859G>C variant, is rare (2%–4%) and mostly reported in Types 2 and 3 SMA (Calucho et al. 2018). Numerous studies show that the higher the *SMN2* copy number the larger the amount of full-length SMN protein produced, the milder the associated SMA phenotype and vice versa (Feldkotter et al. 2002; Wirth et al. 2006). However, this inverse correlation is not absolute. The Type 1 SMA population usually has one (7%) or two (73%) copies of *SMN2*, but some patients with Type 1 SMA have three (20%) and even four (<1%) or 5 (<1%) *SMN2* copies (Calucho et al. 2018). Feldkotter et al. (2002) calculated the posterior probability of a child with homozygous absence of *SMN1* developing Type 1, Type 2, or Type 3 SMA, conditional on the number of *SMN2* copies. A child with one *SMN2* copy has a risk of >99%, and with two *SMN2* copies, a risk of 97%, of developing Type 1 SMA. Thus, patients will be enrolled and treated in the study regardless of the *SMN2* copy number, but the primary analysis will be performed in patients with two *SMN2* copies and without the c.859G>C variant to increase homogeneity of the population in which to assess the efficacy of treatment.

It has been demonstrated that infants with Type 1 SMA undergo a rapid loss of motor units in the first 3 months of life, with more than 95% of motor units lost within 6 months of age (Swoboda et al. 2005; Kolb et al. 2017; Govoni et al. 2018).

Based on data presented so far for the antisense oligonucleotides (nusinersen) and gene therapy (AAV9-SMN), patients with Type 1 SMA treated at an earlier age and even before SMA symptom onset achieved the best outcome measure results. NURTURE (NCT02386553) is an ongoing study, evaluating intrathecal nusinersen in infants with presymptomatic SMA <6 weeks old at first dose. Twenty-five infants were enrolled in the study (n=15 with two *SMN2* copies and n=10 with three *SMN2* copies). At the time of the interim analysis, infants had been enrolled for a median of 317.5 days. All infants were alive without requiring chronic respiratory support and showed improvements and achievement of motor milestones over the expected natural history of Types 1 and 2 SMA. Most infants achieved motor milestones generally consistent with normal development (De Vivo et al. 2017).

CMAP amplitude is an objective measure of the electrophysiologic output from muscle following stimulation of the innervating nerve and has shown to be useful to evaluate disease progression even before clinical symptom onset. Natural history studies among patients with Type 1 SMA demonstrate low ulnar CMAP amplitude levels that rapidly decreased in the first few months of life did not improve after symptom onset. The CMAP amplitude at the time of initial assessment is predictive of the clinical course of patients (Swoboda et al. 2005; Glanzman et al. 2010; Finkel 2013; Passini et al. 2014; Kolb et al. 2017). Kolb et al. (2017) compared ulnar CMAP in infants with Type 1 SMA with two copies of *SMN2* to controls and showed that CMAP amplitude in SMA was significantly reduced early in life (baseline) and rapidly fell over 24 months compared with being stable in controls (controls: mean baseline was 5.24 mV, 6-month visit was 6.00 mV; SMA: mean baseline was 1.53 mV, 6-month visit was 0.23 mV). The CMAP amplitude over time from the 3-month visit was never higher than 0.6 mV in SMA infants. To allow treatment for all patients (with confirmed deletion of the *SMN1* gene and any *SMN2* copies), no CMAP amplitude criteria will be used for inclusion in the current study. However, only patients with baseline (Day -1) CMAP amplitude ≥ 1.5 mV and two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G$>$C) will be included in the analysis for the primary endpoint.

Overall, very early initiation of an effective treatment is anticipated to counteract the deleterious effects of chronic SMN protein deficiency in the body. Thus initiation of treatment no later than 6 weeks from birth in patients genetically diagnosed with SMA prior to clinical symptoms 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 avoid the chronic SMN protein deficiency during the motor function development phase of these patients. This is expected to lead to a clinically relevant beneficial outcome in motor and respiratory function of treated patients (e.g., achievement of sitting milestone).

3.3.3 Rationale for Control Group

This is an open-label study. A placebo-control group will not be included in this study, as the majority of patients with 2 *SMN2* copies will develop Type 1 SMA and it is ethically debatable to treat patients with Type 1 SMA 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) in patients with SMA Type 1.

All patients must receive the local clinical standard of care for SMA, as defined by each site investigator, except for the administration of *SMN2*-targeting oligonucleotides, which is not allowed.

3.3.4 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 will be measured in blood as fluid PD markers (see Section 4.5.11.2). Based on animal data, the increase in SMN protein in blood reflects the increase in brain, spinal cord, and muscle tissue.

In addition to the *SMN2* copy number analysis performed at screening, additional genetic, genomic, or epigenetic markers that influence the progression and severity of the disease or treatment response may be studied in the patients.

Exploratory research on safety biomarkers may be conducted to support future drug development. Research may include further characterization of a safety biomarker or identification of safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation. Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

Blood samples for fluid PD markers will be taken from the Week 1 Day 1 visit and onwards (see schedule of activities in Appendix 1) and only if the limit on blood volume allows (see Section 4.5.11).

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 25 patients with SMA will be enrolled in this study. *Enrollment will be closed when one of the following conditions have been met*

1. *At least 25 patients, including a minimum of 5 patients who meet the criteria for the primary efficacy population (Section 6.3.3) are enrolled, OR*
2. *A total of 10 patients who meet the criteria for the primary efficacy population are enrolled.*

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form by a legally authorized representative for the patient in accordance to International Council on Harmonisation (ICH) and local regulations
- Males and females aged from birth (1 day) to 6 weeks (42 days) of age at the time of first dose (Day 1); a minimum age of 7 days at first dose is required for the first infant to be enrolled

- Gestational age of 37–42 weeks for singleton births; gestational age of 34–42 weeks for twins
- Body weight $\geq 3^{rd}$ percentile for age, using appropriate country-specific guidelines
- Genetic diagnosis of 5q-autosomal recessive SMA, including confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the *SMN1* gene
- Absence of clinical signs or symptoms at screening (Day –42 to Day –2) or at baseline (Day –1) that are, in the opinion of the investigator, strongly suggestive of SMA
- Receiving adequate nutrition and hydration at the time of screening, in the opinion of the investigator
- Adequately recovered from any acute illness at baseline and considered well enough to participate in the study, in the opinion of the investigator
- Able and expected to be able to safely travel to the study site for the entire duration of the study and in accordance to the frequency of required study visits, in the opinion of the investigator
- Able to complete all study procedures, measurements, and visits, and the parent (or caregiver), in the opinion of the investigator, has adequately supportive psychosocial circumstances
- Parent (or caregiver) is willing to consider nasogastric, naso-jejunal, or gastrostomy tube placement during the study to maintain safe hydration, nutrition, and treatment delivery, if recommended by the investigator
- Parent (or caregiver) is willing to consider the use of non-invasive ventilation during the study, if recommended by the investigator

4.1.2 Exclusion Criteria

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

- Concomitant or previous participation in any investigational drug or device study at any time
- Concomitant or previous administration of an *SMN2*-targeting antisense oligonucleotide, *SMN2*-splicing modifier, or gene therapy either in a clinical study or as part of medical care
- Presence of significant concurrent syndromes or diseases
- In the opinion of the investigator, inadequate venous or capillary blood access for the study procedures
- Requiring invasive ventilation or tracheostomy
- Requiring awake non-invasive ventilation
- Awake hypoxemia ($SaO_2 < 95\%$) with or without ventilator support
- Multiple or fixed contractures and/or hip subluxation or dislocation at birth

- Systolic blood pressure or diastolic blood pressure or heart rate considered to be clinically significant by the investigator
- Presence of clinically relevant ECG abnormalities before study drug administration; corrected QT interval using Bazett's method >460 ms; personal or family history (first-degree relatives) of congenital long QT syndrome indicating a safety risk for patients as determined by the investigator. First-degree atrioventricular block or isolated right bundle branch block are allowed.
- The infant (and the mother, if breastfeeding the infant) taking any of the following:
  - Any inhibitor of CYP3A4 taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing, including but not limited to: ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, cimetidine
  - Any inducer of CYP3A4 taken within 4 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing, including but not limited to: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John's wort
  - Use of any OCT 2 and MATE substrates within 2 weeks prior to dosing (including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine)
  - Use of any known FMO1 or FMO3 inhibitors or substrates
- Clinically significant abnormalities in laboratory test results (e.g., Grade >1 anemia, ALT values exceeding $1.5\times$ the upper limit of normal [ULN] unless the elevated ALT level is considered of muscular origin [i.e., in the absence of other evidence of liver disease that is confirmed by elevated creatine kinase and lactate dehydrogenase]). Out of range creatine kinase levels should be reviewed in light of the underlying SMA pathology of the patient; elevated levels per se do not disqualify the patient from the study. In the case of uncertain or questionable results, tests performed during screening may be repeated before enrollment to confirm eligibility.
- Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to risdiplam or to the constituents of its formulation (see the Risdiplam Investigator's Brochure)
- Treatment with oral salbutamol or another $\beta 2$ adrenergic agonist taken orally for SMA is not allowed. Use of inhaled $\beta 2$ adrenergic agonists (e.g., for the treatment of asthma) is allowed.
- Anticipated need for thioridazine, vigabatrin, retigabine, or any other drug known to cause retinal toxicity during the study. Infants exposed to thioridazine, vigabatrin, retigabine, or drugs with known retinal toxicity given to mothers during pregnancy (and lactation) should not be enrolled.
- Diagnosis of ophthalmic diseases (e.g., glaucoma, central serous retinopathy, inflammatory/infectious retinitis unless clearly inactive, retinal detachment, intraocular trauma, retinal dystrophy or degeneration, optic neuropathy, or optic neuritis) that would interfere with the conduct of the study as assessed by an

ophthalmologist. Any other abnormalities detected with SD-OCT during screening *prior to enrollment* (e.g., retinal layer abnormalities, edema, cystic or atrophic changes) must be discussed with the investigator, ophthalmologist, and with the Sponsor, who will jointly determine if the infant may be enrolled in the study. *In the event that an OCT of sufficient quality cannot be obtained prior to enrollment, one must be obtained by Day 14.*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

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

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.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is risdiplam.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Risdiplam

Risdiplam clinical formulation will be supplied by the Sponsor as a powder for constitution to an oral solution. The powder is constituted with purified water (sourced locally) to yield an oral solution containing 0.25 mg/mL or 0.75 mg/mL of risdiplam, respectively, which can be administered orally (via mouth) or via a naso-gastric or gastrostomy tube. For information on the formulation and handling of risdiplam, see the pharmacy manual and Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1. The qualified individual responsible for dispensing the study drug will prepare the correct dose according to the Pharmacy Manual.

Throughout the study, the study drug (risdiplam) should be taken orally once daily in the morning, except when site visits are planned and study medication will be administered at the clinical site. In patients able to swallow, study drug will be administered with a syringe inserted between gum and cheek of the patient as described in the study drug administration instructions for use. The patient should be fed prior to dosing. In the case of breastfeeding, the patient should be fed prior to dosing, winded, and the study medication administered. Thereafter, water (approximately 10–20 mL, if possible, but might need to be less for young babies) should be administered with a patient's bottle or dispenser to prevent prolonged contact of study drug with buccal mucosa. Similarly, the

peribuccal area of the patient with SMA will be washed with water in case of drug drooling or spitting. Breastfeeding should be avoided within 1 hour after study drug administration. Patients unable to swallow the study medication and who have a naso-gastric or gastrostomy tube in situ should receive the study medication by bolus via the tube. Refer to the Study Drug Administration Instructions for Use.

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 parent (or caregiver) will be instructed to not administer study drug for that day. The regular amount should be given at the next scheduled time on the subsequent day, but the dose should not be doubled, and the event should be reported in the medication diary.

A patient diary will be required that will capture information related to drug administration for all doses throughout the 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.

Any dose modification should be noted on the Study Drug Administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.11.

Guidelines for treatment interruption or discontinuation for patients who experience adverse events are provided in Section 4.6.2.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (risdiplam) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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.

4.3.4 Continued Access to Risdiplam

The Sponsor will offer continued access to Roche IMP (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 Roche IMP (risdiplam) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP 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 Roche IMP (risdiplam) after completing the study if any of the following conditions are met:

- The Roche IMP 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 IMP or data suggest that the IMP is not effective for SMA
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for SMA
- Provision of the Roche IMP 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 website:

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

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from date of birth (up to 42 days prior to dosing) up to, and including, the follow-up call, unless stated otherwise (see Section 4.1.2). All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Physiotherapy, occupational therapy, and other forms of exercise therapy are encouraged, but the frequency should remain the same during the clinical study. All

concomitant medication should be reported to the investigator and recorded on the Concomitant Medications page in the eCRF.

Examples of allowed medications include the following:

- 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, except those listed in Section 4.4.2
- Antihistamines except those that are OCT 2 and MATE substrates (see Section 4.4.2)
- Proton pump inhibitors
- Any vaccine considered as part of the local standard of care for the patient
- CYP3A substrates: Risdiplam is a weak inhibitor of CYP3A. A small, but clinically not relevant, interaction was observed in adult subjects (increase in AUC 11% and Cmax 16%). Based on PBPK modeling, a similar magnitude of the effect is expected in children and infants as young as 2 months old. Caution shall be applied for co-administration of risdiplam and CYP3A substrates in infants <2 months of age; *including monitoring patients for potential toxicities from co-administered CYP3A substrates (particularly those with a narrow therapeutic window), and reducing the dosage of the co-administered drug if clinically indicated.*

4.4.2 Prohibited Therapy

All medications (prescription and over-the-counter [OTC]) taken from date of birth (up to 42 days prior to dosing) will be recorded on the Concomitant Medications eCRF.

The following medication is prohibited for patients for 2 weeks prior to and during the study (and for the mother during the study if breastfeeding the patient):

- Any inhibitor of CYP3A4, including but not limited to: ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, cimetidine
- 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, cephalexin, cephradine, fexofenadine

The following medication is prohibited for patients for 4 weeks prior to and during the study (and for the mother during the study if breastfeeding the patient):

- Any inducer of CYP3A4, including but not limited to: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John's wort

Patients should not have received the following drugs at any time in their lives; the drugs are prohibited for the infant (and the mother if breastfeeding the patient) during the study:

- Any known FMO1 or FMO3 inhibitors or substrates
- Medications intended for the treatment of SMA
  - Riluzole
  - Valproic acid
  - Hydroxycarbamide
  - Sodium phenylbutyrate
  - Butyrate derivatives
  - Creatine
  - Carnitine
  - Human growth hormone
  - Anabolic steroids
  - Probenecid
  - Bortezomib
  - Quercetin
  - Oral salbutamol or another β2 adrenergic agonist taken orally
  - Chronic oral or parenteral use of corticosteroids (inhaled corticosteroid use is allowed, see Section 4.4.1)
  - Agents anticipated to increase or decrease muscle strength or agents with known or presumed HDAC inhibition activity
  - Any prior use of nusinersen or any other *SMN2*-targeting antisense oligonucleotide, *SMN2*-splicing modifier or gene therapy
- Medications with known phototoxicity liabilities
  - Oral or topical retinoids, including OTC formulations, amiodarone, phenothiazines, and chronic use of minocycline
- Medications with potential retinal toxicity
  - Quinolines (chloroquine and hydroxychloroquine), thioridazine, vigabatrin and retigabine, deferoxamine, topiramate, latanoprost, niacin (not applicable if used as a nutritional supplement), rosiglitazone, tamoxifen, canthaxanthin, sildenafil, interferon, or any other drugs known to cause retinal toxicity

4.4.3 Prohibited Food

Patients are to avoid grapefruit and Seville orange juices.

Breastfeeding of the patient is allowed if the mother is not consuming any prohibited medications (see Section 4.4.2). Breastfeeding should be avoided within 1 hour after study drug administration. Women breastfeeding will be advised to rinse their breasts with water if breastfeeding occurs shortly after (i.e., <1 hour) study drug administration.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1, Appendix 2, and Appendix 3. All activities should be performed and documented for each patient.

Prioritization of blood samples is described in Section 4.5.11.

The patient study visits when efficacy assessments are performed (see Appendix 1) will be the most extensive visits and include all efficacy assessments in addition to pharmacokinetics, pharmacodynamics, full physical examination, and safety assessments. Accordingly, these visits may be conducted either as a 1-day visit or over 2 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 Appendix 4. Flexibility is given to the site to perform the assessments in any order within each of these blocks. It is critical that in Block 1, the BSID-III, CHOP INTEND, and HINE-2 are always preceded by a break of at least 15 minutes. It is also recommended that assessments are conducted in the same order throughout the trial for a single patient.

Follow-up phone calls are planned in this study. Parents (or caregivers, as appropriate) will be called by the investigator or designee to monitor safety and tolerability when patients are not attending the clinic. Assessments will include review of adverse events, concomitant medications, and significant life events (see Appendix 1). If, in exceptional circumstances, patients are unable to go to site for a scheduled on-site visit, they may be able to have some study assessments, as defined by the Sponsor, by telephone or video call.

At applicable sites, *if exceptional circumstances prevent a patient from attending an on-site visit, some* study assessments, as defined by the Sponsor, may be performed by a site team member or a mobile nursing (MN) professional at the patient's home or another suitable location to improve access and convenience for patients participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that MN services

are appropriate for a patient, the MN network will communicate with the *parents or* patient *caregiver* and the patient's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional.

Delivery of study medication and supplies to the home of the patient or return of unused drug and supplies as required may be scheduled as appropriate. Alternatively, the patients will visit the clinic on these dates.

The exact timing of all study assessments (e.g., PK or PD blood collection) may be shifted depending on emergent data. However, the total number of assessments will not change unless additional PK samples are required to ensure the safety of the patient with regard to reaching the desired target exposure range versus the exposure cap, or additional safety assessments are required to ensure the patient's safety.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within 42 days prior to Day 1 may be used upon agreement with the Sponsor. Informed Consent Forms from the parent (or caregiver) of the enrolled patients and from the parent (or caregiver) of the patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history including clinically significant diseases and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements; see Section 4.4) or physical/occupational/exercise therapy applied to the patient from date of birth will be recorded at baseline.

Demographic data will include age, sex, and self-reported/caregiver-reported race/ethnicity.

Spinal Muscular Atrophy Family History

SMA family history from first-degree relatives (sibling or parent) will be collected as available in the medical records of the patient. The collected parameters will include (list

is not exhaustive, please refer to the eCRF) the following: SMA type including age of onset.

4.5.3 Anthropometric Measurements

Anthropometric measurements include weight, height, head, and chest circumferences and will be measured at the timepoints specified in the schedule of activities (see Appendix 1) as described below:

- Body weight will be measured to the nearest 10 g using baby scales, the naked infant being placed centrally on the scales, until the patient reaches 1 year of age. For patients above 1 year of age, body weight will be measured to the nearest 100 g using appropriate scales. During OLE, as visits are 26 weeks apart, unscheduled visits to assess weight may be expected. If patients are attending site for any other reason during OLE, it is advisable to also measure weight.
- 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. If the patient is unable to stand, but they are too long to be assessed by the fixed board, the height can 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°to110, palm facing downwards and fingers extended but together. Prior to using this method please discuss with the Sponsor. Method of height measurement should be kept consistent for as long as possible.
- Head and chest circumferences will be measured to the nearest centimeter using an automated flexible, non-stretchable tape device as follows:

  Head circumference (or occipital-frontal circumference) will be measured at the level of the plane passing above the glabella (the most anterior protrusion of the forehead) and over the opisthocranion (the most posterior protrusion from glabella on the back of the head), perpendicular to the mid-sagittal plane. The patient'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 patient 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 (see Sections 6.5.2 and 6.6).

4.5.4 Physical and Neurological Examinations

A full physical examination should include an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Full physical examination will be carried out at timepoints specified in the schedule of activities (see Appendix 1). If medically indicated, the physical examination should include the mouth (buccal cavity and mucosa), pharynx, and gastrointestinal and skin systems, as possible and appropriate according to the age of the patient. The physical examination will not include pelvic or rectal examinations unless deemed necessary by the study site physician.

Any abnormality identified at baseline should be recorded on the Medical History eCRF.

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

Photographs may be taken to document the nature of skin findings (or other adverse events) from any patient in this study. These photographs will be used to follow the resolution of adverse events, document their appearance, and to allow consultations with experts. These photographs may be shared with the Sponsor to allow for safety monitoring.

A neurologic examination will be performed during the physical examination. Given the motor assessments will be performed in the other examinations, the neurologic examination will focus on mental status and behavior, cognitive, and speech assessments. The examination will be performed by asking the parent (or caregiver) about the patient's development, overall behavior, sleep, and mood (such as number of tantrums and vocalization). The investigator will observe and interact with the patient using tasks or paradigms adapted to the patient's age and motor ability (e.g., observing patient's reaction to a sound, speech development, shifting attention to a newly introduced toy, observing the patient interact with the parent [or caregiver]).

During the neurologic examination, any abnormality that may be related to SMA should be recorded on the neurologic examination page in the eCRF.

4.5.5 Vital Signs

Vital signs will include measurements of blood pressure, pulse rate, respiratory rate, and body temperature (oral or tympanic) and will be recorded at the timepoints specified in schedule of activities (see Appendix 1). Measurements should be obtained in a quiet room at a comfortable temperature, with the patient positioned in a relaxed (e.g., semi-supine/supine) position with the arms unconstrained by clothing or other material.

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.

4.5.6 Electrocardiograms

Triplicate ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1). ECGs acquired on different days should be as closely time-matched as feasible. Three interpretable ECG recordings (e.g., without artifacts, 2–3 minutes apart) must be obtained. The average of the three readings will be used to determine ECG intervals (e.g., PR, QRS, QT). Single ECG recordings may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the patient has been resting in a relaxed (e.g., semi-supine/supine) position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

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 and PR, QT and RR intervals, will be recorded on the eCRF. QTcB (Bazett's correction; Phan et al. 2015) and 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 adverse event 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.

4.5.7 Ophthalmological Examination

Ophthalmological examination will be performed at timepoints specified in the schedule of activities (see Appendix 3). Examinations will be carried out by a pediatric

ophthalmologist or neuro-ophthalmologist with the support of a pediatric ophthalmology imaging specialist. Ophthalmologic examination and retinal imaging include:

- SD-OCT imaging will be recorded with the Envisu hand-held device from Bioptigen Inc. (or other hand-held device SD-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.
- Visual development
- 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).
- External ocular examination: eyelids, conjunctiva, sclera, cornea
- 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.
- Cover/uncover test
- Fix and follow test: Failure to fix and follow will be assessed in the context of the patient's medical conditions and age.
- Ocular examination under magnification (slit lamp/ophthalmoscope of anterior and posterior segments including assessment [with dilation or not] of the retina and optic nerve).
- Color fundus photography should be attempted at least once at each scheduled visit. If unsuccessful, an image of the fundus may be captured during funduscopy.

The details of the visual tests will be included in a separate technical operating manual.

Additional ophthalmic assessments may be carried out as needed in case of abnormalities or upon recommendation from the site or central ophthalmologist.

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.

4.5.8 Nutritional Check

Nutritional assessment will be performed for all patients at the timepoints indicated in the schedule of activities (see Appendix 1) and will include:

- Head-to-chest circumference ratio from anthropometric measurements (see Section 4.5.3)
- Nutritional status interview of the parent (or caregiver), including questions about ability to swallow and level of solid food intake
- Standard swallowing assessment will be performed by a speech language pathologist or other suitably qualified individual according to local practice at the baseline visit and then according to the schedule of activities. This will include assessing the ability of the patient to swallow age-appropriate foods.

On the basis of the assessment, specific nutritional advice may be given individually to the parent (or caregiver) by the investigator or nutritionist.

4.5.9 Motor Function and Motor Development Assessments

Assessments of motor function and motor development will be performed as detailed in the schedule of activities (see Appendix 1).

4.5.9.1 Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III)

The BSID-III is the current version of the most extensively used measure of infant and toddler development (0 to 42 months) in clinical and research practice (Bayley 2006).

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 of decline or improvement against normally developing children.

The BSID consists of a core battery of five scales. Three main scales are administered with child interaction: the Cognitive Scale, which includes items such as attention to familiar and unfamiliar objects, looking for a fallen object, and pretend play; the Language Scale, which taps understanding and expression of language (e.g., recognition of objects and people, following directions, and naming objects and pictures); and the Motor Scale, which assesses gross and fine motor skills such as grasping, sitting, stacking blocks, and climbing stairs. In addition, 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 two main scales will be administered as indicated in the schedule of activities: motor (gross and fine) and cognitive. The Gross Motor Scale of the BSID-III will be used as the primary outcome measure to assess attainment of motor milestones;

thus, it will be administered before the other scales. The sitting, standing, and walking series should be done separately prior to the full Gross Motor Scale at all visits. The Gross Motor Scale test, which is expected to take about 25 minutes to be administered in this population, will assess static positioning (e.g., head control, sitting); dynamic movement, including locomotion (e.g., crawling); quality of movement (e.g., kicking); balance; and motor planning.

The scales will be administered using a standardized instrument kit, and the test will be administered by an experienced clinician specifically trained to the test procedures, which will be described in a separate manual.

The sitting, standing, and walking series and the BSID-III Gross Motor assessment will be video-recorded in a standardized manner and centrally reviewed by two independent readers. The assessment of the central readers will be used for the primary analysis.

The Fine Motor Scale, Gross Motor Scale and Cognitive Scale will be administered according to standard administration procedures as described in the BSID-III manual. Thus, starting criteria for testing will be performed in accordance with the age of the patient, and the order of item administration will be fixed to allow direct clinical comparison of any stabilization of decline or improvement against normally developing children. Because the BSID-III is only designed to evaluate patients up to 42 months of age, these assessments will be stopped for each patient after they reach 42 months of age. The final BSID-III visit for all patients will be Week 182. The Fine Motor Scale may be video recorded upon request, but only where permitted by local regulations and where the optional consent has been given for the use of video recordings for purposes additional to assessment of the study objectives.

4.5.9.1.1 Rescheduling of Sitting, Standing, Walking and Gross Motor Scale Assessments

If the patient is not cooperative during the assessment of the sitting, standing, walking assessment or the Gross Motor Scale, the action to be taken will depend on the situation.

If the assessment has commenced and at least one item scored, then the assessment should be completed at that visit. It may be necessary for the patient to have a rest before continuing.

If the assessment has not yet begun, but the patient is uncooperative and, in the judgment of the Clinical Evaluator, the assessment will not reflect the capabilities of the patient, the assessment can be rescheduled for another day. Before this decision is taken it must be checked that the caregiver is able to bring the patient back for an extra study appointment, and that the visit window is respected. To emphasize, this decision is at the discretion of the Clinical Evaluator, based on clinical judgment and knowledge of the individual patient.

If the decision is made to reschedule the sitting, standing, walking assessment to a different day due to the patient being uncooperative, then the Gross Motor Scale should not be performed at the original visit, it should also be rescheduled to be performed on the same day as the sitting, standing, walking assessment.

If the sitting, standing, walking assessment is successfully performed at the original visit but the Gross Motor Scale cannot be assessed, and needs to be rescheduled, then the sitting, standing, walking assessment should be performed again, at the rescheduled visit, prior to the Gross Motor Scale. In this scenario, there will be two sitting, standing, walking assessments – one from the original visit, and one from the rescheduled visit.

4.5.9.2 Hammersmith Infant Neurological Examination–Module 2 (HINE-2)

The HINE is a neurologic examination initially designed to evaluate patients between 2 months and 24 months of age. It is a simple and scorable method that includes 26 items assessing different aspects of neurologic 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. The assessment may be video recorded for quality control purposes as indicated in the Training and Quality assurance methodology manual. The HINE is only designed to evaluate patients up to 24 months of age. Therefore, from Week 104 in the study, this assessment will be stopped for each infant once the maximum score is reached at two consecutive visits. *At the earliest, the final HINE-2 evaluation will be at Week 104.*

4.5.9.3 Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)

The CHOP INTEND is a measure of motor function that was developed from the Test of Infant Motor Performance 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 patients with Type 1 SMA (Glanzman et al. 2010; Glanzman et al. 2011).

The CHOP INTEND has been used in several studies in patients with Type 1 SMA, including both non-drug longitudinal studies, such as the Pediatric Neuromuscular Clinical Research network (Glanzman et al. 2010) and the National Institute of Neurological Diseases and Stroke 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 are associated with *SMN2* copy number (Glanzman et al. 2011).

In this study, the CHOP INTEND will be administered by an experienced and specifically trained clinician. Refer to the CHOP INTEND test administration manual for specific instruction regarding administration. The assessment may be video recorded for quality control purposes as indicated in the Training and Quality assurance methodology manual. Because the CHOP INTEND is only designed to evaluate patients up to 24 months of age, this assessment will be stopped after 24 months of treatment. However, after the Week 52 visit, the CHOP INTEND can be discontinued prior to Month 24*, upon notification by the Sponsor,* if the patient has demonstrated the ability to sit independently (item 22 of the BSID-III) at two consecutive visits, and has achieved a CHOP INTEND score of at least 60, at the same two consecutive visits, at any point up to Month 24.

4.5.9.4 Hammersmith Functional Motor Scale Expanded (HFMSE)

The HFMSE was developed to assess the motor function ability of individuals aged two years or older, with Type 2 and 3 SMA (O'Hagen et al 2007). The scale contains 33 items, which are scored on a 3-point Likert scale (0-2) and summed to derive the total score, with lower scores indicating greater impairment. The HFMSE contains a series of assessments designed to assess important functional abilities, including standing, transfers, ambulation, and proximal and axial function. The original Hammersmith Functional Motor Scale (HFMS) contained 20 items and was developed primarily to assess an SMA Type 2 population. Thirteen items, adapted from the Gross Motor Function Measure (GMFM), were added to improve the sensitivity of the scale, particularly for measuring motor function ability in Type 3 SMA patients. The HFMS and HFMSE have been used in previous and ongoing clinical trials for SMA, including as a primary endpoint (ClinicalTrials.gov Identifiers NCT02292537, NCT01302600; Chiriboga et al. 2016). The intra-rater reliability of the HFMSE was assessed in a sample of 38 Type 2 and 3 SMA patients using data at baseline and 2 months, with strong evidence demonstrated: intra-class correlation coefficient = 0.99 (O'Hagen et al. 2007). The validity of the HFMSE was assessed in a sample of 70 individuals with Type 2 and 3 SMA (Glanzman et al. 2011). Convergent validity was demonstrated by strong correlations with the GMFM ($r = 0.98$), forced vital capacity (percentage of predicted normal; $r = 0.87$), functional rating ($r = 0.92$), measures of extension and flexion ($r = 0.74–0.77$). The HFMSE also demonstrated an ability to differentiate between groups defined by SMN2 copy number, bi-level positive airway pressure use, ambulatory status, and SMA type. In this sample, time of administration averaged 12 minutes.

A users' manual and scoring sheet will be provided to the sites prior to the first assessment required (Week 104) (see Appendix 1 for HFMSE visit schedule). The scale will be administered by a Clinical Evaluator who has received training on the administration of the HFMSE according to the users' manual. Scores will be recorded on the scoring sheet and on the eCRF and the total score will be derived. *The*

assessment may be video recorded for quality control purposes as indicated in the Training and Quality assurance methodology manual.

4.5.9.5 World Health Organisation (WHO) Milestones

The WHO motor milestones evaluate gross motor development and comprise of the time windows of achievement for six gross motor milestones based on data derived from the WHO Multicenter Growth Reference Study (MGRS) (Acta Paediatrica Supplement 2006;450:86–95). The windows represent normal variation among healthy children and are recommended for descriptive comparisons among populations.

The six gross motor milestones are: sitting without support, hands-and-knees crawling, standing with assistance, walking with assistance, standing alone and walking alone. These items are considered fundamental to the acquisition of self-sufficient erect locomotion and are simple and quick to test (about 10 minutes). The milestones are assessed using standardized testing procedures and specific MGRS performance criteria (Wijnhoven et al. 2004). A milestone is considered achieved only if all criteria are met. The assessment can be carried out by a Clinical Evaluator who has received appropriate training.

In this study, the WHO motor milestones will be used to assess whether patients newly attain one or more of the six gross motor milestones at Months 48, 54, and 60. It will also provide information on maintenance of effect on gross motor milestone attainment during the long term OLE phase of the study.

4.5.9.6 Six-Minute Walk Test (6MWT; Ambulant Patients Only)

The 6MWT is an objective evaluation of functional exercise capacity that measures the maximum distance a person can walk in 6 minutes over a 25-meter linear course. Originally developed for chronic respiratory disease and heart failure, the test has since then been widely used as a performance-based measure of functional exercise capacity in many other populations and diseases, and normative data are available for adults and children. In particular, the 6MWT has been widely used as an outcome measure in clinical trials in neuromuscular diseases, including Duchenne Muscular Dystrophy, Becker Muscular Dystrophy, and SMA. In addition to providing a clinically relevant measure of the patient's walking ability that has a direct impact on autonomy, the 6MWT was shown to detect physiological fatigue in ambulatory SMA patients as demonstrated by a 17% decrease in gait velocity from the first minute to the last (Montes et al. 2010).

In this study, the 6MWT will be administered by a Clinical Evaluator who has received training on the administration of the 6MWT. Patients must be aged ≥3.5 years and must be able to walk unassisted (i.e., without braces, crutches or calipers, or person [e.g., hand-held] assistance) for at least 10 meters in order to perform this test. The 6MWT procedure will be based on the American Thoracic Society guidelines (ATS 2002), adapted as required with age-appropriate (for young SMA patients) instructions and encouragement. The course is a 25-meter linear course in a quiet

corridor at least 30-meter long. It is marked with a horizontal line at the beginning, the end, and at each intervening meter. A cone is placed at each end. Participants will be instructed that the test aims to see how far they can walk over a 6-minute period going around the cones. They must not run or jog. The use of assisted devices, such as ankle foot orthoses, crutches, walkers, or canes, will not be permitted during the assessment. However, suitable shoes and socks are to be worn. Patients will be permitted to rest against the wall, without sitting, if necessary. The total distance walked is recorded as well as how far they walk in each minute of the test.

4.5.10 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 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).

Maximum ulnar CMAP amplitude and area will be obtained by stimulating the ulnar nerve at the elbow and recording from the abductor digiti minimi muscle. The laterality of muscle groups studied with CMAP must remain consistent for each patient throughout the study.

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.

4.5.11 Laboratory, Biomarker, and Other Biological Samples

The following blood samples will be taken in the study at the timepoints specified in the schedule of activities (see Appendix 1):

- Clinical genotyping (see Section 4.5.11.1)
- Fluid PD samples (see Section 4.5.11.2)
- Safety laboratory (see Section 4.5.11.3)
- Plasma protein binding (see Section 4.5.11.4)
- Pharmacokinetics (see Section 4.5.11.5)

The total blood volume to be collected at any timepoint should not exceed 0.8 mL/kg or 2.4 mL/kg over any 4-week period throughout the study (E.U. 2008). However, should the total blood volume to be collected at any timepoint according to the schedule of activities exceed 0.8 mL/kg or the volume collected over any 4-week period throughout

the study exceed 2.4 mL/kg, the prioritization order indicated in Table 1 should be followed.

Table 1 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 plasma protein binding
3	Fluid PD samples (SMN protein levels)
4	Fluid PD samples (*SMN2* mRNA, exploratory biomarkers)

PD = pharmacodynamic; PK = pharmacokinetic; SMN = survival motor neuron (protein).

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.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Biological samples will be destroyed when the final Clinical Study Report has been completed, with the following exceptions:

- Fluid PD 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.
- Blood samples collected for clinical genotyping will be destroyed no later than 5 years after the date of final lock of the clinical database.

If a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on mutations, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.11.1 Clinical Genotyping 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 (see Section 4.1.1) and to confirm *SMN1* gene mutation or deletion. The result of the mandatory genotyping sample may not be required prior to enrollment given that genetic diagnosis of 5q autosomal recessive SMA has already been confirmed by using local assays.

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.

4.5.11.2 Fluid Pharmacodynamic Assessments

The following fluid PD assessments will be performed as detailed in the schedule of activities (see Appendix 1).

- In vivo splicing modification of *SMN2* mRNA in whole blood to measure:

  In vivo splicing modification of *SMN1*, *SMN2* full-length, and SMNΔ7 mRNA. Housekeeping genes for the quantitative analysis of RNA will be measured.
- SMN protein levels (venous blood)
- Exploratory biomarker for exploratory biomarker studies related to the pathology or disease progression of SMA or treatment response to risdiplam

  If blood volume allows, a serum sample will be taken for exploratory biomarker studies related to the pathology or disease progression of SMA or treatments response to risdiplam.

4.5.11.3 Safety Laboratory Assessments

Timepoints for safety blood samples are indicated in the schedule of activities (see Appendix 1).

Normal ranges for the study laboratory parameters should be supplied to the Sponsor. Laboratory safety tests shall be collected at timepoints specified in the schedule of activities (see Appendix 1 and Appendix 2).

At any time and as described in Section 4.5.11, safety laboratory samples will be given priority over any other sample, such that the volume of blood taken at any single timepoint will not exceed 0.8 mL/kg, and the volume collected over any 4-week period throughout the study will not exceed 2.4 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 micro-collection method should always be favored to limit the amount of blood collected.

Where the clinical significance of abnormal laboratory results is considered uncertain, screening laboratory tests may be repeated before enrollment to confirm eligibility.

In the event of unexplained abnormal clinically significant laboratory test values, the tests should be repeated and followed up in a timely manner 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.

Laboratory test samples will be collected for the following analyses:

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

4.5.11.4 Plasma Protein Binding

A venous blood sample will be collected from all patients at screening to measure plasma protein binding (i.e., to measure the free fraction of the study drug; see Section 3.3.1). Results for a patient must be available and checked by the Sponsor before any study drug is administered (Day 1) to each individual patient, if the patient is below the age range for which free fraction data is already available from other patients. If free fraction data from other patients in this age range is already available, then treatment of the new enrolled patient may be initiated without free fraction being available, however, the result of the screening free fraction sample must be reviewed by the Sponsor within 4 weeks of treatment start for this patient.

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

4.5.11.5 Pharmacokinetic Assessments

Blood for determination of plasma concentrations of risdiplam, and its metabolite(s) as applicable, will be collected as detailed in the schedule of activities (see Appendix 1 and Appendix 2).

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 will be collected for PK samples. If venous blood cannot be obtained after two attempts, capillary blood collection should be attempted for pharmacokinetics.

Plasma concentrations of risdiplam and derived metabolite(s) as applicable will be measured by appropriate assays, 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.

4.5.12 Parent/Caregiver-Reported Outcomes

The infant/toddler quality of life questionnaire–short-form 47-item version (ITQOL-SF47) is a parent (or caregiver)-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. 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 items], Bodily Pain [2 items], Temperament and Moods [6 items], Behavior [12 items], General Health Perception [5 items], Parent-Emotional Health [4 items] and Parent-Time Limitations [4 items]). 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.

Throughout the study, the same parent (or caregiver) should complete the ITQOL-SF47.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Unable to continue to comply with study requirements
- Any event that meets stopping criteria defined in Section 5.1.3

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 and participate in the follow-up call 30 days later (see Appendix 1). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF.

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.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

4.6.2 Patient Discontinuation from Study

Parent (or caregiver) has the right to voluntarily withdraw the patient from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- The parent (or caregiver) withdrawals consent
- Study termination or site closure
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain information on patients who withdraw from the study but have not withdrawn consent. The primary reason for withdrawal from the study should be documented on the appropriate eCRF.

If a parent (or caregiver) requests the patient to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who are withdrawn from the study will not be replaced.

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

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

4.6.3 Study 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 if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing 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 ICH guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

4.6.5 Assessments at Study Completion/Early Withdrawal Visit

The EOS is when the last patient completes 5 years in the study. All patients should attend a study completion/early withdrawal visit when they either complete the study or discontinue study drug early, as shown in the schedule of activities (Appendix 1, Appendix 2, and Appendix 3). If risdiplam is approved in the country of the site before the Week 260 (Year 5) visit, then the final visit for the patient will be at 260 weeks in the study – in this case the study completion/early withdrawal visit will be performed in place of the Week 260 visit. If risdiplam is not approved in the country of the site at the time of the Week 260 visit, the patient should attend the Week 260 visit, and all OLE visits beyond Week 260 until risdiplam is approved or until EOS (whichever occurs first), ensuring that the final site visit is the study completion/early withdrawal visit.

4.6.6 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 Section 5.5, Section 5.6 and the schedule of activities(Appendix 1, Appendix 2, and Appendix 3).

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Risdiplam has only been approved in the USA for patients 2 months of age and older. Clinical development is ongoing. The safety plan for patients in this study aims at managing potential risks that were identified following findings in preclinical studies with risdiplam. The potential safety risks for risdiplam are outlined below. Please refer to the Risdiplam Investigator's Brochure for a complete summary of safety information.

The exposure cap of a mean $AUC_{0\text{-}24,ss}$ 2000 ng • hr/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; see 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 toxicology studies and in monkey toxicology 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 prepostnatal toxicity study in rats (see Risdiplam Investigator's Brochure).

Several measures will be taken to ensure the safety of patients participating in this study. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below. The pharmacokinetics will be monitored in each individual patient to ensure that each infant is in the targeted exposure range and in compliance with the exposure cap. Free fraction will be measured from a sample taken at screening, and the dose adjusted if the free fraction is different for a particular infant.

The stopping rules detailed in Section 5.1.3 will be applied in case of specific adverse events.

5.1.1 Risks Associated with Risdiplam

Based on observed toxicity in nonclinical studies (see Risdiplam Investigator's Brochure for details), the following safety precautions should be followed for this study. For effects on the skin, oral and larynx mucosa, hematology, conjunctival mucous membranes, and retinal toxicity no safety data are available in the age group of 2 months and younger.

5.1.1.1 Skin Toxicity

Patients treated with risdiplam may be at risk for developing skin redness, dry or peeling skin, or cracking in the corner of the mouth. Aggressive skin treatments, on body or face, should be avoided as well as scented lotions, soaps, and deodorants. Parents (or caregivers) will be instructed to apply alcohol-free hypoallergenic moisturizing cream early in case of dry skin and to quickly contact the investigator.

5.1.1.2 Oral and Larynx Mucous Membranes

Patients treated with risdiplam are at risk of developing effects on oral and larynx mucous membranes. Parents (or caregivers) who will administer the study medication orally will be instructed to rinse the patient's mouth with water (that should be swallowed) after administration and to generally ensure that oral mucosa is well-lubricated with fluids. Similarly, the peribuccal area of the patient will be washed with water in case of drug drooling or spitting. Parents (or caregivers) will be instructed to promptly consult the study investigator in case of symptoms of laryngitis for a specialized examination.

5.1.1.3 Effects on Hematology Parameters

Patients treated with risdiplam are at risk of developing hematological effects with decreased cellularity in bone marrow and peripheral blood. Regular monitoring of hematological parameters will be performed.

5.1.1.4 Conjunctival Mucous Membranes

Patients treated with risdiplam are at risk of developing adverse effects affecting conjunctival mucous membranes. Use of ocular lubricants (artificial tears) will be advised in patients who exhibit signs of dry eye (paradoxical tearing, ocular discomfort, conjunctival injection).

5.1.1.5 Visual Impairments

Patients treated with risdiplam are at risk of developing retinal toxicities (irreversible loss of photoreceptor cells in the peripheral retina and potentially reversible microcystic macular degeneration). Ophthalmology monitoring including SD-OCT will be performed throughout the study. Parents or caregivers will be informed that in case of visual impairments, young children could present with, for example, strabismus or behavioral changes (e.g., fixation losses, not reaching/grabbing objects, rubbing of the eyes). Parents or caregivers will be instructed by the investigators to comply with concomitant medications restriction (i.e., use of drugs with known human retinal toxicity, see Section 4.4.2).

5.1.2 Management of Patients Who Experience Adverse Events

5.1.2.1 Dose Modifications

Dose modifications are not permitted, unless based on weight changes (weight must be measured at the site or, in exceptional circumstances, at home or local clinic upon discussion with the Sponsor (see Section 3.3.1) or requested by the Sponsor based on the PK monitoring.

5.1.3 Stopping Rules

5.1.3.1 Individual Patient Stopping Rules

While the investigators, the Roche Clinical Science Leader (CSL), the Roche Safety Science Leader, and the external iDMC (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:

- Skin or subcutaneous reaction, pharyngeal/laryngeal or mucosal reaction (Grade ≥ 2, CTCAE, v5) considered to be clearly related to study drug as confirmed by a dermatologist/ear, nose, and throat specialist, making the benefit–risk ratio non-favorable

- Functional or structural eye abnormalities

  Clinically relevant abnormalities on 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 that pose an unacceptable risk for the patient
- Patients with any elevated ALT or AST of $>3\times$ ULN, ALP $<2\times$ ULN, and associated with an increase in bilirubin ($>2\times$ 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 serious adverse event or any other severe adverse event that, at the joint discretion of Roche CSL, Roche Safety Science Leader, and the investigator, indicate that dosing should be halted.

In addition to the above stopping rules, dosing may be stopped if safety, tolerability, or efficacy data suggest risdiplam is not beneficial for the patient, in the investigator's judgment. The investigator should then look for the best standard of care option available in the country.

5.1.3.2 Management Guidelines

Specific adverse events related to pharyngeal/laryngeal, skin, and ophthalmological adverse events should be managed as described in Table 2.

Table 2 Guidelines for Management of Patients Who Experience Adverse Events

Event	Action to take
Symptoms or signs of oropharyngitis	Examine, treat symptomatically, and document resolution and outcome. Consult otolaryngology specialist in case of unusual findings.
Grade ≥ 2 skin toxicity reaction Grade ≥ 2 larynx toxicity reaction	Consult a dermatologist. Discontinue study treatment if determined to be study-drug related. Promptly contact the study investigator, consult as quickly as possible a dermatologist/otolaryngology specialist. Discontinue study treatment immediately if determined to be study-drug related.
Ophthalmological event	Consult a study trained ophthalmologist as quickly as possible for ophthalmic examination and contact promptly the study investigator. If findings are consistent with preclinical findings, 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.

5.1.4 Safety Monitoring

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

- Physical examinations (see Section 4.5.4), with specialty medical doctors (ophthalmologist, dermatologist, and otolaryngology specialist) 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.

  Photographs may be taken of any skin, mouth, or pharynx lesions for documentation, at the discretion of the investigator or specialty medical doctors. These photographs may be shared with the Sponsor to allow for safety monitoring and will be stored in a computer system with restricted access (the sites will be instructed not to submit photographs that identify the patient, e.g., photos of a cheek skin lesion in which the entire face is captured).
- Ophthalmological assessments (see Section 4.5.7)
- Stopping rules for individual patients have been defined that include criteria for treatment discontinuation in case of skin, pharynx/larynx, or ophthalmic events (see Section 5.1.3.1).

- Follow-up phone calls (as per the timepoints in the schedule of activities; Appendix 1): parents (or caregivers) will be called by the investigator or designee to monitor safety and tolerability when not attending the clinic. Assessments will include review of adverse events, concomitant medications, and significant life events.

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting 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.

5.2.1 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) (see Sections 5.3.5.8 and 5.3.5.9 for more information)
- 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)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)

- Is 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 5.3.5.10)
- 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)
- Is a 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 (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE]; see 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).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

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 are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see 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.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 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 (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see 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 and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

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 final 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 timepoints. Examples of non-directive questions include the following:

"How have you/your child felt since your last clinic visit?"

"Have you/your child had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5) will be used for assessing adverse event severity. Table 3 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 3 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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 most recent version of NCI CTCAE (v5), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[b] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

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 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, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- 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

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 That Are Secondary to Other Events

In general, adverse events that are 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. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event 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 consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both 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 timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes

more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event 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 must be reported as an adverse event if it meets any of the following criteria:

- Is 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
- Is 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 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) 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 whether 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.5 Abnormal Vital Sign Values

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

- Is 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
- Is 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 only be recorded once on the Adverse Event eCRF (see Section 5.3.5.3 for details on recording persistent adverse events).

5.3.5.6 Abnormal Liver Function Tests

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

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$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 (see 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 an adverse event of special interest (see Section 5.4.2).

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.2), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of SMA.

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.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

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 Medical History 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 Lack of Efficacy or Worsening of Spinal Muscular Atrophy

Medical occurrences or symptoms of deterioration that are anticipated as part of SMA should be recorded as an adverse event if judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study. When recording an unanticipated worsening of SMA on the Adverse Event eCRF, it is important to convey the concept that the condition has changed by including applicable descriptors (e.g., "accelerated worsening of Spinal Muscular Atrophy").

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), 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 experienced 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.

5.3.5.11 Reporting Requirements for Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be administered by the parent (or caregiver), drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events, but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness 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). For

risdiplam, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with risdiplam, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.

- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.12 Patient/Caregiver-Reported Outcome Data

Adverse event reports will not be derived from parent (or caregiver)-reported outcome data by the Sponsor, and safety analyses will not be performed using these data. Sites are not expected to review these data for adverse events.

5.3.5.13 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

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 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Medical device complaints (see Sections 5.4.2 and 5.4.3 for details on reporting requirements).

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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 Institutional Review Board (IRB)/Ethics Committee (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 Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

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. The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 30 days after the study completion/early withdrawal visit. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the appropriate Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management department.

In the event that the EDC system is unavailable, the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the

EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur more than 30 days after the study completion/early withdrawal visit are provided in Section 5.6.

5.4.3 Reporting Requirements for Medical Device Complaints

In this study, dispenser for oral drug administration is considered a medical device. The investigator must report all medical device complaints to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in 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.

5.5.2 Sponsor Follow-Up

For serious adverse events and adverse events of special interest, the Sponsor or a designee may follow up by telephone, fax, email, 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 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (as defined in Section 5.3.1), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to

the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest 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 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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary objective of the study is to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants genetically diagnosed with SMA but not yet presenting with symptoms.

A database lock will occur for the purpose of the primary analysis and analyses of the 12-month secondary and exploratory endpoints once the last infant *enrolled* has either completed his/her 12-month assessment or has been withdrawn. At the time of the primary analysis, all available efficacy data after Month 12 and all available safety data will also be reported. Following the primary analysis, another database lock will occur for the analyses of the 24-month secondary and exploratory endpoints once the last patient *enrolled* has completed his/her 24-month assessment or has been withdrawn. All available safety data and efficacy data after Month 24 will also be reported.

Subsequent locks of the database may occur to perform exploratory efficacy and safety analyses of the data at further timepoints in response to information that may emerge during the course of the study. Final database lock will occur at the end of the study. Full details of the statistical methods will be described in the Data Analysis Plan (DAP).

6.1 DETERMINATION OF SAMPLE SIZE

The purpose of the study is to estimate the proportion of infants with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G>C) and a baseline CMAP amplitude $\geq$1.5 mV who are sitting without support after 12 months of treatment and to test whether this proportion is higher than a performance criterion set at 5%. The 5%

threshold was chosen based on the natural history of the disease (typically patients with Type 1 SMA never achieve sitting without support by definition) and based on the assumption that there is a 97% chance that a presymptomatic infant with two *SMN2* copies develops Type 1 SMA (Feldkotter et al. 2002).

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

If recruitment is completed prior to enrolling 10 patients with two SMN2 copies and a baseline CMAP amplitude ≥1.5 mV, the number of patients needed to be observed sitting without support for a statistically significant result may differ. Table 4 shows the minimum number of patients that would need to achieve the primary endpoint (based on the number enrolled), in order for the endpoint to meet statistical significance (the critical value). In each case, the lower limit of the two-sided 90% Clopper-Pearson (Exact) confidence interval would be above 5%.

Table 4: Number of Patients in the Primary Analysis Population Needed to Achieve the Primary Endpoint

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

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who are enrolled, discontinued, continuing treatment at the time of 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.

6.3 ANALYSIS POPULATION

6.3.1 Safety Analysis Population

All patients who receive at least one dose of risdiplam, whether prematurely withdrawn from the study or not, will be included in the safety population. Selected key safety outputs will be produced for All Patients and separately for the subgroups CMAP amplitude $\geq$1.5 mV and CMAP amplitude $<$ 1.5 mV.

6.3.2 Pharmacokinetic and Pharmacodynamic Analysis Population

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

6.3.3 Intent-to-Treat and Primary Efficacy Analysis Population

The intend-to-treat (ITT) population is defined as all enrolled patients, regardless of whether they receive risdiplam or not. The primary efficacy analysis population is defined as all infants in the ITT population with two *SMN2* copies (excluding the known *SMN2* gene modifier mutation c.859G$>$C) and a baseline CMAP amplitude $\geq$1.5 mV. The primary efficacy analysis population will be the population for the primary efficacy analysis (see Section 6.5.1). The ITT population will be used for all secondary and exploratory efficacy summaries; however, any hypothesis testing if performed will be limited to the primary efficacy analysis population.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and other baseline characteristics will be summarized by overall population, by *SMN2* copy number for the ITT population and for the primary efficacy analysis 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 the first dose of risdiplam unless specified otherwise in the DAP.

6.5 EFFICACY ANALYSES

6.5.1 Primary Efficacy Endpoint

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

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

Ho: p≤5% (null) versus Ha: p>5% (alternative).

If the one-sided p-value is ≤5% (Type 1 error rate), then the null hypothesis will be rejected. If the lower limit of the two-sided 90% confidence interval is above the 5% threshold, the primary objective of the study will be considered achieved. The number and percentage of infants sitting at each timepoint will also be presented, using the same responder/non-responder definition described above.

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

If recruitment is completed prior to enrolling 10 patients with two SMN2 copies and a baseline CMAP amplitude ≥1.5 mV, the number of patients needed to meet the primary endpoint for a statistically significant result may differ (see Table 4).

6.5.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

Development of clinically manifested SMA

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

Survival and ventilation-free survival

- Time to death (from enrollment)
- Time to permanent ventilation (from enrollment)

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

Motor function and development milestones

- Proportion of patients who achieve the attainment levels of the motor milestones as assessed in the HINE-2 (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) at Month 12 of treatment
- Proportion of patients who achieve the attainment levels of motor milestones as assessed in the HINE-2 (head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking) at Month 24 of treatment
- Proportion of patients with two copies of the *SMN2* gene sitting without support (at Month 12 of treatment [as assessed in Item 22 of BSID-III Gross Motor Scale]) for 5 seconds (independent of the CMAP value at baseline)
- Proportion of patients sitting without support at Month 24 of treatment (as assessed in Item 22 of BSID-III Gross Motor Scale) for 5 seconds
- Proportion of patients sitting without support at Month 12 of treatment (as assessed in Item 26 of BSID-III Gross Motor Scale) for 30 seconds
- Proportion of patients sitting without support at Month 24 of treatment (as assessed in Item 26 of BSID-III Gross Motor Scale) for 30 seconds
- Proportion of patients standing at Month 24 of treatment (defined as “Stands Alone” for at least 3 seconds as assessed in Item 40 of the BSID-III Gross Motor Scale)

- Proportion of patients walking at Month 24 of treatment (defined as “Walks Alone” takes at least 3 steps as assessed in Item 42 of the BSID-III Gross Motor Scale)
- Proportion of patients demonstrating the ability to achieve a scaled score within 1.5 standard deviations of chronological reference standard at Months 24 and 42 of treatment (as assessed through the use of the BSID–III Gross Motor Scale)
- Change from baseline score in the CHOP INTEND motor function scale at Month 12 of treatment
- Proportion of patients who achieve a score of 40 or higher in the CHOP INTEND motor function scale at Month 12 of treatment
- Proportion of patients who achieve a score of 50 or higher in the CHOP INTEND motor function scale at Month 12 of treatment
- Proportion of patients who achieve a score of 60 or higher in the CHOP INTEND motor function scale at Month 12 of treatment
- Proportion of patients who meet CHOP INTEND stopping criteria at any point up to Month 24
- Change from baseline (Month 24) in the HFMSE at Month 60 of treatment

Growth measures

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

- Change from baseline percentiles for weight-for-age, length/height-for-age and weight-for-length/height at Month 48 of treatment
- Change from baseline percentiles for weight-for-age, length/height-for-age and weight-for-length/height at Month 60 of treatment
- Change from baseline in chest circumference at Month 12 of treatment
- Change from baseline in chest circumference at Month 24 of treatment
- Ratio between chest and head circumferences at Month 12 of treatment

  Head circumference will be the denominator of the ratio.
- Ratio between chest and head circumferences at Month 24 of treatment

  Head circumference will be the denominator of the ratio.

Nutrition

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

Muscle electrophysiology

- Change from baseline in CMAP amplitude at Month 12 of treatment
- Change from baseline in CMAP amplitude at Month 24 of treatment

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

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 patients who are surviving ventilation-free at Months 12 and 24 of treatment 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 in the study until the date of death from any cause or date of permanent ventilation, whichever event occurs first. Patients with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be alive and ventilation free.

The number and percentage of patients within each attainment response category of the HINE-2 motor milestones at Month 12 and Month 24 of treatment will be presented.

For the primary efficacy population only, the proportion of infants who at 12 months of treatment are alive and sitting without support for 30 seconds (as assessed in item 26 of the BSID-III Gross Motor Scale), and the proportion of patients who at 24 months of treatment are alive and 1) sitting without support for 5 seconds (as assessed in Item 22 of the BSID-III Gross Motor Scale), 2) sitting without support for 30 seconds (as assessed in Item 26 of the BSID-III Gross Motor Scale), 3) standing (as assessed in Item 40 of the BSID-III Gross Motor Scale), and 4) walking (as assessed in Item 42 of the BSID-III Gross Motor Scale) will be analyzed as for the primary endpoint (using the same performance criterion of 5%) testing the null hypothesis that the proportion of patients who are alive and have achieved the motor milestone $\leq 5\%$ (null) versus $p > 5\%$ (alternative).

Further details of the statistical methods, definitions, and analyses for all the secondary endpoints will be provided in the DAP.

6.5.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints will include, but may not be limited to, the following:

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

- Speech development as assessed by neurological examination at Months 12, 24, 36, 48, and 60 of treatment
- Change from baseline in ITQOL questionnaire at Month 12 of treatment
- Change from baseline in ITQOL questionnaire at Month 24 of treatment
- Number of hospitalizations (for any reason, except if for study purpose only [e.g., to facilitate study assessments]) per patient-year and number of nights admitted to hospital per patient at Months 12, 24, 36, 48, and 60 of treatment
- Proportion of patients with no hospitalizations at Months 12, 24, 36, 48, and 60 of treatment
- Proportion of patients who experience at least one disease-related adverse event by Month 12 of treatment
- Proportion of patients who experience at least one disease-related adverse event by Month 24 of treatment
- Number of disease-related adverse events per patient-year at Month 12 of treatment
- Number of disease-related adverse events per patient-year at Month 24 of treatment

  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/preferred terms to the adverse event dataset. The baskets will be defined in the DAP.

Further details of the statistical methods, definitions, and analyses for all exploratory endpoints will be specified in the DAP.

6.5.4 Subgroup Analyses

Subgroup analyses may be performed. Further details of the statistical methods, definitions and analyses will be specified in the DAP.

6.6 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

All safety analysis will be based on the safety analysis population. Safety data collected from each of the endpoints will be summarized descriptively for the first 12-month period

(i.e., 12-month data for each individual infant) at the time of the 12-month analysis reporting event and for all available safety data collected at the time of 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 iDMC data review will be performed as described in the associated iDMC Charter.

6.6.1 Adverse Events

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

6.6.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Data 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 laboratory abnormalities or values outside the normal ranges. In addition, tabular summaries including shift tables to compare the status at baseline to each timepoint post-baseline and overall will be used, as appropriate.

6.6.3 Vital Signs

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

6.6.4 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.

6.6.5 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.

6.7 PHARMACODYNAMIC ANALYSES

All PD parameters will be presented by listings and descriptive summary statistics, as appropriate. Further details will be in the DAP.

6.8 PHARMACOKINETIC ANALYSES

All PK 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 PK 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 manner. Data may be pooled with data from other studies with risdiplam 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 predose samples (and also may be performed on PK samples throughout the study, as required) and reported.

Additional PK analyses will be conducted as appropriate.

6.9 INTERIM ANALYSIS

As this study is open-label, once at least 3 of the 10 infants *(if 10 of these patients have been enrolled)* have met the primary endpoint of sitting without support at Month 12 (as assessed by the independent central readers), the minimum number of infants needed for a statistically significant result will have been achieved and the primary objective of the study will be considered achieved at this earlier timepoint. The study will not be stopped and all infants enrolled will continue to receive 12 months of treatment in order to provide an unbiased estimate of the proportion of infants sitting at Month 12. An interim analysis may also be performed to summarize descriptively the safety and efficacy data to support the initial filing and registration of risdiplam in pre-symptomatic patients and patients below the age of 2 months.

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

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. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Local laboratory data and other electronic data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Patient-reported outcome (PRO) data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

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

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review 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, PROs, 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, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

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 and review, 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 study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study 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, electronic or paper PRO data (if applicable), 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 European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Informed Assent Form or Mobile Nursing Informed Consent Form, if applicable) 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.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or 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 or 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 authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. 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 be disclosed to third parties only 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.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted clinical study reports and other summary reports will be provided upon request.

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 1 year after completion of the study (see definition of end of study in Section 3.2).

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, including an audit trail containing a complete record of all changes to data.

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

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 12–15 sites globally will participate to enroll approximately 25 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An iDMC will be employed to monitor and evaluate patient safety until the last patient enrolled in this study has completed 12 months of treatment or until the last patient in Studies BP39055 and BP39056 completes 2 years of treatment, whichever occurs later.

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 congresses. 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 protocol amendments will be prepared by the Sponsor. 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 changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Activities

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

Appendix 1: Schedule of Activities (cont.)

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

Appendix 1: Schedule of Activities (cont.)

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

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

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

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

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

[d] Follow-up telephone calls should be done at Days 4, 11, 19, 25, 33, 42, 63, and 77. The investigator must agree with the parent (or caregiver) when to perform the follow-up telephone calls at the most appropriate time (day) between study visits. After Week 11, additional follow-up telephone calls are per investigator decision.

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

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

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

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

[i] Oral dosing should be performed during site visits. Oral dosing once daily in the morning when at home. See Section 4.3.2 for details. At study completion/early withdrawal visit, no study drug will be dispensed and used and unused study drug bottles are to be returned.

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

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

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

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

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

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

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

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

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

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

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

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

[v] This includes SMA related surgeries and procedures.

[w] Only serious adverse events.

Appendix 2
Blood Samples

Week/Visit	Day	Scheduled Time (hr)	PK Blood Sample	Safety Laboratory (Hematology and Blood Chemistry)	Fluid PD Markers [a]	Plasma Protein Binding	Clinical Genotyping
Screening				x		x	x
Week 1	Day 1	Predose			x		
		2 hr	x				
		4 hr	x				
		6 hr	x				
	Day 2	Predose (24 hr) [b]	x				
Week 2	Day 14	Predose	x	x			
Week 4	Day 28	Predose	x				
		2 hr	x				
		4 hr	x				
		6 hr	x				
Week 8	Day 56	Predose	x	x			
		2 hr	x		x		
		4 hr	x				
		6 hr	x				
Week 16	Day 112	Predose	x	x			
Week 28	Day 196	Predose	x	x	x		
		2 hr	x				
		4 hr	x				
		6 hr	x				
Week 40	Day 280	Predose	x	x			
Week 52	Day 364	Predose	x	x	x		
		2 hr	x				
		4 hr	x				
		6 hr	x				

Appendix 2: Blood Samples (cont.)

Week/Visit	Day	Scheduled Time (hr)	PK Blood Sample	Safety Laboratory (Hematology and Blood Chemistry)	Fluid PD Markers [a]	Plasma Protein Binding	Clinical Genotyping
Week 64	Day 448	Predose	x	x			
Week 78	Day 546	Predose	x	x			
		2 hr	x				
		4 hr	x				
		6 hr	x				
Week 92	Day 644	Predose	x	x			
Week 104	Day 728	Predose	x	x	x		
		2 hr	x				
		4 hr	x				
		6 hr	x				
OLE		Predose	x	x			
Study Completion /Early Withdrawal			x	x	x		

OLE = open-label extension; PD = pharmacodynamic; PK = pharmacokinetic.

[a] Fluid PD markers will only be collected if the limit on total blood volume allows: Total blood volume to be collected at any timepoint should not exceed 0.8 mL/kg or 2.4 mL/kg over any 4-week period.

[b] Patients will have a PK sample taken 24 hours after the first dose and prior to receiving the second dose of risdiplam.

Appendix 3
Ophthalmology Assessments

Week	Screening	8	28	52	104	OLE	Study Completion/EW [a]
Day		56	196	364	728		
Examination [b, c]	x	x	x	x	x	x [b]	x
SD-OCT	x [d]	x	x	x	x	x [b]	x
Color fundus photography [e]	x		x	x			

EW = early withdrawal; OLE = open-label extension; SD-OCT = spectral-domain optical coherence tomography.

[a] *Ophthalmology assessments are not required at the Study Completion/Early Withdrawal Visits if the assessments have occurred within the prior 6 months.*

[b] *Ophthalmologic* examination and SD-OCT *are required once per year from Week 52, including during OLE (the first ophthalmologic assessment in OLE will be performed at Week 156, then at alternating OLE visits thereafter).*

[c] The ophthalmology examination as appropriate for age of patient includes: visual development, red reflex, external ocular examination, pupillary response, cover/uncover, fix and follow test, and ocular examination under magnification.

[d] *Screening ophthalmologic assessments are to be performed between Day –42 and Day 14.*

[e] Fundus photography should be attempted at least once at each scheduled visit up to Week 52. After Week 52, fundus photography will no longer be *required*.

Appendix 4
Order and Blocks of Assessments at Visits When Efficacy Measurements Are Performed up to and Including Week 104 [a]

Block 1	• ECG, vital signs, physical examination (including weight) (Note: At Visit 1 only, should be performed 4 hours after dosing.) **BREAK** • BSID-III (Sitting, Standing Walking; Gross; Fine Motor; Cognition) **BREAK** • CHOP INTEND **BREAK** • HINE-2 **BREAK** • Blood sample (or insertion of catheter) • Dose administration **BREAK**
Block 2	• Infant Toddler Quality of Life Questionnaire **BREAK** • CMAP **BREAK**
Block 3	• Ophthalmological examination

BSID-III = Bayley Scales of Infant and Toddler Development®, Third Edition; CMAP = compound muscle action potential; HINE-2 = Hammersmith Infant Neurological Examination–Module 2.

[a] The Week 104 visit will be the first HFMSE assessment for all patients and the last CHOP-INTEND assessment (for patients who did not already meet the CHOP-INTEND stopping criteria prior to Week 104). At Week 104, if CHOP-INTEND is required, then the order of assessments should be BSID-III, CHOP-INTEND, HINE-2, HFMSE, If CHOP-INTEND is not required, then the HFMSE can replace the CHOP-INTEND so that the order is BSID-III, HFMSE, HINE-2.

After Week 104, continue to use the Block 1 order as a recommendation, with the motor function and milestone assessments being completed prior to the blood sample and dose administration. The order of priority for motor function and milestone assessments is: BSID-III (up to and including Week 182, Month 42), HFMSE, HINE-2 (until the max score is reached at two consecutive visits), WHO milestones (starting at Week 208, Month 48) and 6MWT (starting at Week 182, Month 42).

Please ensure that motor function and milestone assessments are each preceded by a break of at least 15 minutes, with the exception of between the HINE-2 and WHO milestones (if they occur at the same visit) where no break is required.