Official Title: A Phase II, Open-Label Study to Investigate the Pharmacokinetics and Safety of Risdiplam in Infants with Spinal Muscular Atrophy

NCT Number: NCT05808764

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PROTOCOL

PROTOCOL TITLE:	**A *PHASE II*, OPEN-LABEL STUDY TO INVESTIGATE THE PHARMACOKINETICS AND SAFETY OF RISDIPLAM IN INFANTS WITH SPINAL MUSCULAR ATROPHY**
PROTOCOL NUMBER:	BN44619
STUDY NAME:	*PUPFISH*
VERSION NUMBER:	2
TEST COMPOUND:	Risdiplam (RO7034067)
STUDY PHASE:	*Phase II*
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 128972 EU CT Number: 2023-505602-42-00 NCT Number: NCT05808764
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL:	See electronic signature and date stamp on the final page of this document.

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PROTOCOL HISTORY

Protocol	
Version	**Date Final**
2	See date stamp on the final page of this document.
1	19 December 2022

PROTOCOL AMENDMENT, VERSION 2: RATIONALE

Protocol BN44619 has been amended to make it applicable for sites in Europe (by the inclusion of mandatory text relating to Clinical Trials Regulation [CTR] requirements) and Canada. Substantive changes to the protocol, along with a rationale for each change, are summarized below:

- The study phase has been updated from Phase IV to Phase II to reflect the use of risdiplam as an investigational medicinal product in regions where it is used outside of marketing authorization (title page, Protocol Amendment Acceptance Form, and synopsis).
- Regions for recruitment have been updated to include Europe and Canada (Section 4.1).
- The reference to the United States Prescribing Information for the starting dose has been removed, and language has been revised to state that the starting dose of risdiplam is based on pharmacokinetic data from risdiplam studies and from modeling and simulation (Section 4.3).
- comprehensive list of investigational medicinal products has been added to align with CTR requirements (Section 6 and Appendix 6).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**A *PHASE II*, OPEN-LABEL STUDY TO INVESTIGATE THE PHARMACOKINETICS AND SAFETY OF RISDIPLAM IN INFANTSWITH SPINAL MUSCULAR ATROPHY**
PROTOCOL NUMBER:	BN44619
STUDY NAME:	*PUPFISH*
VERSION NUMBER:	2
TEST COMPOUND:	Risdiplam (RO7034067)
SPONSOR NAME:	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**.

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	**A *PHASE II*, OPEN-LABEL STUDY TO INVESTIGATE THE PHARMACOKINETICS AND SAFETY OF RISDIPLAM IN INFANTS WITH SPINAL MUSCULAR ATROPHY**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 128972 EU CT Number: 2023-505602-42-00 NCT Number: NCT05808764

STUDY RATIONALE

The purpose of this study is to generate pharmacokinetic (PK) and safety data on the use of risdiplam treatment in patients with *spinal muscular atrophy* (SMA) aged *under* 20 days *of age* at first dose. Spinraza® (nusinersen) and Zolgensma® (onasemnogene abeparvovec) are currently approved for patients with SMA from birth. Despite the availability of these therapies, there remains an unmet medical need for additional treatment options for newborn patients, especially when considering prompt treatment initiation to prevent irreversible motor neuron loss and disease progression. There is currently limited risdiplam data in newborn patients. Thus, this study seeks to extend the characterization of the PK and safety profile in newborns.

OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics and safety of risdiplam in *patients* with SMA under 20 days of age at first dose.

Primary Objectives	Corresponding Endpoints
• To characterize the risdiplam PK profile	• Plasma concentration of risdiplam and metabolite(s) as applicable at specified timepoints • AUC • Concentration at the end of a dosing interval to assess steady state • Other PK parameters as appropriate • Risdiplam free fraction
• To evaluate the safety of risdiplam	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 • 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 • Physical examination, including detailed examination of the skin and mouth

AUC = area under the concentration-time curve; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK = pharmacokinetic.

OVERALL DESIGN AND STUDY POPULATION

The study is a non-randomized, open-label, single-arm interventional study to investigate the pharmacokinetics and safety of risdiplam in patients with SMA *aged* < 20 days at first dose.

Approximately 10 patients with SMA are planned to be enrolled with a minimum of 3 participants *aged* < 7 days. The recruitment target may be adjusted based on review of PK data; however, recruitment will not exceed 15 participants.

The study will *be comprised* of the following phases:

- **Screening:** Informed consent must be obtained prior to first study screening assessment and may be obtained after prenatal diagnosis and before participant's birth. Screening runs until Day 1 when the participant receives the first dose of risdiplam. Screening assessments may be repeated before enrollment to confirm eligibility. Rescreening is permitted.
- **Treatment**: During the treatment phase, all participants will receive risdiplam orally once daily for 4 weeks at a dose of 0.15 mg/kg (however, the dose may be adjusted during the study upon review of PK data). The treatment period will end *on* Day 28 with a Day 28/Study Completion visit. Alternatively, if the participant discontinues treatment before Day 28, they will attend an Early Withdrawal visit.
- **Follow-up**: A safety follow-up telephone call will only be conducted for participants who stop study treatment (*on* or before Day 28) *and* who do not go on to receive further risdiplam (through commercial access or through the Continued Provision of Investigational Medicinal Product [IMP] Phase) AND who do not start treatment with another disease-modifying therapy (DMT) *for SMA*. For eligible patients, the safety follow-up telephone call will occur 30 days after the last dose of study treatment.

Upon completion of Day 28, participants with no immediate access to any commercial DMT for SMA may continue to receive risdiplam in a Continued Provision of IMP Phase until the end of study at the latest, defined as the last *participant's* last visit. These participants continuing to receive risdiplam after Day 28 are not required to attend additional study visits. Risdiplam will be provided as per current study procedures. Only adverse events must continue to be reported to maintain study safety reporting requirements. Therefore, investigators should proactively contact those participants every 8 weeks (if the participant is still in the study) to ensure adverse events are reported in the *electronic Case Report Form* and document this contact in the patient notes.

Once a participant gains access to any commercial DMT, the participant will leave the study.

Key aspects of the study design and study population are summarized below.

Phase:	*Phase II*	**Population Type:**	Pediatric patients
Control Method:	None	**Population Diagnosis or Condition:**	Spinal muscular atrophy
Interventional Model:	Single group	**Population Age:**	< 20 days at first dose
Test Compound:	Risdiplam	**Site Distribution:**	Multi site *and multi-region*
Active Comparator:	Not applicable	**Study Intervention Assignment Method:**	All participants are assigned to the same treatment
Number of Arms:	One	**Number of Participants to Be Enrolled:**	Approximately 10, up to a maximum of 15

STUDY TREATMENT

Risdiplam 0.15 mg/kg once daily, orally (via mouth) or via a nasogastric or gastrostomy tube, for 28 days.

Modification of the 0.15 mg/kg risdiplam dose is not permitted, unless requested by the Sponsor. As the weight-based dose is 0.15 mg/kg, the total administered dose should be adjusted based on body weight changes.

DURATION OF PARTICIPATION

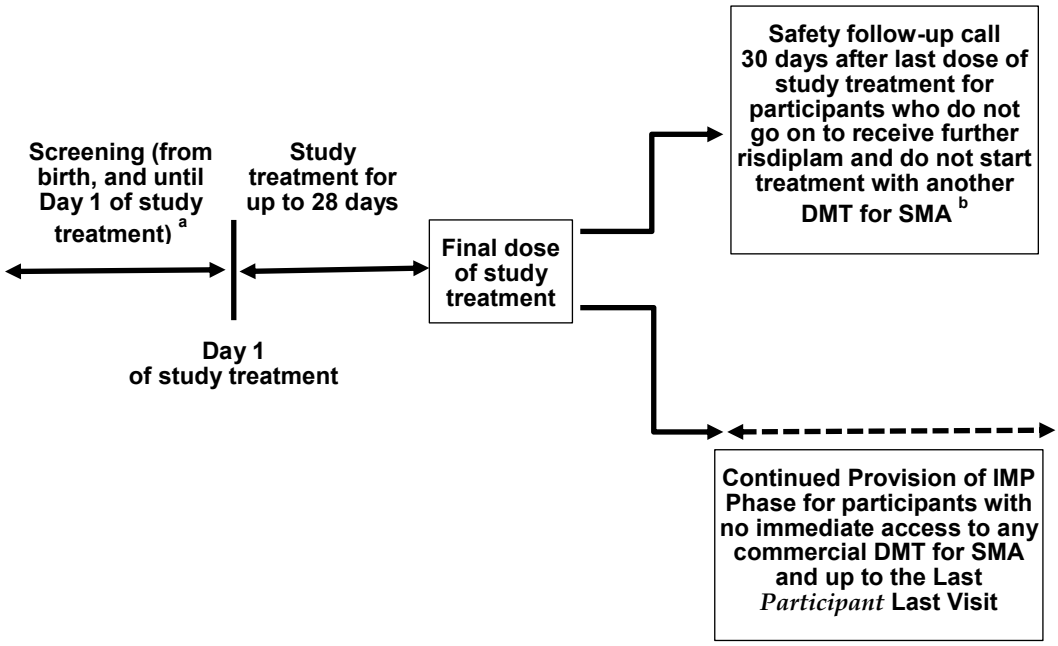
The total duration of study participation for each individual is expected to be a maximum of 2 months (28 days of study treatment and 30 days of safety follow-up, if applicable). The duration of study participation may be longer for participants who enter the Continued Provision of IMP Phase.

COMMITTEES

Independent Committees:	Not applicable
Other Committees:	Not applicable

1.2 STUDY SCHEMA

Figure 1 Study Schema



DMT = disease-modifying therapy; IMP = investigational medicinal product; SMA = spinal muscular atrophy.

[a] Informed consent must be obtained prior to first study screening assessment, and may be signed after prenatal diagnosis and before participant's birth.

[b] Safety follow-up is only applicable if a participant stops treatment with risdiplam prior to or *on* Day 28, AND does not go on to receive further risdiplam (through commercial access or through the Continued Provision of IMP Phase) AND if they do not commence treatment with another DMT for SMA.

1.3 SCHEDULE OF ACTIVITIES

Table 1 Schedule of Activities

Day(s) (Window)	Protocol Reference	Screening	Treatment					Early Withdrawal [b]	Safety Follow-Up [c]
		From birth up to Day 1	1	2	5	10 (±1)	28 (±2) (Study Completion [a])		
Site visit [d]		x	x	x	x	x	x	x	
Phone call									x
Informed consent [e]	8	x							
Demographics	8	x							
Medical history and baseline conditions [f]	8	x							
Vital signs [q]	8.2.3	x	x		x	x	x	x	
Weight [q]	8.2.2	x	x		x	x	x	x	
Height	8.2.2	x					x	x	
Physical examination [q]	8.2.1	x					x	x	
Single 12-lead ECG	8.2.4	x	x				x	x	
Hematology [g, q]	8.2.5 Appendix 2	x			x		x	x	
Chemistry [g, q]	8.2.5 Appendix 2	x				x	x	x	
Study medication administration	6.1		x [h]	Daily [i]					
Study medication dispensation/return [j]			x	x	x				
Diary of time of drug administration				Daily [i]					

Table 1 Schedule of Activities (cont.)

Day(s) (Window)	Protocol Reference	Screening	Treatment					Early Withdrawal [b]	Safety Follow-Up [c]
		From birth up to Day 1	1	2	5	10 (±1)	28 (±2) (Study Completion [a])		
Plasma PK sample [g, k]	8.4		1 [l]	1 [m]	2 [n]	2 [n]	2 [n]		
PPB [g, k, o]	8.4.1	x	x						
Prior/Concomitant medications [q, r]	6.8	x	x						
Adverse events [p]	8.3 Appendix 3 Appendix 4	x	x						

Table 1 Schedule of Activities (cont.)

DMT = disease-modifying therapy; eCRF = electronic Case Report Form; PPB = plasma protein binding; PK = pharmacokinetic; SMA = spinal muscular atrophy.

Notes: On study visit days, all assessments should be performed prior to administration of study medication, unless otherwise specified. Priority should be given to the timing of PK sampling. Refer to the cited protocol reference for activity specific details.

Unscheduled visits may be performed if clinically indicated. Assessments may be performed as clinically indicated, per investigator discretion.

[a] Participants who complete the treatment period (Day 28) will attend the Day 28/Study Completion visit.

[b] Participants who discontinue study treatment prematurely (i.e., before Day 28) will attend an Early Withdrawal visit. This can be merged with a scheduled visit or can take place as a separate Early Withdrawal visit. For separate Early Withdrawal visits: 1) if occurring >7 days after the previous site visit, the visit should be performed in full; 2) if occurring <7 days after the previous site visit only those assessments that have not been performed within the last 7 days must be repeated (however, no PK sample will be taken at the Early Withdrawal visit).

[c] The Safety Follow-Up telephone call will only be conducted for participants who stop study treatment (on or before Day 28) **and** who do not go on to receive further risdiplam (through commercial access or through the Continued Provision of IMP Phase) **and** who do not commence treatment with another DMT for SMA. For eligible participants, the Safety Follow-Up telephone call will occur 30 days after the last dose of study treatment.

[d] Home visits may be scheduled as appropriate for drug dispensation to ensure drug supply for the participant, return of unused drug and supplies, and any unscheduled assessments (or scheduled assessments, in exceptional circumstances).

[e] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained after prenatal diagnosis and before participant's birth. Where applicable, the person who may breastfeed the infant at any time during the study will be asked to sign a separate Study Partner informed consent in order to be able to collect information on concomitant medications taken by the person breastfeeding during the study (see Section 8).

[f] Data on medical history and baseline conditions obtained prior to informed consent may be used; such assessments do not need to be repeated for screening.

[g] The total blood volume that is permitted to be collected should not exceed 0.8 mL/kg at any timepoint, or 2.4 mL/kg over any 4-week period (PK samples will be given priority over any other sample, see Section 8.2.5). Additional blood samples (safety or PK) may be taken if required for safety reasons.

[h] First dosing (Day 1) at site once all eligibility criteria are met and Site has received approval/green light from the study team. Precise clock time to be recorded in the eCRF.

Table 1 Schedule of Activities (cont.)

[i] Oral administration once daily in the morning when at home. The time of drug administration will be entered into the diary daily. The diary will be examined at each site visit for completeness. On site visit days (Days 2, 5, 10, and 28), participants will be given study treatment at site and should not be given study treatment at home that day. See Section 6.1 for details. Precise clock time to be recorded in the eCRF. At applicable sites, in exceptional circumstances, study treatment may be administered by a trained nursing professional at the participant's home or another suitable location, if the caregiver has given written informed consent to participate in mobile nursing visits.

[j] At Day 28/Study Completion visit or Early Withdrawal visit, used and unused study drug bottles are to be returned. Further risdiplam may be dispensed for participants eligible for the Continued Provision of IMP Phase (see Section 4.1.1).

[k] The PPB sample obtained prior to first dose of study medication and the PK samples obtained on Days 1, 2, 5, 10, and 28 will be shipped as soon as possible for analysis (refer to the laboratory manual for more details).

[l] The PK sample should be collected 4 hours postdose (precise clock time to be recorded in the eCRF).

[m] The PK sample should be collected 24 hours after the first dose and prior to receipt of the second dose of risdiplam (precise clock time to be recorded in the eCRF).

[n] The PK samples should be collected predose and between 2 to 4 hours postdose (precise clock time to be recorded in the eCRF).

[o] The PPB sample may be collected at screening **or** on Day 1 prior to first dose of study treatment if unable to collect at screening.

[p] After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study treatment, all adverse events will be reported until 1) 30 days after the final dose of study treatment (unless the participant has received another DMT for SMA, in which case adverse event reporting for risdiplam should stop at the point when the participant receives their first dose of DMT), or 2) the participant exits the Continued Provision of IMP Phase. After the adverse event reporting period ends, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior exposure to study drug (see Section 8.3.1). In the Continued Provision of IMP Phase, investigators should proactively contact the participants every 8 weeks to ensure adverse events are reported in the eCRF and document this contact in the patient notes.

[q] At participating sites, for participants whose caregiver has provided written informed consent to participate in mobile nursing visits, this assessment or procedure may be performed in exceptional circumstances by a trained nursing professional at the participant's home or another suitable location.

[r] Concomitant medications will be recorded for the infant participating in the study, and if applicable, for the person breastfeeding the participant.

2. INTRODUCTION

2.1 STUDY RATIONALE

The purpose of this study is to generate pharmacokinetic (PK) and safety data on the use of risdiplam treatment in patients with *spinal muscular atrophy* (SMA) under 20 days of age at first dose. Spinraza® (nusinersen) and Zolgensma® (onasemnogene abeparvovec) are currently approved for patients with SMA from birth. Despite the availability of these therapies, there remains an unmet medical need for additional treatment options for newborn patients, especially when considering prompt treatment initiation to prevent irreversible motor neuron loss and disease progression. There is currently limited risdiplam data in newborn patients. Thus, this study seeks to extend the characterization of the PK and safety profile in newborns.

2.2 BACKGROUND

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. The timing of therapeutic intervention is crucial since 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).

Risdiplam (Evrysdi®), also known as RO7034067, is the first orally administered small molecule *SMN2* (survival of motor neuron 2) splicing modifier developed for the treatment of SMA. It directly targets the underlying molecular deficiency of the disease, promoting the inclusion of exon 7 to generate full length *SMN2* pre-messenger ribonucleic acid and thereby increasing the production of functional SMN protein.

Spinraza (nusinersen) and Zolgensma (onasemnogene abeparvovec) are approved for the treatment of SMA in patients from birth. Both therapies are subject to limitations of route and/or setting of administration, and safety risks associated with route of administration and/or required concomitant medication. There is a crucial and narrow window of opportunity for optimal efficacy of any SMA treatment in neonates and young infants up to 2 months of age who are expected to present with a severe phenotype. Thus, the option of an oral therapy with an easy and sustainable at-home administration schedule and a favorable safety profile should be available to physicians and parents/caregivers as soon as possible, to support an early treatment plan for a life-long disease.

Risdiplam is approved for the treatment of SMA.

Detailed information on risdiplam is provided in the Risdiplam Investigator's Brochure.

2.3 BENEFIT–RISK ASSESSMENT

The purpose of this study is to assess the pharmacokinetics and safety of risdiplam in patients with SMA from birth to less than 20 days of age at first dose.

Risdiplam has a high therapeutic benefit across populations with infantile onset (Type 1) SMA and later-onset (Type 2 and 3) SMA, as demonstrated in Study BP39056 (FIREFISH) and Study BP39055 (SUNFISH), respectively (Baranello et al. 2021; Darras et al. 2021; Mercuri et al. 2022). In addition, Study BN40703 (RAINBOWFISH) is evaluating the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in patients with presymptomatic SMA up to 6 weeks of age; preliminary efficacy data indicate patients treated with risdiplam are achieving important motor milestones and developing high levels of motor function.

The favorable safety and tolerability profile supports the use of risdiplam in patients with SMA. Preliminary safety data from Study BN40703 (RAINBOWFISH) showed that risdiplam is well-tolerated in infants commencing risdiplam treatment between 16 days and 6 weeks of age.

The following are identified risks for risdiplam: diarrhea; rash; cutaneous vasculitis. These risks will be monitored throughout the study through adverse event monitoring.

The following are potential risks for risdiplam: embryo-fetal toxicity; effects on male germ cells; visual impairment due to retinal toxicity, effects on epithelial tissues and effects on hematological parameters. Embryo-fetal toxicity and effects on male germ cells are not relevant in this prepubertal population to be included in the present study. Risk of retinal toxicity is not expected following short-term treatment, as shown in 483 patients in clinical trials with risdiplam to date. Given the short duration of treatment in this study, no effects on the retina are expected and therefore specific ophthalmological monitoring is not required. The open-label extension phase of the pivotal trials is ongoing to explore effects of long-term exposure to risdiplam on the retina. Effects on epithelial tissues and hematological parameters will be monitored closely throughout the study.

Refer to Appendix 4 for information on anticipated risks for risdiplam and risk mitigation measures, including guidelines for managing adverse events associated with risdiplam.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of risdiplam may be found in the Risdiplam Investigator's Brochure and prescribing information.

Taking into account the existing efficacy, safety and PK data in infants with presymptomatic SMA or Type 1 SMA and infants, children and adults with Type 2 and 3 SMA, the benefit–risk ratio is acceptable for risdiplam in patients with SMA under 20 days of age at first dose.

3. OBJECTIVES AND ENDPOINTS

This study will evaluate the pharmacokinetics and safety of risdiplam in $patients$ with SMA under 20 days of age at first dose. Table 2 presents the objectives and corresponding endpoints.

Table 2 Objectives and Endpoints

Primary Objectives	Corresponding Endpoints
• To characterize the risdiplam PK profile	• Plasma concentration of risdiplam and metabolite(s) as applicable at specified timepoints • AUC • Concentration at the end of a dosing interval to assess steady state • Other PK parameters as appropriate • Risdiplam free fraction
• To evaluate the safety of risdiplam	• Incidence and severity of adverse events, with severity determined according to the NCI CTCAE v5.0 • 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 • Physical examination, including detailed examination of the skin and mouth

AUC = area under the concentration-time curve; NCI CTCAE v5.0 = National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0; PK = pharmacokinetic.

4. STUDY DESIGN

4.1 OVERALL DESIGN

The study is a non-randomized, open-label, single-arm interventional study to investigate the pharmacokinetics and safety of risdiplam in patients with SMA aged <20 days at first dose. Approximately 10 patients with SMA are planned to be enrolled with a minimum of 3 participants aged <7 days.

- For patients aged <7 days, recruitment will remain open until a minimum of 3 participants are enrolled.
- For patients aged ≥ 7 days, recruitment will remain open for a target of 7 participants to enroll. Recruitment to this age group may close earlier if recruitment to the younger age group is expanded or completed, and/or upon Sponsor review of PK data.

The recruitment target may be adjusted based on review of PK data; however, recruitment will not exceed 15 participants.

Participants will be recruited at sites in the United States, Europe, and Canada.

The primary objectives are to evaluate the PK profile of risdiplam (plasma concentration and other PK parameters as appropriate) and the safety of risdiplam (see Table 2).

A study schema is provided in Section 1.2 (see Figure 1). A schedule of activities is provided in Section 1.3 (see Table 1).

The study will be comprised of the following phases:

- **Screening:** Informed consent must be obtained prior to first study screening assessment and may be obtained after prenatal diagnosis and before participant's birth. Screening runs until Day 1 when the participant receives the first dose of risdiplam. Screening assessments may be repeated before enrollment to confirm eligibility. Rescreening is permitted.
- **Treatment**: During the treatment phase, all participants will receive risdiplam orally once daily for 4 weeks at a dose of 0.15 mg/kg (however, the dose may be adjusted during the study upon review of PK data). The treatment period will end on Day 28 with a Day 28/study completion visit. Alternatively, if the participant discontinues treatment before Day 28, they will attend an early withdrawal visit.
- **Follow-up**: A safety follow-up telephone call will only be conducted for participants who stop study treatment (on or before Day 28) AND who do not go on to receive further risdiplam (through commercial access or through the Continued Provision of Investigational Medicinal Product [IMP] Phase [see Section 4.1.1]) AND who do not start treatment with another disease-modifying therapy (DMT) for SMA. For eligible patients, the safety follow-up telephone call will occur 30 days after the last dose of study treatment.

4.1.1 Continued Provision of Investigational Medicinal Product Phase

Upon completion of Day 28, participants with no immediate access to any commercial DMT for SMA may continue to receive risdiplam in a Continued Provision of IMP Phase until the end of study at the latest, defined as the last participant's last visit (see Section 4.4).

These participants continuing to receive risdiplam after Day 28 are not required to attend additional study visits. Risdiplam will be provided as per current study procedures. Only adverse events must continue to be reported to maintain study safety reporting requirements. Therefore, Investigators should proactively contact those participants every 8 weeks (if the participant is still in the study) to ensure adverse events are reported in the electronic Case Report Form (eCRF) and document this contact in the patient notes.

Once a participant gains access to any commercial DMT, the participant will leave the study.

4.2 RATIONALE FOR STUDY DESIGN

This is an open-label study. A placebo-control group will not be included in this study. Per published recommendations for the treatment of infants diagnosed with SMA via newborn screening (Glascock et al. 2018, Glascock et al. 2020), the working group's consensus was to immediately treat patients with 1–4 *SMN2* copies; it is therefore not ethical to treat patients with SMA with placebo, considering that early treatment can provide the maximal therapeutic benefit. The open-label design is considered justified in the context of the study objectives which are to assess pharmacokinetics and safety. The efficacy of risdiplam in SMA has already been demonstrated in other risdiplam clinical trials.

4.2.1 Rationale for Study Population

The study will include patients with SMA aged <20 days at first dose with the main objectives being pharmacokinetics and safety evaluation. The age range (from birth to <20 days of age at first dose) reflects the population for which no PK data have yet been generated in other ongoing risdiplam studies at the therapeutic dose. Therefore, the selected population in this study was chosen in order to complete the PK assessment of risdiplam in all pediatric age groups across the risdiplam development program.

4.3 JUSTIFICATION FOR DOSE AND SCHEDULE

The *starting* dose *of risdiplam* administered *for all participants* in this study will be *based on risdiplam PK data obtained from the risdiplam clinical studies conducted in participants aged ≥16 days and from modeling and simulation* (*see* Table 3).

Table 3 Risdiplam Dosing Regimen

Age and Body Weight	Recommended Daily Dosage
Less than 2 months of age	0.15 mg/kg
2 months to less than 2 years of age	0.20 mg/kg
2 years of age and older weighing less than 20 kg	0.25 mg/kg
2 years of age and older weighing 20 kg or more	5 mg

Pharmacokinetics will be assessed *on* Days 1, 2, 5, 10 and 28 in all participants, to confirm that the 0.15 mg/kg dose reaches the targeted exposure. In case the observed exposure deviates significantly from the expected range, the dose may be adjusted for all or individual participants in this study upon ongoing review of the PK data by the Sponsor Clinical Pharmacologist.

Dose adjustments between the scheduled visits based on a change in body weight are allowed (e.g., if weight change is >10%). The body weight used to perform the dose calculation between visits should be taken at site (e.g., by bringing the patient in for an unscheduled visit). Dose adjustments may only be performed by the site and cannot be made by the parent/caregiver themselves.

Plasma protein binding (i.e., free fraction) of risdiplam will be measured in all participants from a sample taken prior to the first dose of study treatment with an in vitro assay. Should the measured free fraction in participants in this study deviate significantly from the free fraction observed in older infants and children, the dose may be adjusted for this difference.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he or she has completed all phases of the study, including:

- The Study Completion or Early Withdrawal visit, AND the safety follow-up telephone call (for participants who do not go on to receive further risdiplam through commercial access or through the Continued Provision of IMP Phase AND who do not start treatment with another DMT for SMA); OR
- The Study Completion or Early Withdrawal visit (for participants who gain access to a commercial DMT for SMA);

  OR
- The Study Completion visit and until the participant exits the Continued Provision of IMP Phase.

The end of this study is defined as the date of the last visit/telephone call of the last participant in the study as outlined above.

See Section 6.6 for conditions regarding post-trial access to risdiplam.

4.5 DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be a maximum of 2 months (28 days of study treatment, and 30 days of safety follow-up, if applicable).

The duration of study participation may be longer for participants who enter the Continued Provision of IMP Phase.

5. STUDY POPULATION

A total of 10 patients with SMA are planned to be enrolled with a minimum of 3 participants aged <7 days. The recruitment target may be adjusted based on review of PK data; however, recruitment will not exceed 15 participants.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Potential participants are eligible to be included in the study only if all of the following criteria apply:

- Signed Informed Consent Form by a legally authorized representative for the participant in accordance $with$ International Council on Harmonisation (ICH) and local regulations
- Male or female newborn infant aged <20 days at first dose
- Newborn infants with genetic diagnosis of 5q-autosomal recessive SMA

  OR

  Newborn infants identified as positive for SMA via newborn screening or via prenatal testing. These infants can be enrolled in the study and initiate study treatment while pending confirmatory genetic test results, if clinically indicated per investigator's judgment
- Gestational age $\geq$37 weeks
- 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 $with$ the frequency of required study visits, in the opinion of the investigator
- Able to complete all study procedures, measurements, and visits, and the parent/caregiver, in the opinion of the investigator, has adequately supportive psychosocial circumstances
- Parent/caregiver is willing to consider nasogastric, nasojejunal, or gastrostomy tube placement during the study to maintain safe hydration, nutrition, and treatment delivery, if recommended by the investigator

5.2 EXCLUSION CRITERIA

Potential participants are excluded from the study if any of the following criteria apply:

- Concomitant or previous participation in any investigational drug or device study at any time
- Presence of clinical symptoms or signs consistent with SMA Type 0, such as generalized hypotonia and weakness, significant respiratory compromise or bulbar impairment or severe contractures at birth
- In the opinion of the investigator, inadequate venous or capillary blood access for the study procedures

- Systolic blood pressure or diastolic blood pressure or heart rate abnormalities considered to be clinically significant by the investigator
- Presence of clinically relevant ECG abnormalities before study drug administration; corrected QT interval using Bazetts 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 (or the person 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 and including food or drinks known to modulate CYP3A activity (e.g., Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices)
  - 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 multidrug and toxin extrusion (MATE) substrates taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing
- Concurrent or previous administration of nusinersen or onasemnogene abeparvovec
- 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)
- Any serious medical condition that, in the investigator's judgment, precludes an individual's safe participation in and completion of the study

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

The study has the following meal and dietary restrictions:

- Participants (and if breastfed, the person breastfeeding the infant) should refrain from the consumption of Seville oranges, grapefruit or grapefruit juice, pomelos, exotic citrus fruits, grapefruit hybrids, or fruit juices until the final dose of study treatment.

Breastfeeding of the infant is allowed if the person breastfeeding the infant is not consuming any prohibited medications (see Section 6.8.4). Breastfeeding should be avoided within 1 hour after study drug administration. The person breastfeeding the infant will be advised to rinse their breasts with water if breastfeeding occurs shortly after (i.e., $<$1 hour) study drug administration.

5.3.2 Caffeine, Alcohol, and Tobacco

Participants (and if breastfed, the person breastfeeding the infant) should abstain from alcohol, caffeine, or tobacco consumption.

5.3.3 Activity

This study has no activity restrictions.

5.3.4 Contraception Requirements

Contraception requirements are not applicable in this study population.

5.4 SCREEN FAILURES

Individuals who do not meet the criteria for participation in this study (screen failure) may qualify for re-screening opportunities (for a total of 2 screenings per individual) at the investigator's discretion. Parents/caregivers must re-sign the consent form prior to re-screening. The investigator will maintain a record of reasons for screen failure (see Section 8).

6. STUDY TREATMENT, OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN, AND CONCOMITANT THERAPY

The IMP for this study is risdiplam. *Appendix 6 identifies all IMPs for this study.*

6.1 STUDY TREATMENT ADMINISTERED

Table 4 provides a description of assigned study treatment for this study.

Table 4 Study Treatment Description

	Risdiplam
Use	Experimental
Drug form	Powder for constitution to an oral solution
Unit dose strength	0.75 mg/mL
Dosage level	0.15 mg/kg once daily [a]
Formulation	Refer to pharmacy manual and/or Investigator's Brochure
Packaging	60 mg/80 mL (0.75 mg/mL) glass bottle
Labeling	Per local requirements
Route of administration	Orally (via mouth) or via a nasogastric or gastrostomy tube
Source	Sponsor

[a] The dose may be adjusted for all or individual participants in this study upon ongoing review of the PK data by the Sponsor Clinical Pharmacologist.

Throughout the study, the study drug (risdiplam) should be given orally once daily in the morning, except when site visits are planned and study medication will be administered at the clinical site. On site visit days (Days 2, 5, 10, and 28), participants will be given study treatment at site and should not be given study treatment at home that day. In participants able to swallow, study drug will be administered with a syringe inserted between gum and cheek of the participant as described in the study drug administration instructions for use. The participant should be fed prior to dosing. In the case of breastfeeding, the participant 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 participant's bottle or dispenser to prevent prolonged contact of study drug with buccal mucosa. Similarly, the peribuccal area of the participant will be washed with water in case of drug drooling or spitting. Breastfeeding should be avoided within 1 hour after study drug administration. Participants unable to swallow the study medication and who have a nasogastric or gastrostomy tube in situ should receive the study medication by bolus via the tube. Refer to the Study Drug Administration Instructions for Use. Any change in route of administration should be noted on the Study Drug Administration eCRF.

If a parent/caregiver does not administer the dose at the regular time, but realizes prior to 12:00 (noon) local time, they should administer the regular dose at that time. If a parent/caregiver realizes a missed administration only after 12:00 (noon) local time, this will be considered a missed dose and parent/caregiver should 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.

At applicable sites, in exceptional circumstances, study treatment may be administered by a trained nursing professional at the participant's home or another suitable location, if

the patient has given written informed consent to participate in mobile nursing (MN) visits.

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 Appendix 3.

Guidelines for treatment interruption or discontinuation for participants who experience adverse events are provided in Appendix 4.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

All IMP required for completion of this study will be provided by the Sponsor. The study site (i.e., investigator or other authorized personnel e.g., pharmacist or mobile nurse) is responsible for maintaining records of IMP delivery to the site, IMP inventory at the site, IMP use by each participant, and disposition or return of unused IMP, thus enabling reconciliation of all IMP received, and for ensuring that participants are provided with doses specified by the protocol.

The study site should follow all instructions included with each shipment of IMP. The study site will acknowledge receipt of IMP supplied by the Sponsor by completing the appropriate documentation form to confirm the shipment condition and content. Any damaged shipments will be replaced. The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit, either by time monitoring (shipment arrival date and time) or temperature monitoring, for all IMP received and that any discrepancies have been reported and resolved before use of the IMP. All IMP must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the investigator and authorized staff.

Only participants enrolled in the study may receive IMP, and only authorized staff may supply or administer IMP.

IMP 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 with the appropriate documentation. The site's method of destroying Sponsor-supplied IMP 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 IMP received at, dispensed from, returned to, and disposed of by the study site should be recorded on the drug accountability log.

Refer to the pharmacy manual and/or the Risdiplam Investigator's Brochure for information on IMP preparation, storage, handling, and accountability.

6.3 TREATMENT ASSIGNMENT

This is an open-label study, and all patients will receive risdiplam. There is no interactive voice or web-based response system in this study. Details regarding enrollment and allocation of patient number (including any rescreening procedures) are described in the site manual. The process for drug supply will be described in the pharmacy manual.

6.4 STUDY TREATMENT COMPLIANCE

When participants are dosed at the site, they will receive study treatment directly from the investigator or designee, under medical supervision. The dose of study treatment and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study treatment. Details on treatment administration (e.g., dose and timing) should be noted in the source documents and on the Study Drug Administration eCRF.

When participants receive study treatment at home administered by parent/caregiver, compliance with study treatment will be assessed. A Patient Medication Diary will be provided to the parent/caregiver with instructions on study drug administration at home. The date and time of drug administration, the route of administration and the ingested volume will be entered into the Patient Medication Diary by the participant's parent/caregiver for all doses throughout the study. The diary will be examined at each site visit for completeness by the investigator or designee and information will be reported in the Study Drug Administration eCRF.

All bottles and unused drug and drug supplies will be returned to the site during a study visit or collected during a home visit.

Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Appendix 3.

6.5 DOSE MODIFICATION

Modification of the 0.15 mg/kg risdiplam dose is not permitted, unless requested by the Sponsor.

As the weight-based dose is 0.15 mg/kg, the total administered dose should be adjusted based on body weight changes. Body weight must be measured at the site (see Section 8.2.2) or, in exceptional circumstances, at home or in a local clinic.

6.6 CONTINUED ACCESS TO STUDY TREATMENT AFTER THE END OF THE STUDY

The Sponsor will offer continued access to Roche IMP (risdiplam) free of charge to eligible participants in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Roche IMP (risdiplam) after completing the study if all of the following conditions are met:

- The participant 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 participant.
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them.

A participant 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 participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant).
- 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 a treatment for SMA.
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant'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

6.7 TREATMENT OF OVERDOSE

An overdose is the administration of a drug in a quantity that is higher than the assigned dose. There is no known antidote for treating an overdose. Cases of overdose, along with any associated adverse events, should be reported as described in Appendix 3.

In the event of an overdose, the investigator should take the following steps:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any adverse event or serious adverse event and laboratory abnormalities until resolution of the event or normalization of the laboratory abnormality.

6.8 CONCOMITANT THERAPY

Any concomitant medication (including over-the-counter or prescription medicines, vitamins, vaccines and/or herbal supplements) used by a participant in addition to protocol–mandated treatment from birth up to the safety follow-up telephone call must be recorded on the Concomitant Medications and associated eCRF(s) along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.1 Concomitant Therapies Taken by Persons Breastfeeding

Any concomitant medication (including over-the-counter or prescription medicines, vitamins, vaccines and/or herbal supplements) taken by the person breastfeeding the infant during the study, up to the safety follow-up telephone call must be recorded on the Concomitant Medications and associated eCRF(s) along with the following information:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor may be consulted if there are any questions related to concomitant or prior therapy.

6.8.2 Permitted Therapy

Use of concomitant therapies not listed in Section 6.8.4 is permitted, per investigator's judgment.

6.8.3 Medications Given with Precaution due to Effects Related to CYP Enzymes

Risdiplam is a weak inhibitor of CYP3A. A small, but clinically not relevant, interaction was observed in adult subjects (increase in area under the concentration-time curve [AUC] 11% and maximum plasma concentration observed [C_{max}] 16%). Based on physiologically-based PK modeling, a similar magnitude of the effect is expected in children and infants as young as age 2 months. Caution should be applied for coadministration of risdiplam and CYP3A substrates in infants age $<$2 months, 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.

6.8.4 Prohibited Therapy

Use of the following concomitant therapies is prohibited for participants (and, if applicable, for the person breastfeeding the infant) as described below, to limit confounding PK and safety results:

- Investigational therapy from birth and during study treatment
- Nusinersen or onasemnogene abeparvovec from birth and during study treatment
- Any inhibitor of CYP3A4 taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to first dosing and during study treatment, 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 first dosing and during study treatment, including but not limited to: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John's wort
- Any MATE substrates, such as metformin taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to first dosing and during study treatment

In breastfed infants, the person breastfeeding the infant should not take any medications prohibited during breastfeeding.

7. DISCONTINUATION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

Study and site closure is described in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

It may be necessary for a participant to permanently discontinue (definitive discontinuation) study treatment. If study treatment is definitively discontinued, the participant will remain in the study for additional assessments. Refer to the schedule of activities (see Section 1.3) for data to be collected at the time of discontinuation of study treatment and for any further follow-up evaluations that need to be completed.

Participants must permanently discontinue study treatment if any of the following criteria are met:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant'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 participant
- Participant commences treatment with a DMT for SMA other than risdiplam
- Any event that meets stopping criteria defined in A4–2.2

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Participants who discontinue study treatment prematurely (i.e., before Day 28) will attend the clinic for an Early Withdrawal visit. This can be merged with a scheduled visit or can take place as a separate visit. For separate Early Withdrawal visits: if occurring >7 days after the previous site visit, the visit should be performed in full. If participants return for Early Withdrawal visit, only those assessments that have not been performed within the last 7 days must be repeated (however, no PK sample will be taken at the Early Withdrawal visit).

For participants who discontinue study treatment prematurely, a safety follow-up telephone call will only be conducted for participants who do not go on to receive further risdiplam (through commercial access or through the Continued Provision of IMP Phase) AND who do not commence treatment with another DMT for SMA. For eligible participants, the safety follow-up telephone call will occur 30 days after the last dose of study medication.

Refer to the schedule of activities in Section 1.3 (see Table 1) for details on follow-up assessments to be performed for participants who permanently discontinue study treatment. If a participant's parent/caregiver requests the participant to be withdrawn from treatment or follow-up assessments, this request must be documented in the source documents and signed by the investigator.

7.2 PARTICIPANT DISCONTINUATION OR WITHDRAWAL FROM THE STUDY

The parent/caregiver may withdraw the participant from the study at any time at his or her own request or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons.

The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant's parent/caregiver requests the participant to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator.

At the time of discontinuing from the study, if possible, an early withdrawal visit should be conducted, as shown in the schedule of activities (see Section 1.3). Refer to the schedule of activities for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

The participant will be permanently discontinued both from the study treatment and from the study at that time.

If a parent/caregiver withdraws consent from the study, the Sponsor may retain and continue to use any data collected before withdrawal of consent. Samples collected prior to withdrawal may be analyzed, unless the parent/caregiver specifically requests that the samples be destroyed (as documented in the source documents) 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.

If a participant commences treatment with another DMT for SMA, the participant will be withdrawn from the study.

7.3 PARTICIPANTS LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if the parent/caregiver repeatedly fails to return the participant for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the parent/caregiver and reschedule the missed visit as soon as possible and counsel the parent/caregiver on the importance of maintaining the assigned visit schedule. If the participant/caregiver is unable or unwilling to comply with study visits, site personnel should assess reasons the participant/caregiver is unable or unwilling to return to the clinic and determine if there are ways to support participant participation.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the parent/caregiver (where possible, three telephone calls and, if necessary, a certified letter to the parent/caregiver's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the parent/caregiver continue to be unreachable, the participant will be considered lost to follow-up and will be withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled individuals and for individuals who are not subsequently enrolled will be maintained at the study site.

Where applicable, the person who may breastfeed the infant at any time during the study will be asked to sign a separate Study Partner informed consent in order to be able to collect information on concomitant medications taken by the person breastfeeding *the infant* during the study. The Study Partner Consent Form should be signed as soon as possible but is not required to be signed prior to the enrollment of the participant (for example, if the person breastfeeding the infant is not available to sign their consent at

the time of signing the main consent), so as not to delay the enrollment or Day 1 dose for the participant.

Study procedures and their timing are summarized in the schedule of activities (see Section 1.3). Protocol waivers or exemptions are not allowed.

Urgent safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment.

Adherence to the study design requirements, including those specified in the schedule of activities, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a detailed record of all participants screened, to document eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the participant's routine clinical management (e.g., complete blood count) and obtained before signing of the Informed Consent Form may be utilized for screening or baseline purposes provided the procedures meet the protocol-specified criteria and are performed within the timeframe defined in the schedule of activities.

Medical history and baseline conditions, including clinically significant diseases, surgeries, will be recorded at screening. Any medication and/or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) used by the participant or the person breastfeeding the infant from birth prior to initiation of study treatment will be recorded. Demographic data, including age, sex, and parent/caregiver-reported race or ethnicity, will also be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications (for the participant and the person breastfeeding the infant) and allergies should be recorded.

Participants will be closely monitored for safety throughout the study.

At applicable sites, certain study assessments may be performed by a MN professional at the participant's home or another suitable location to improve access and convenience for participants participating in the study. The Sponsor will select a health-care 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 participant and the

participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Section 1.3) will specify the assessments that may be performed by an MN professional.

8.1 EFFICACY ASSESSMENTS

No efficacy assessments will be performed in this study.

8.2 SAFETY ASSESSMENTS

8.2.1 Physical Examinations

A complete physical examination will include, at a minimum, assessments of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. 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.

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.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Changes from abnormalities identified at screening should be recorded in participant notes. New or worsened clinically significant abnormalities i.e., beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF. Limited physical examinations may be performed by an MN professional.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities i.e., beyond expected variation or normal age-related changes should be recorded as adverse events on the Adverse Event eCRF.

8.2.2 Weight and Height

Measurement of weight and height will be measured at timepoints specified in the schedule of activities (see Section 1.3) as described below:

- Body weight must be measured at the site or, in exceptional circumstances, at home or in a local clinic. Body weight will be measured to the nearest 10 g using baby scales, the naked infant being placed centrally on the scales.
  - Any dose calculations based on a change in the participant's body weight should be made using a weight measurement taken at site (e.g., by bringing the participant in for an unscheduled visit). However, if the participant 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.
- Height (or length) will be measured to the nearest centimeter with the infant in lying position using an inflexible length board with fixed headboard and moveable footboard.

In exceptional circumstances, measurement of weight may be performed by an MN professional.

8.2.3 Vital Signs

Oral or tympanic temperature, pulse rate, respiratory rate, and blood pressure will be assessed.

Blood pressure and pulse measurements should be obtained in a quiet room at a comfortable temperature, with the participant positioned in a relaxed (e.g., semi-supine/supine) position with the arms unconstrained by clothing or other material. Measurements will be made with a completely automated device. Manual techniques will be used only if an automated device is not available.

Vital signs (to be taken before blood collection for laboratory tests) will consist of one pulse measurement and one blood pressure measurement.

In exceptional circumstances, temperature, pulse rate, respiratory rate and blood pressure will be assessed by an MN professional.

Any abnormality identified at screening or prior to initiation of study treatment should be recorded on the General Medical History and Baseline Conditions eCRF (unless considered related to a protocol-mandated intervention). After initiation of study treatment, any new or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

8.2.4 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the schedule of activities (see Section 1.3) using an ECG machine that automatically calculates the heart rate and

measures PR interval, QRS interval, QT interval, and QT interval corrected through use of Fridericia's formula (QTcF)/QT interval.

Single 12-lead ECG recordings will be obtained at specified timepoints (see Table 1) and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed on a device that is equipped with reliable, automated algorithms for measuring heart rate and ECG intervals and capable of local printing. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site (see instructions in the Site Manual for further details).

Lead placement should be as consistent as possible. ECG recordings should be performed after the patient has been resting in a supine or semi-supine position for at least 10 minutes, and the patient should remain in a supine or semi-supine position during recording. The same positioning should be maintained for each patient throughout the study. ECG recordings should be performed 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.

Paper copies of all ECG tracings must be reviewed, annotated to indicate any clinical findings, signed, and dated by a medically qualified member of the site staff. For each timepoint, heart rate, RR interval, PR interval, QRS interval, uncorrected QT interval, and QTcF based on machine readings of ECG tracings should be recorded on the appropriate eCRF. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

If at a particular postdose timepoint the QTcF is $>$500 ms or $>$60 ms longer than the baseline value (i.e., last value prior to initiation of study treatment), another ECG must be recorded, ideally within the next 5 minutes, and ECGs should be repeated at least hourly until two successive ECGs show resolution of the findings. A PK sample should be obtained if not already scheduled for that timepoint. Guidelines for management of increases in QT interval are provided in Appendix 4.

8.2.5 Clinical Safety Laboratory Tests

See Appendix 2 for the list of clinical laboratory tests to be performed and to the schedule of activities (see Section 1.3) for the timing and frequency.

In exceptional circumstances, blood samples for safety laboratory tests will be collected by an MN professional.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the Adverse Event CRF (see Appendix 3).

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days of the final dose of study treatment should be repeated until the values return to normal or baseline or are considered to be stable and no longer considered clinically significant by the investigator. If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the Sponsor notified.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., serious adverse event or adverse event or dose modification), the results must be recorded on the eCRF.

Samples collected for safety laboratory tests will be destroyed no later than the time of completion of the final Clinical Study Report.

PK 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.

8.3 ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND OTHER SAFETY REPORTING

The definitions of adverse event and serious adverse event can be found in Appendix 3.

Adverse events will be reported by the participant (or, when appropriate, by a parent/caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an adverse event or serious adverse event and remain responsible for following up adverse events that are serious, are considered related to the study treatment or study procedures, or caused the participant to discontinue the study treatment/study (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

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

(see Appendix 3). All other medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the General Medical History and Baseline Conditions eCRF, not the Adverse Event eCRF.

All adverse events will be reported from the start of treatment until

1. 30 days after the final dose of study treatment (unless the participant has received another DMT for SMA, in which case adverse event reporting for risdiplam should stop at the point when the participant receives their first dose of DMT),

   OR

2. the participant exits the Continued Provision of IMP Phase,

at the timepoints specified in the schedule of activities (see Section 1.3).

All serious adverse events will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The investigator will submit any updated serious adverse event data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek adverse event or serious adverse event information after conclusion of study participation. However, if the investigator learns of any serious adverse event, including a death, at any time after a participant has been discharged from the study, and he or she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of adverse events and serious adverse events and the procedures for completing and transmitting serious adverse event reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting adverse events and/or serious adverse events. Open-ended and non-leading verbal questioning of the participant's parent/caregiver is the preferred method to inquire about adverse event occurrences.

8.3.3 Follow-Up of Adverse Events and Serious Adverse Events

After the initial adverse event or serious adverse event report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All adverse events will be followed until the event has resolved to baseline grade or better, or the event is assessed as stable by the investigator, or the participant is lost to follow-up (as defined in Section 7.3), or the participant's parent/caregiver withdraws consent. Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification (i.e., within 24 hours of awareness) by the investigator to the Sponsor of a serious adverse event is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards or Ethics Committees (IRBs/ECs), and investigators.

For all studies except those utilizing medical devices, investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

To determine reporting requirements for serious adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the document listed below:

Drug	Document
Risdiplam	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.

An investigator who receives an investigator safety report describing a serious adverse event or other specific safety information (e.g., summary or listing of serious adverse events) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5 Cardiovascular and Death Events

Information on reporting deaths is provided in Appendix 3.

8.3.6 Anticipated Events Not Qualifying for Expedited Reporting

Events not qualifying for expedited reporting will not be defined for this study.

8.3.7 Adverse Events of Special Interest

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 the investigator becomes aware

of the event; see Section A3–5 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 A3–7.6)
- Suspected transmission of an infectious agent by a study treatment, 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 participant exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

Descriptions of risks and management of the above-listed adverse events are provided in Appendix 4.

8.3.8 Medical Device Complaints

In this study, dispenser for oral drug administration is considered a medical device. The investigator must report all medical device complaints and any associated adverse events to the Sponsor, as described in Appendix 5.

8.3.9 Medical Monitors and Emergency Medical Contacts

To ensure the safety of study participants access to Medical Monitors is available 24 hours per day, 7 days per week. An Emergency Medical Call Center will also be available 24 hours per day, 7 days per week. The Emergency Medical Call Center will connect the investigator with an Emergency Medical Contact, provide medical translation service if necessary, and track all calls. Contact information, including toll-free numbers for the Emergency Medical Call Center, will be distributed to investigators.

8.4 PHARMACOKINETICS

Blood samples will be collected for measurement of plasma concentration of risdiplam and its metabolite(s) as applicable, as specified in the schedule of activities (see Section 1.3). PK samples will be given priority over any other sample (see Section 8.2.5).

Samples may be collected at additional timepoints during the study if warranted and if the maximal allowable volume of total blood sample collection has not been reached, and agreed upon between the investigator and the Sponsor. The timing of sampling may be altered during the course of the study on the basis of newly available data (e.g., to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

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

Instructions for the collection and handling of biological samples will be provided by the Sponsor. Actual date and time (24-hour clock time) of dosing on the day of PK sampling (and the two preceding dosing occasions) and of each sample collection must be documented in the eCRF.

Samples will be used to evaluate the pharmacokinetics of risdiplam and metabolite(s) as applicable. Samples collected for analyses of risdiplam (plasma) concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study. Plasma concentrations of risdiplam and derived metabolite(s) as applicable will be measured by validated assays, and PK samples may also be used for exploratory metabolite identification or additional validation experiments related to risdiplam PK.

Genetic analyses will not be performed on these plasma samples.

PK samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.

8.4.1 Plasma Protein Binding

A venous blood sample will be collected from all patients prior to the first dose of study treatment (see Section 1.3) to measure plasma protein binding (PPB), i.e., to measure the free fraction of the study drug (see Section 4.3). The blood sample for PPB must not be collected by capillary sampling.

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

8.5 PHARMACODYNAMICS

Pharmacodynamic biomarker assessments will not be performed in this study.

8.6 GENETICS

Genetic biomarker assessments will not be performed in this study.

8.7 BIOMARKER ASSESSMENTS

Biomarker assessments will not be performed in this study.

8.8 IMMUNOGENICITY ASSESSMENTS

Immunogenicity assessments will not be performed in this study.

8.9 HEALTH ECONOMICS AND MEDICAL RESOURCE UTILIZATION

Health economics and medical resource utilization assessments will not be performed in this study.

8.10 ADDITIONAL ASSESSMENTS AND PROCEDURES REQUIRING SEPARATE CONSENT OR PERFORMED ONLY AT PARTICIPATING SITES

Consenting persons who decide to breastfeed the infant at any time during the study will have details of any concomitant medications they take during the study recorded in the study notes and in the eCRF (see Section 6.8.1). In this respect, persons who breastfeed the infant during the study will act as a Study Partner to the infant participant. A separate Study Partner Consent Form will address this. The investigator or authorized designee will explain to the Study Partner the reasons why details of the medications of the person breastfeeding are required to be recorded. The investigator should document whether or not the Study Partner has given consent to collection of details on medications and the date of consent, by completing the eCRF.

9. STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

No formal statistical hypotheses will be tested for this study.

9.1.1 Sample Size Determination

Approximately 10 participants are planned to be enrolled in this study, with at least 3 participants age < 7 days. This sample size was selected based on practical considerations. The PK data will be reviewed throughout the study in an ongoing manner. If the PK data collected are judged sufficient to characterize the pharmacokinetics in this age group, recruitment may be stopped before 10 participants are enrolled. The recruitment target may be adjusted based on review of PK data; however, recruitment will not exceed 15 participants.

If a participant is withdrawn from the study before completing the 28 days of study treatment, they may be replaced, unless the participant was withdrawn for safety reasons.

9.2 ANALYSIS SETS

The participant analysis sets for the purposes of analyses are defined in Table 5.

Table 5 Participant Analysis Sets

Participant Analysis Set	Description
SAS	All participants exposed to study treatment will be included in the analysis data set. Participants will be analyzed according to the treatment that they actually received.
PKAS	All patients with at least one timepoint with a measurable drug concentration will be included in the analysis data set. Patients will only be excluded from the analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable, not plausible, or incomplete that may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion.

PKAS = pharmacokinetic analysis set; SAS = safety analysis set.

9.3 STATISTICAL ANALYSES

All results will be summarized using descriptive statistics.

9.3.1 Estimation Methods for the Primary Endpoints

All pharmacokinetic parameters will be summarized with descriptive statistics.

Safety will be assessed through summaries of exposure to study treatment, adverse events, changes in laboratory test results, and changes in vital signs and ECGs.

Study treatment exposure (such as treatment duration, total dose received, dose modifications) will be presented in listings and summarized with descriptive statistics.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities thesaurus terms, and adverse event severity will be graded according to National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] (NCI CTCAE) v5.0. All adverse events, serious adverse events, adverse events leading to death, adverse events of special interest, and adverse events leading to study treatment discontinuation that occur on or after the first dose of study treatment (i.e., treatment–emergent adverse events) will be summarized by mapped term, appropriate thesaurus level, and severity grade. For events of varying severity, the highest grade will be used in the summaries. Deaths and cause of death will be presented in listings.

Relevant laboratory, vital sign (pulse rate, respiratory rate, blood pressure, pulse oximetry, and temperature), and ECG data will be displayed by time, with grades identified where appropriate. Additionally, a shift table of selected laboratory tests will be

used to summarize the baseline and maximum postbaseline severity grade. Changes in vital signs and ECGs will be summarized.

9.3.1.1 Summaries of Conduct of Study

Enrollment, study treatment administration, and discontinuation from the study will be summarized. The reasons for study treatment discontinuation will also be presented in listings and tabulated. Major protocol deviations, including major deviations with regard to the inclusion and exclusion criteria, will be summarized.

9.3.1.2 Summaries of Demographics and Baseline Characteristics

Demographics and baseline characteristics (including but not limited to: age, sex, birth weight) will be summarized. Baseline data are the last data obtained prior to initiation of study treatment. Descriptive statistics (mean, standard deviation, median, and range) will be presented for continuous variables and counts and percentages will be presented for categorical variables.

9.3.1.3 Pharmacokinetic Analyses

All PK parameters will be presented by listings and descriptive summary statistics.

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 and body weight) on these parameters will be investigated. 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.

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Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

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A1–1 REGULATORY AND ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable International Council for Harmonisation (ICH) E6 guideline for Good Clinical Practice
- Applicable laws and regulations.

The protocol, Informed Consent Forms, Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board or Ethics Committee (IRB/EC) by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any substantial amendments to the protocol will require IRB/EC and health authority approval (as locally required) before implementation of changes, with the exception of administrative changes or changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- 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
- Notifying the IRB/EC of serious adverse events or other significant safety findings, as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and ensuring adherence to requirements of 21 CFR (U.S. sites only), the ICH Guideline for Good Clinical Practice, the IRB/EC, Clinical Trials Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) (EEA sites only), and all other applicable local regulations

A1–2 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 study and for 1 year after completion of the study (see definition of end of study in Section 4.4).

A1–3 INFORMED CONSENT PROCESS

The investigator or authorized designee will explain the nature of the study, including the risks and benefits, to the participant or his or her legally authorized representative and the study partner and answer all questions regarding the study.

Participants and the study partner must be informed that their participation is voluntary. Participants or their legally authorized representative and the study partner will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50 (U.S. sites only), the ICH Guideline for Good Clinical Practice, and the IRB/EC.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the Informed Consent Form.

If the Informed Consent Forms are revised (through an amendment or an addendum) to communicate information that might affect a participant's or study partner's willingness to continue in the study, the participant or the participant's legally authorized representative or the study partner must re-consent by signing the most current version of the Informed Consent Form or the addendum, in accordance with applicable laws and IRB/EC policy.

A copy of each Informed Consent Form must be provided to the participant or the participant's legally authorized representative and the study partner.

A1–4 DATA PROTECTION

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; the participant's name or any information that would make the participant identifiable will not be transferred.

Participants and study partners must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to participants and study partners, who will be required to give consent for their data to be used as described in the Informed Consent Form.

Participants must be informed that their medical records may be examined by auditors or other authorized individuals representing the Sponsor or Sponsor collaborators and licensees, by appropriate IRB/EC members, and by inspectors from health authorities.

A1–5 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.

U.S., *Canada*, and/or E.U. sites will participate to enroll approximately 10 participants (the recruitment target may be adjusted based on review of PK data; however, recruitment will not exceed 15 participants).

Central facilities will be used for certain assessments throughout the study (e.g., PK analyses), as specified in Section 8. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

A1–6 DISSEMINATION OF CLINICAL STUDY DATA

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/or other summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and will be provided upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

A1–7 DATA QUALITY ASSURANCE

All participant and study partner data relating to the study will be recorded on printed or electronic Case Report Forms (CRFs) unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of non-compliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided prior to study initiation, in the various functional monitoring plans (including, but not limited to, Quality Tolerance Limit Management Plan and Trial Monitoring Plan).

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).

Study monitors will perform ongoing monitoring activities as specified in the Trial Monitoring Plan to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, the ICH Guideline for Good Clinical Practice, and all applicable regulatory requirements.

Records and documents pertaining to the conduct of this study, including signed Informed Consent Forms, must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

The Sponsor will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

A1–8 SOURCE DOCUMENTS

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF or entered in the electronic Case Report Form (eCRF) that are transcribed from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data and its origin can be found in the Trial Monitoring Plan.

A1–9 STUDY AND SITE CLOSURE

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. 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 participants.
- Participant enrollment is unsatisfactory.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigators shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to, the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH Guideline for Good Clinical Practice
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs/ECs, the health authorities, and any contract research organizations used for the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should ensure appropriate participant therapy and/or follow-up.

A1–10 PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of results of multicenter studies only in their entirety and not as individual site 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.

A1–11 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on participant 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.

Appendix 2
Clinical Safety Laboratory Tests

The tests detailed in Table A2-1 will be performed by the local laboratory.

Additional tests may be performed at any time during the study if determined to be necessary by the investigator or if required by local regulations.

Table A2-1 Protocol-Required Safety Laboratory Assessments

Local Laboratory Tests
• Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, and reticulocytes) • Chemistry panel (serum or plasma): sodium, potassium, chloride, glucose, BUN or urea, creatinine, albumin, total and direct bilirubin, ALT, AST

Investigators must document their review of each laboratory safety report.

Appendix 3
Safety Parameters: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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A3–1 DEFINITION OF ADVERSE EVENT

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient or clinical study participant temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

Note: An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events Meeting the Adverse Event Definition

The following events meet the definition of adverse event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease)
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition
- New condition detected or diagnosed after study treatment administration, even though it may have been present before the start of the study
- Signs, symptoms, or clinical sequelae of a suspected drug–drug interaction
- Signs, symptoms, or clinical sequelae of a suspected overdose of either study treatment or a concomitant medication

    Overdose per se will not be reported as an adverse event or serious adverse event unless it is an intentional overdose taken with possible suicidal or self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Definition of Adverse Event

The following events do not meet the definition of adverse event:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy)

    The condition that leads to the procedure is the adverse event.

- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of a preexisting disease or condition present or detected at the start of the study that do not worsen

A3–2 DEFINITION OF SERIOUS ADVERSE EVENT

If an event is not an adverse event per the definition in Section A3–1, it cannot be a serious adverse event even if serious conditions are met (e.g., hospitalization for signs or symptoms of the disease under study, death due to progression of disease).

A serious adverse event is defined as any untoward medical occurrence that, at any dose:

- Results in death
- Is life threatening

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization

  In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are adverse events. If a complication prolongs hospitalization or fulfills any other seriousness criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the adverse event should be considered serious.

  Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an adverse event.

- Results in persistent disability or incapacity

  The term "disability" means a substantial disruption of a person's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
- Other situations:

Medical or scientific judgment should be exercised in deciding whether serious adverse event reporting is appropriate in other situations such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

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 NCI CTCAE; see Section A3–3.2); 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 electronic Case Report Form (eCRF).

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event) (see Section A3–5 for reporting instructions).

A3–3 RECORDING AND FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.1 ADVERSE EVENT AND SERIOUS ADVERSE EVENT RECORDING

When an adverse event or serious adverse event occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant adverse event or serious adverse event information on the eCRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the Sponsor in lieu of completion of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event on the basis of signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs or symptoms) will be documented as the adverse event or serious adverse event.

A3–3.2 ASSESSMENT OF SEVERITY

The investigator will assess the severity of each adverse event reported during the study through use of the NCI CTCAE (v5.0) grading scale. The investigator will use the grading scale in Table A3-1 for assessing the severity of adverse events that are not specifically listed in the NCI CTCAE.

Table A3-1 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 [a]
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 [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

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

Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Examples of instrumental activities of daily living include preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by participants who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section A3–5 for reporting instructions), per the definition of serious adverse event in Section A3–2.

A3–3.3 ASSESSMENT OF CAUSALITY

The investigator is obligated to assess the relationship between study treatment and each occurrence of each adverse event or serious adverse event.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

The investigator will use clinical judgment to determine the relationship.

Alternative causes, such as underlying diseases, concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.

The investigator will also consult the Investigator's Brochure and/or prescribing information (for marketed products) in his or her assessment.

For each adverse event or serious adverse event, the investigator **must** document in the medical notes that he or she has reviewed the adverse event or serious adverse event and has provided an assessment of causality.

There may be situations in which a serious adverse event has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the serious adverse event data to the Sponsor.

The investigator may change his or her opinion of causality in light of follow-up information and send a serious adverse event follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

A3–3.4 FOLLOW-UP OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

A3–3.4.1 Investigator Follow-Up

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the adverse event or serious adverse event as fully as possible. This may include additional laboratory tests or investigations, histopathologic examinations, or consultation with other health care professionals.

New or updated information should be recorded on the originally completed Adverse Event eCRF. 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 the investigator becomes 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

During the adverse event reporting period (defined in Section 8.3.1), resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the participant's medical record to facilitate source data verification.

A3–3.4.2 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.

A3–4 REPORTING OF SERIOUS ADVERSE EVENTS

A3–4.1 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA AN ELECTRONIC COLLECTION TOOL

The primary mechanism for reporting a serious adverse event to the Sponsor will be the electronic data collection tool, as described in Section A3–5.

If the electronic system is unavailable, the site will use the paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5, to report the event within 24 hours.

The site will enter the serious adverse event data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new serious adverse event from a study participant or receives updated data on a previously reported serious adverse event after the electronic data collection tool has been taken off line, the site can report this information

on a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–4.2 SERIOUS ADVERSE EVENT REPORTING TO THE SPONSOR VIA PAPER CRF

Under certain circumstances, serious adverse events may be reported to the Sponsor through use of a paper Clinical Trial Adverse Event/Special Situations Form, as described in Section A3–5.

A3–5 REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS AND ADVERSE EVENTS OF SPECIAL INTEREST

A3–5.1 EVENTS THAT OCCUR PRIOR TO STUDY TREATMENT INITIATION

After informed consent has been obtained but prior to initiation of study treatment, only serious adverse events caused by a protocol-mandated intervention (e.g., biopsy, discontinuation of medications) should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either by faxing or by scanning and emailing the form, using the fax number or email address provided to investigators.

A3–5.2 EVENTS THAT OCCUR AFTER STUDY TREATMENT INITIATION

After initiation of study treatment, serious adverse events and adverse events of special interest will be reported until 30 days after the final dose of study treatment. Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after the investigator becomes aware of the event) on the 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 by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event /Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after the investigator becomes aware 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 final dose of study treatment are provided in Section A3–6.

A3–6 REPORTING 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 (defined as 30 days after the final dose of study treatment), if the event is believed to be related to prior exposure to study 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 Adverse Event /Special Situations Form, using the fax number or email address provided to investigators.

A3–7 PROCEDURES FOR RECORDING ADVERSE EVENTS

When an adverse event occurs, it is the responsibility of the investigator to review all documentation related to the event (e.g., hospital progress notes, laboratory reports, and diagnostics reports). The investigator will then record all relevant adverse event information on the Adverse Event eCRF. It is not acceptable for the investigator to send photocopies of the participant's medical records to the Medical Monitor in lieu of completion of the eCRF. Investigators should use correct medical terminology and 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 of the Adverse Event eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor.

A3–7.1 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.

A3–7.2 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.

A3–7.3 PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent adverse event is one that extends continuously, without resolution, between participant 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 the investigator becomes aware that the event became serious; see Section A3–5 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 participant evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

A3–7.4 ABNORMAL LABORATORY VALUES

Not every abnormal laboratory value qualifies as an adverse event. A laboratory value abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A laboratory value abnormality that is not associated with the underlying disease 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., dose 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., ALP 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 A3–7.3 for details on recording persistent adverse events).

A3–7.5 ABNORMAL VITAL SIGN VALUES

Not every abnormal vital sign value qualifies as an adverse event. A vital sign abnormality that is associated with the underlying disease should not be reported as an adverse event unless judged by the investigator to be more severe than expected. A vital sign abnormality that is not associated with the underlying disease 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., dose 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 (e.g., 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 A3–7.3 for details on recording persistent adverse events).

A3–7.6 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 A3–7.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), either as a serious adverse event or an adverse event of special interest (see Section A3–5).

A3–7.7 DEATHS

All deaths that occur during the protocol-specified adverse event reporting period (see Section 8.3.1), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section A3–5). This includes death attributed to progression of Spinal muscular atrophy.

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 solely to progression of Spinal muscular atrophy, "spinal muscular atrophy progression" should be recorded on the Adverse Event eCRF.

Deaths that occur after the adverse event reporting period should be reported as described in Section A3–6.

A3–7.8 PREEXISTING MEDICAL CONDITIONS

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

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

A3–7.9 LACK OF EFFICACY OR WORSENING OF SPINAL MUSCULAR ATROPHY

Medical occurrences or symptoms of deterioration that are anticipated as part of SMA should not be recorded as adverse events. However, deterioration that is judged by the investigator to have unexpectedly worsened in severity or frequency or changed in nature at any time during the study should be recorded as an adverse event. 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").

A3–7.10 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 A3–2), 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
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The participant was hospitalized for an elective procedure that was planned prior to the study, was scheduled during the study despite the fact that the condition had not worsened, or was scheduled during the study when treatment became necessary because of the expected normal progression of the condition
  - The participant 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 that was necessary because of participant requirement for outpatient care outside of normal outpatient clinic operating hours
- 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.

A3–8 SPECIAL SITUATIONS (OVERDOSE, MEDICATION ERROR, DRUG ABUSE, AND/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
- 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 to the participant at home by the parent/caregiver, drug misuse could involve the drug being administered to someone other than the participant.

After initiation of study drug, special situations associated with risdiplam and any associated adverse events will be reported until 30 days after the final dose of study drug.

Special situations, regardless of whether they result in an adverse event, should be reported on the Special Situations eCRF. If there are any associated adverse events, each event should be recorded separately on the Adverse Event eCRF.

Special situations and any associated adverse events should be reported within 30 days after the investigator becomes aware of the situation. However, if an associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, both the event and the special situation should be reported to the Sponsor immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as described in Section A3–5.

Appendix 4
Safety Plan: Management of Identified and Potential Risks

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A4–1 RISKS ASSOCIATED WITH RISDIPLAM

Clinical development is ongoing. The safety plan for patients in this study aims at managing potential risks that were identified following findings in nonclinical 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 mean area under the concentration–time curve from time 0 to 24 hours at steady state of 2000 ng • h/mL corresponds to the no-observed-adverse-effect level 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/caregivers of male participants 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.

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 participant to ensure that each participant is in the targeted exposure range. Free fraction will be measured from a sample taken prior to risdiplam treatment start, and the dose may be adjusted if the free fraction is significantly different in this study population compared to older infants.

The stopping rules detailed in A4–2.2 will be applied in case of specific adverse events.

Based on observed toxicity in nonclinical studies (see Risdiplam Investigator's Brochure for details), the safety precautions outlined in A4–1.1 and A4–1.2 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 16 days and younger.

Risdiplam has been safe and well tolerated in 483 patients *aged* 16 days to 60 years at first dose in clinical studies to date.

A4–1.1 EFFECTS ON EPITHELIAL TISSUES

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/caregivers will be instructed to apply alcohol-free hypoallergenic moisturizing cream early in case of dry skin and to quickly contact the investigator.

Patients treated with risdiplam are at risk of developing effects on oral and larynx mucous membranes. Parents/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/caregivers will be instructed to promptly consult the study investigator in case of symptoms of laryngitis for a specialized examination. 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).

A4–1.2 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.

A4–2 MANAGEMENT OF PARTICIPANTS WHO EXPERIENCE ADVERSE EVENTS

A4–2.1 DOSE MODIFICATIONS

Modification of the 0.15 mg/kg risdiplam dose is not permitted, unless requested by the Sponsor. Dose modifications are not permitted for participants who experience adverse events (see also Section 6.5).

A4–2.2 TREATMENT INTERRUPTION

Risdiplam may be withheld in participants who experience toxicity considered to be related to study drug.

Risdiplam should be discontinued permanently if the following specific safety stopping criteria for an individual subject are met:

- Skin or subcutaneous reaction, pharyngeal/laryngeal or mucosal reaction (Grade ≥ 2, NCI CTCAE, v5.0) 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

- 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 ($>2\times$ ULN) (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 Clinical Science Lead, Roche Safety Science Leader, and the investigator, indicate that dosing should be halted.

The investigator should then look for the best standard of care option available in the country.

A4–2.3 MANAGEMENT GUIDELINES

Guidelines for management of specific adverse events related to effects on epithelial tissues Table A4-1.

Table A4-1 Guidelines for Management of Participants Who Experience Adverse Events

Event	Action to Be Taken
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.

Appendix 5
Reporting Requirements for Medical Device Complaints

A5–1 REPORTING REQUIREMENTS FOR MEDICAL DEVICE COMPLAINTS

In this study, dispenser for oral drug administration is considered a medical device. The investigator must report all device deficiencies to the Sponsor in the form of a medical device complaint. A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance, and it can include malfunctions, use errors, and inadequate labeling. In reporting a medical device complaint, 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 the investigator becomes aware of the event) (refer to the pharmacy manual for further details). If the medical device deficiency results in an adverse event to the study participant, the event must be reported on the Adverse Event electronic Case Report Form (eCRF) and submitted through the electronic data system. If the event fulfills seriousness criteria, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after the investigator becomes aware of the event), as outlined in Section A3–5.

Appendix 6
Investigational Medicinal Product Designation (for Use in European Economic Area and United Kingdom)

Table A6-1 Investigational Medicinal Product Designation for European Economic Area and United Kingdom

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA and U.K.*	*Used within Marketing Authorization*
Risdiplam (RO7034067)	*IMP (test product)*	*Authorized*	*No* [a]

AxMP= auxiliary medicinal product; EEA =European Economic Area; IMP=investigational medicinal product; SMA =spinal muscular atrophy; SMN2 =survival of motor neuron 2 (gene).

[a] *In this study, risdiplam (IMP) is used outside of current indication "Risdiplam is indicated for the treatment of 5q SMA in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies".*

Appendix 7
Abbreviations

Abbreviation or Term	Definition
AUC	area under the concentration–time curve
C_{max}	maximum plasma concentration observed
DMT	disease-modifying therapy
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
ICH	International Council for Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
MATE	multidrug and toxin extrusion
MN	mobile nursing
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PK	pharmacokinetic
PPB	plasma protein binding
QTcF	QT interval corrected through use of Fridericia's formula
SMA	spinal muscular atrophy
SMN	survival of motor neuron (gene)
SMN	survival of motor neuron (protein)
ULN	upper limit of normal

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