Official Title: An Open-Label Study to Investigate the Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Risdiplam (RO7034067) in Adult and Pediatric Patients with Spinal Muscular Atrophy

NCT Number: NCT03032172

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PROTOCOL

PROTOCOL TITLE:	**AN OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS/PHARMACODYNAMICS OF RISDIPLAM (RO7034067) IN ADULT AND PEDIATRIC PATIENTS WITH SPINAL MUSCULAR ATROPHY**
PROTOCOL NUMBER:	BP39054
STUDY NAME:	JEWELFISH
VERSION NUMBER:	5
TEST PRODUCT:	Risdiplam (RO7034067)
STUDY PHASE:	Phase II
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 128972 EU CT Number: 2023-506739-14-00 EudraCT Number: 2016-004184-39 NCT Number: NCT03032172
SPONSOR'S NAME AND LEGAL REGISTERED ADDRESS:	F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 4070 Basel, Switzerland
APPROVAL DATE:	See electronic signature and date stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country and/or Region-Specific Protocols		
Version	**Date Final**	**Country and/or Region**	**Version**	**Date Final**
5	See electronic date stamp on final page of this document	—	—	—
4	23 June 2020	—	—	—
3	27 February 2019	Germany	Addendum 1	5 March 2019
2	29 June 2018	France	Addendum 1	13 December 2018
		Germany	Addendum 1	16 November 2018
1	2 November 2016	Rest of World	1	2 November 2017
		United States	1	26 October 2017
		Switzerland	1	18 August 2017
		United Kingdom	1	14 June 2017

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol BP39054 has primarily been amended to remove ophthalmology monitoring. Additionally, digital biomarker assessments that were discontinued in 2022 have been removed from the protocol. Substantive changes to the protocol, along with a rationale for each change, are summarized below.

- Background on risdiplam has been streamlined to remove outdated nonclinical and clinical data (Sections 1.2.1 and 1.2.2 have been deleted); more up-to-date data can be found in the Risdiplam Investigator's Brochure.
- Given that no retinal toxicity has been observed to date and that further monitoring will not provide additional reassurance, ophthalmological assessments have been removed at all timepoints to reduce burden on patients, their families and caregivers and the study sites (Sections 1.3.2, 3.3.1, 4.6.1.11, 4.6.2.2, 4.7.1.1, 5.2.1, 5.2.2, 5.2.3 [original section deleted; renumbered section amended], and 6.5; Appendices 1A, 1B, 3A and 3B; former Appendix 5 has been deleted and subsequent appendices renumbered).
- The requirement for a safety follow-up telephone call approximately 30 days after the study completion/early withdrawal visit has been updated. For patients who continue to receive risdiplam following this visit (receiving risdiplam investigational medicinal product (IMP) prior to end of study via continued access, or receiving risdiplam through commercial or post-trial access), the follow-up telephone call is no longer a requirement since these patients do not stop risdiplam treatment (Section 3.1.1, 3.1.3, 4.6.1, 4.6.2.4 and 5.3.1; Appendices 1B and 3B; new Appendix 5).
- The definition for the end of study (EOS) has been updated to clarify that the end of the study is the date of the last visit or telephone call (whichever occurs later) of the last patient (Section 3.1.3).
- Digital biomarker assessments have been removed since major hardware and software upgrades would have been required to continue to collect digital biomarker data. Additionally, the smartphone deployed to patients to perform this assessment needed replacement for patients to be able to upload data and this would have involved significant burden for the patients and site personnel. As such, digital biomarker data had already ceased to be collected from patients since July 2022 (Sections 3.2.3, 3.3.3, 4.6.1.16, 4.6.2.2, and 6.9; Appendices 1A and 1B).
- Information about the two-bottle formulation of risdiplam has been removed because this formulation is no longer used in this study (Section 4.4.1).
- The text regarding treatment with risdiplam IMP after Week 260 (the final visit/telephone call) until EOS for patients who do not have access to commercial risdiplam has been clarified. Terminology has been updated throughout the protocol to refer to this as 'continued access' or 'treatment until EOS'. Language has been added to clarify these patients are not required to attend additional study visits and only adverse events must continue to be reported (new Sections 4.4.4 and 4.6.2.5; Appendices 1B and 3B; new Appendix 5).

- Text has been updated to clarify that topical medications are permitted, including the topical form of all medications that are listed as prohibited therapies (Section 4.5.1).
- The list of prohibited medications has been updated to remove medications with retinal toxicity given the absence of ophthalmological findings and the discontinuation of ophthalmology monitoring. A textual clarification has been made regarding the prohibition of medications with known phototoxicity liabilities (Section 4.5.2).
- The study visit occurring every 13 weeks during the open-label extension (OLE) phase now has the option to be performed remotely (e.g., by telephone) at the investigator's discretion. The risk of performing a remote visit is considered to be low and this will reduce significant burden for patients and their caregivers. The Schedules of Assessments have been updated to reflect this change.
- The Schedules of Assessments (Appendix 1B and 3B) have been updated to confirm administration of study medication at the completion/early withdrawal visit for patients who will receive risdiplam until EOS. The prior Schedule of Assessments in Protocol Version 4 did not have the daily administration of study medication checked as applicable for the completion/early Withdrawal visit.
- To comply with E.U. Clinical Trial Regulations requirements and other guidelines, the following changes have been made:
  - The Medical Monitors' name has been removed from the protocol, and text regarding emergency medical contacts has been amended for clarity (front matter and Section 5.4.1).
  - The synopsis has been simplified.
  - A section describing duration of participation has been added (Section 3.1.4).
  - A comprehensive list of investigational medicinal products and auxiliary medicinal products has been added (Section 4.4 and Appendix 6).
  - It has been made explicit that expedited safety reports are notified to EudraVigilance (Section 5.7).
  - A description of the technical and organizational security measures taken to protect personal data has been added (Section 8.4).
  - Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports. The name of a Roche policy on data sharing has also been corrected (Section 9.5).

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

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PROTOCOL AMENDMENT ACCEPTANCE FORM

PROTOCOL TITLE:	**AN OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS/PHARMACODYNAMICS OF RISDIPLAM (RO7034067) IN ADULT AND PEDIATRIC PATIENTS WITH SPINAL MUSCULAR ATROPHY**
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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 to your local study monitor.

PROTOCOL SYNOPSIS

PROTOCOL TITLE:	**AN OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS/ PHARMACODYNAMICS OF RISDIPLAM (RO7034067) IN ADULT AND PEDIATRIC PATIENTS WITH SPINAL MUSCULAR ATROPHY**
REGULATORY AGENCY IDENTIFIER NUMBERS:	IND Number: 128972 EU CT Number: 2023-506739-14-00 EudraCT Number: 2016-004184-39 NCT Number: NCT03032172

STUDY RATIONALE

The purpose of this study is to investigate the safety, tolerability, pharmacokinetics and pharmacokinetic (PK)/pharmacodynamic (PD) relationship of risdiplam in adults and children and infants with spinal muscular atrophy (SMA) previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101 (adeno associated virus 9 based gene therapeutic that delivers a normal copy of the SMN1 gene), or olesoxime.

OBJECTIVES AND ENDPOINTS

Primary Objective	*Corresponding Endpoints*
• *To evaluate the safety and tolerability of risdiplam*	• *Incidence and severity of adverse events with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0* • *Incidence of treatment discontinuations due to adverse events* • *Incidence of abnormal laboratory values* • *Incidence of abnormal ECG values* • *Incidence of abnormal vital signs (body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate)* • *Physical examination. For patients aged 9-17 years, physical examination will include formal Tanner staging for pubertal status* • *Incidence of clinically significant findings on neurological examination* • *Anthropometric examination including height, weight, and head and chest circumference* • *Incidence of emergence or worsening of symptoms as measured by the Columbia-Suicide Severity Rating Scale (adult version for adults and adolescents, pediatric version for patients aged 6-11 years)* • *Ophthalmological assessments as appropriate for age* • *This objective was in place in Protocol Versions 1-4, inclusive. Ophthalmological*

	assessments have been removed starting in Protocol Version 5.
• *To investigate the pharmacokinetics of risdiplam and metabolites as appropriate*	• *Concentration per timepoint listed* • C_{max} • *AUC* • C_{trough} *to assess steady-state* • *Other PK parameters as appropriate*
Secondary Objective	***Corresponding Endpoints***
• *To investigate the PK/PD relationship of risdiplam. The PD investigations will include analyses of SMN mRNA splice forms and SMN protein*	• *SMN mRNA concentration in blood* • *SMN protein levels in blood*

AUC = area under the concentration-time curve; PD = pharmacodynamic; PK = pharmacokinetic; SMN = survival motor neuron.

OVERALL DESIGN *AND STUDY POPULATION*

DESCRIPTION OF STUDY

This is a multi-center, exploratory, non-comparative and open-label study to investigate the safety, tolerability, PK and PK/PD relationship of risdiplam in adults and children and infants with SMA previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101 (adeno-associated virus 9 based gene therapeutic that delivers a normal copy of the SMN1 gene), or olesoxime.

Treatment with risdiplam will initially be evaluated over a *2-year* period. After completion of the *2-year* treatment period, the patient will be given the opportunity to enter the *open-label* extension *(OLE)* phase of the study, which will include regular monitoring of safety, tolerability and efficacy. Unless the Sponsor stops the development of risdiplam, the patient's treatment in the extension will continue for an additional 3 years (patients will be treated for a total duration of at least 5 years). After a patient has completed 3 years in the *OLE*, the patient may continue *to receive risdiplam IMP* until the end of study (EOS), provided that risdiplam is not commercially available *to the patient*.

The final analysis will investigate the safety, tolerability, and PK/PD relationship of risdiplam after all patients have completed the study.

The duration of the study for patients enrolled will be divided as follows:

- Screening: Up to 30 days prior to first dose of study drug
- Baseline: Day -1
- Treatment period: Up to *2 years*
- Thereafter, patients will be given the opportunity to enter the *OLE* phase of the study *for 3 years*
- If a patient completes or withdraws early from study treatment, the patient will be requested to attend a study completion/early withdrawal visit.
- *A follow-up telephone call, if applicable, approximately 30 days after the study completion/early withdrawal visit. The follow-up call will only be conducted for patients [a] who do not go on to receive risdiplam IMP through continued access or to receive risdiplam through commercial or post-trial access; or [b] who switch to another treatment for SMA within 30 days of stopping risdiplam. If a patient switches to another treatment for SMA during the 30-day follow-up period after the study completion/early withdrawal visit, a telephone call should still be performed to collect information up to the time that the patient begins the new treatment.*

Several key aspects of the study design and study population are summarized below.

Phase:	*Phase II*	***Population Type:***	*Adult and pediatric patients*
Control Method:	*None*	***Population Diagnosis or Condition:***	*Spinal muscular atrophy; who have been previously enrolled in Study BP29420 (Moonfish) or previously treated with nusinersen, AVXS-101, or olesoxime*
Interventional Model:	*Single group*	***Population Age:***	*6 months to 60 years of age at screening*
Test Product:	*Risdiplam*	***Site Distribution:***	*Multi site and multi region*
Active Comparator:	*Not applicable*	***Study Treatment Assignment Method:***	*All participants are assigned to the same treatment*
Number of Arms:	*One*	***Number of Participants to Be Enrolled:***	*Up to 180 patients (At least 80 patients will have previously received treatment with nusinersen or AVXS-101)*

STUDY TREATMENT

For patients aged 2-60 years, the dose in this study will be 5 mg for patients with a body weight ≥20 kg and 0.25 mg/kg for patients with a body weight <20 kg, given orally once daily. For patients aged 6 months to < 2 years (infants), the dose will be 0.2 mg/kg. The pharmacokinetics in all infants will be regularly monitored by the Clinical Pharmacologist, and the dose of all or individual infants may be adjusted to ensure that infants are in the targeted exposure range and in compliance with the exposure cap.

DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to *be approximately 5 years (2-year* treatment *phase* and *3-year OLE phase)* and 1 *month (*if *30-day follow-up applies).*

The total duration of study participation *for an individual* is expected to be *approximately 5 years (2-year treatment phase and 3-year OLE phase) and 1* month *(if 30 day follow-up applies).*

COMMITTEES

Independent Committees:	*Independent Data Monitoring Committees*
Other Committees:	*Internal Monitoring Committee* *Permanent Ventilation Adjudication Committee*

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
6MWT	six-minute walk test
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration–time curve
$AUC_{0–24}$	area under the concentration–time curve from 0 to 24 hours
$AUC_{0\text{-last}}$	area under curve from time 0 to last measurable concentration
BCVA	best corrected visual acuity
BP	blood pressure
BSID-III	Bayley Scales of Infant and Toddler development – Third Edition
BW	body weight
CDC	Centers for Disease Control and Prevention
C_{max}	maximum concentration observed
CNS	central nervous system
CPK	creatine phosphokinase
CRO	contract research organization
CRP	C-reactive protein
C-SSRS	Columbia-Suicide Severity Rating Scale
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DAP	Data Analysis Plan
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EOS	end of study
ePRO	electronic patient-reported outcome
ERG	electroretinogram
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	(U.S.) Food and Drug Administration
FEV	forced expiratory volume
FMO	flavin monooxygenase

FoxM1	forkhead box protein M1
FP	fundus photography
FVC	forced vital capacity
γ-GT	gamma-glutamyl-transferase
GMFM	Gross Motor Function Measure
HDAC	histone deacetylase
HFMSE	Hammersmith Functional Motor Scale Expanded
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IEC	independent Ethics Committee
ILM	inner limiting membrane
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISCEV	International Society for Clinical Electrophysiology of Vision
IxRS	interactive voice or web-based response system
LDH	lactate dehydrogenase
LH	luteinizing hormone
LPLO	last patient, last observation
LPLV	last patient, last visit
MADD	MAP-kinase activating death domain
MATE	multidrug and toxin extrusion
MFM	motor function measure
MMRM	mixed model repeated measures
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NOEL	No-observed-effect level
OAT	organic anion transporter
OCT	organic cation transporter or Optical Coherence Tomography (in Ophthalmology sections)
ONL	outer nuclear layer
OTC	over-the-counter
PCF	peak cough flow
PedsQL	Pediatric Quality of Life Inventory
PD	pharmacodynamic
PK	pharmacokinetic

PRO	patient-reported outcome
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate using the Bazett's correction factor
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	red blood cell
RBR	Research Biosample Repository
RPE	retinal pigment epithelium
RR	RR interval
RULM	Revised Upper Limb Module
SAD	single-ascending dose
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SD-OCT	spectral domain-optical coherence tomography
SMA	spinal muscular atrophy
SMAIS	SMA Independence Scale
SMN	survival of motor neuron
SNIP	sniff nasal inspiratory pressure
SoA	schedule of assessments
SOC	Scientific Oversight Committee
TML	Translational Medicine Leader
TSH	thyroid–stimulating hormone
ULN	upper limit of normal
U.S.	United States
USP/NF	United States Pharmacopeia/National Formulary
VA	visual acuity
VAS	visual analogue scale
VEP	visual evoked potential
VF	visual field
WGS	whole genome sequencing

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON DISEASE

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

Clinically, SMA ranges in disease severity. For classification purposes, patients are usually categorized into four main subtypes based on clinical criteria, including achieving (or failing to achieve) physical motor milestones, age of onset and life span (Munsat et al 1992): Type 1 SMA or Werdnig-Hoffmann disease (severe infantile type, onset before 6 months of age with death due to respiratory distress, usually within 2 years), Type 2 SMA (intermediate chronic infantile type with onset before the age of 18 months, unable to stand or walk without support), Type 3 SMA or Kugelberg-Welander disease (chronic juvenile type with onset after the age of 18 months, children are able to stand and walk until the disease progresses) and Type 4 SMA (adult onset). A fifth type, denoted as Type 0, has been proposed for extremely severe SMA that manifests during fetal life and results in death within a few weeks after birth (Kolb et al 2011). This clinical trial will enroll Type 1, Type 2 and Type 3 SMA patients.

SMA is caused by a homozygous deletion (95% of cases) or mutation of the survival of motor neuron (*SMN*) 1 gene on chromosome 5q (locus 5q13), which encodes SMN, an essential protein expressed in both neuronal and non-neuronal cells (Lefebvre et al 1995). In humans, there are two SMN genes, the *SMN1* gene and its paralog *SMN2*. Species other than human have only one SMN gene, which is equivalent to the human *SMN1* gene. Due to a translationally synonymous C to T mutation at nucleotide 6 in exon 7, the *SMN2* pre-mRNA undergoes alternative splicing, which excludes exon 7 from 85–90% of mature *SMN2* transcripts producing an unstable SMNΔ7 protein that is rapidly degraded (Lorson et al 1999; Cho et al 2010). Accordingly, full-length *SMN2* mRNA is generated in only 10–15% of splicing events. Since SMA patients only have the *SMN2* gene, their SMN protein levels are significantly decreased (Kolb et al 2011).

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

and osteoporosis with pathological fractures, poor cough and secretion clearance, reduced vital capacity, gastroesophageal dysmotility, urinary incontinence, hip dislocation, and joint and muscle pain.

The medical need in SMA is very high, and several drug candidates are currently under investigation in the nonclinical and clinical setting (Lewelt et al 2012; d'Ydewalle et al 2015). The SMN2-targeting antisense oligonucleotide nusinersen (SPINRAZA®) has been approved by health authorities in the United States (U.S.), the European Union (E.U.), Canada, and other jurisdictions, for the treatment of SMA in pediatric and adult patients. Alternative management strategies focus on prevention and treatment of comorbidities, such as failure to thrive, surgical and non-surgical treatment of scoliosis and contractures, pulmonary hygiene, non-invasive ventilation, mobility and seating support, and physical and occupational therapy.

1.2 BACKGROUND ON RISDIPLAM

One of the promising strategies currently being pursued is to restore SMN protein levels in SMA patients by modulating *SMN2* splicing to favor the inclusion of exon 7 into the mRNA transcript, thereby increasing expression of stable full-length protein from the *SMN2 gene* (Kolb et al 2011; Nurputra et al 2013). One such compound currently being developed is risdiplam (previously referred to as RO7034067), which directly targets the underlying molecular deficiency of the disease and promotes the inclusion of exon 7 to generate full-length *SMN2* mRNA, which therefore increases the production of functional SMN protein. SMN protein increase after treatment with risdiplam has been shown in fibroblasts and motor neurons derived from patients with SMA.

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

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

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

SMA is the leading genetic cause of death in infants and young children. In milder forms, it results in profound motor and respiratory disabilities and major orthopedic deformities. One drug was recently approved in the U.S., the European Union (E.U.), Canada and other jurisdictions for the treatment of SMA in pediatric and adult patients (the antisense oligonucleotide nusinersen) but the medical need in SMA for alternative

treatment options is still very high. There is currently no oral treatment for SMA that provides stabilization or improvement of motor function, which would be of immense value for patients and parents/caregivers.

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

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

This exploratory, open-label study is designed to assess the safety, tolerability, PK and PD of risdiplam in patients with SMA (aged 6 months to 60 years) previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101, or olesoxime. Considering the different therapeutic agents currently approved or in development for SMA and the possibility that patients with a poor response to and/or lack of tolerability towards another agent may need alternative treatment options, it is important to evaluate the safety and PK/PD response to risdiplam in these patients compared to treatment-naïve patients. The results of this study will allow an assessment of the safety and tolerability of risdiplam and to characterize the PK/PD relationship of risdiplam in these non-naïve patients in order to inform clinical development of risdiplam. The PK of risdiplam will be assessed throughout the study. The PD characteristics of risdiplam will be measured in terms of SMN protein and SMN mRNA splice forms.

1.3.2 Benefit–Risk Assessment

The SAD Study (BP29840) established the proof of mechanism in healthy subjects that risdiplam is able to modulate the splicing of *SMN2* mRNA, leading to an exposure-dependent increase in the amount of full-length *SMN2* mRNA and a corresponding decrease in the amount of *SMN2* mRNA lacking exon 7. In Part 1 of

Studies BP39055 and BP39056, risdiplam led to an exposure-dependent increase in SMN protein, confirming proof of mechanism in patients with SMA types 1, 2, and 3. Accordingly, available data to date suggest that risdiplam may provide significant benefits for patients with SMA.

In all above mentioned studies, risdiplam was safe and well-tolerated.

In light of the adverse findings in the animal toxicology studies, in this study, an exposure cap of 2000 ng • hr /mL (mean $AUC_{0\text{-}24,ss}$) corresponding to the overall NOAEL of the 39-week toxicology study in cynomolgus monkeys and the NOAEL of the 26-week toxicity study in rats, along with a thorough clinical safety monitoring plan is justified, considering the potential benefit for the patients enrolled. Available data suggest that a 100% increase in SMN protein levels is expected to turn more severe SMA phenotypes into milder forms, while further increase is likely to provide even greater benefit. At the dosing regimen selected for the study (i.e., 5 mg for patients with a BW ≥20 kg, 0.25 mg/kg for patients with a BW <20 kg [for patients aged ≥2–60 years], and 0.2 mg/kg for patients aged 6 months to <2 years), the mean predicted exposure is 1690 ng•hr/mL [95% CI: 1600–1780 ng • hr/mL] for children and adults aged 2–25 years and 2020 ng•hr/mL in infants aged ≥5 months. Because the prediction for patients aged 6 months to <2 years is based on a small number of patients from Part 1 of Study BP39056, in this study exposure will be monitored in all infants aged 6 months to <2 years and the dose may get modified, if necessary, to ensure that infants are in the targeted exposure range.

This Study BP39054 will include patients up to age 60 years; no relevant difference in PK is expected for adults within the age range of 18-60 years. In Part 1 of Study BP39055 a median SMN protein increase of 151% (range 49%–251%) versus baseline was observed with 5 mg in the age group of 12–25 years, and a 96% increase (range 17%–150%) was noted with the 0.25 mg/kg dose in the age group of 2–11 years. In Part 1 of Study BP39056, a median 2-fold increase (range 1.0–5.4) in SMN protein in blood versus baseline was observed for infants with an exposure ($AUC_{0\text{-}24}$) ≤1000 ng•hr/mL, and a median 3.2-fold increase (range 1.6–6.5) was observed in infants with an exposure ($AUC_{0\text{-}24}$) >1000 ng•hr/mL.

Safety precautions are provided and a thorough safety monitoring plan focusing on the findings identified in the nonclinical toxicology studies will be implemented to address potential safety concerns for the patients enrolled in the trial (Section 5.2). Toxicological findings observed in the nonclinical studies include reversible toxicity involving skin, pharynx/larynx, hematological changes, male fertility, and potentially irreversible retinal toxicity that could translate into some visual impairment at exposures above twice the mean cap exposure defined for this study.

With regard to retinal effects *(as detailed in the Risdiplam Investigator Brochure),* it is essential to note that the changes found by SD-OCT scanning (and on histopathology) in

the peripheral retina in the 39-week monkey study may produce peripheral visual field defects that are usually asymptomatic and would normally not impact visually oriented behavior and quality of life. These defects would be similar to those found in early stage peripheral retinal degeneration, and pan-retinal photocoagulation for diabetic retinopathy; initially central visual function is spared in these conditions. *As of 18 August 2023, almost 7000 SD-OCT assessments from 486 patients in Studies BP39055 (SUNFISH), BP39056 (FIREFISH), BN40703 (RAINBOWFISH) and BP39054 (JEWELFISH) have not shown any retinal toxicity in any patient exposed to risdiplam at any dose.*

The key elements of risk management in this study considering nonclinical findings and clinical experience gained from the SAD study in healthy volunteers and in SMA patients from Part 1 of studies BP39055 and BP39056 are summarized below:

- Frequent PK assessments (particularly at the beginning of the study; see Appendix 1A and Appendix 3A) to ensure that the average targeted exposure remains below the exposure cap. For patients aged 6 months to < 2 years (infants), the PK data will be regularly reviewed by the Clinical Pharmacologist, and, on the basis of the PK monitoring, the dose of individual or all infants may be modified to ensure that infants are in the targeted exposure range and in compliance with the exposure cap.
- Safety monitoring throughout the treatment period, *OLE* phase, study completion/early withdrawal visit and follow-up (Section 5.2.2), including dermatology and clinical laboratory measures. *Ophthalmology assessments were conducted under Protocol Versions 1-4 inclusive, but are no longer performed under Protocol Version 5.*
- Periodic review of clinical data by the safety data monitoring committees (Section 3.1.2).
- Clear definition of study and individual patient stopping rules (Section 5.2.3).
- Appropriate inclusion/exclusion criteria and guidance regarding prohibited therapy (including OCT-2 *and* MATE substrates; Section 4.5).
- Clinical experience gathered from ongoing trials with risdiplam in patients with SMA (BP39055 and BP39056).

The strategy and rationale for dose selection is described in Section 3.2.1. Table 1 gives an overview of the margins versus key toxicities of risdiplam at the target exposure of this study and at the exposure cap. The safety margins at the targeted exposure in patients aged 6 months to <2 years (infants) are similar to safety margins at the exposure cap, because the highest possible dose at the exposure cap has been selected to maximize the increase in SMN protein and hence the chance for clinical efficacy in infants with a severe early onset type of this disease.

Table 1 Overview of the Margins versus Key Toxicities of Risdiplam

Type of Toxicity	Margin at NOAEL versus predicted exposure of 1690 ng•hr/mL in children and adults [mean $AUC_{0-24,ss}$ 95% CI:1600–1780 ng•hr/mL] [a]	Margin at NOAEL vs Cap Exposure of 2000 ng•hr /mL (AUC_{0-24}) [b]
Micronucleus induction in rat bone marrow	~2	~1.5
Testis toxicity in rats and monkeys	No	No
Epithelial findings (skin, eyelid, larynx) in monkeys (with chronic dosing)	>3	>2.5
Hematology changes (red blood cells [RBC] and lymphocytes) in monkeys, rats and mice	>3	>4
Retina changes in monkeys	~1	~1
Overall NOAEL (13 weeks of treatment: juvenile rat)	~4	>3
Overall NOAEL (39 weeks of treatment: monkey)	~1	~1
Overall NOAEL (26 weeks of treatment: adult albino rat)	~1,5	

NOAEL = no-observed-effect level; SMA = spinal muscular atrophy.

[a] The exposure of 1690 ng•hr/mL (95% CI: 1600-1780 ng•hr/mL) is the mean predicted exposure across the SMA patient population at the dose of 5 mg for patients with a BW ≥20 kg and 0.25 mg/kg for patients with a BW <20 kg (for patients aged ≥2–60 years).

[b] Corresponds to the targeted exposure in patients aged 6 months to <2 years. Margins are based on the mean exposures in animal studies in the more sensitive species/sex.

Overall, considering the severity of SMA and the potential for patients to benefit from treatment with risdiplam, Roche considers the safety margins in this study appropriate, and currently available data from Part 1 of Studies BP39055 and BP39056 continue to justify the benefit–risk of treatment with risdiplam for patients aged 6 months–60 years with SMA, including those previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247, or previously treated with nusinersen, AVXS-101, or olesoxime.

2. OBJECTIVES

This study will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in adult and pediatric patients with SMA. Specific objectives for the study are outlined below. Unless otherwise specified, patient age in this protocol refers to age at screening.

2.1 PRIMARY OBJECTIVES

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of risdiplam
- To investigate the PK of risdiplam and metabolites as appropriate

2.2 SECONDARY OBJECTIVE

The secondary objective for this study is as follows:

- To investigate the PK-PD relationship of risdiplam. The PD investigations will include analyses of SMN mRNA splice forms and SMN protein.

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are defined below.

- To evaluate the efficacy of treatment with risdiplam in terms of the proportion of patients who experience a pre-specified disease-related adverse event.
- To evaluate the efficacy of treatment with risdiplam in terms of motor function as assessed through the following measures:
  - Motor function measure (MFM) (patients aged 2–60 years)
  - Hammersmith Functional Motor Scale Expanded (HFMSE) (patients aged 2–60 years)
  - Revised Upper Limb Module (RULM) (patients aged 2–60 years)
  - Six-minute walk test (6MWT) of walking capacity in ambulant patients (patients aged 6–60 years)
  - Bayley Scales of Infant and Toddler development – Third Edition (BSID-III) (patients aged 6 months to <2 years)
- To evaluate the efficacy of treatment with risdiplam in terms of achievement of motor milestones as assessed through the Hammersmith Infant Neurological Examination (HINE) Module 2 (patients aged 6 months to <2 years).
- To evaluate the efficacy of treatment with risdiplam on respiratory function as assessed through the following measures:
  - Sniff nasal inspiratory pressure (SNIP) (patients aged 2–60 years)
  - Forced vital capacity (FVC) (patients aged 6–60 years)
  - Forced expiratory volume in 1 second (FEV1) (patients aged 6–60 years)
  - Peak cough flow (PCF) (patients aged 6–60 years)
- To evaluate time-matched QT profiles in patients treated with risdiplam (patients aged 12-60 years)
- To evaluate the efficacy of treatment with risdiplam in terms of patient-reported independence (patients aged 12–60 years) and caregiver-reported independence as assessed through the SMA Independence Scale (SMAIS) (patients aged 2–60 years)

- To evaluate patients' adherence to smartphone-based monitoring (patients aged 6–60 years)
- To evaluate the collected sensor data from smartphone-based monitoring and its potential correlations with patients' MFM score (patients aged 6–60 years)
- To assess time to death (patients aged 6 months to < 2 years)
- To assess time to loss of swallowing (patients aged 6 months to < 2 years)
- To assess time to permanent ventilation (patients aged 6 months to < 2 years)

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a multi-center, exploratory, non-comparative, and open-label study to investigate the safety, tolerability, PK, and PK/PD relationship of risdiplam in adults, children and infants with SMA previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101 (adeno-associated virus 9 based gene therapeutic that delivers a normal copy of the SMN1 gene), or olesoxime.

Up to 180 patients will be enrolled to receive risdiplam. At least 80 patients will have previously received treatment with nusinersen or AVXS-101.

Treatment with risdiplam will initially be evaluated over a 2-year period. After completion of the 2-year treatment period, the patients will be given the opportunity to enter the OLE phase of the study, which will include regular monitoring of safety, tolerability and efficacy. Unless the Sponsor stops the development of risdiplam, the patient's treatment in the OLE will continue for an additional 3 years (patients will be treated for a total duration of at least 5 years). After a patient has completed 3 years in the OLE, the patient may continue to receive risdiplam IMP until the end of study (EOS; as defined in Section 3.1.3), provided that risdiplam is not commercially available to the patient (see Section 4.4.4). However, the overall study will not exceed a total of approximately 5 years after the last patient is enrolled in the study.

When a patient completes or withdraws early from study treatment, the patient will be requested to attend a study completion/early withdrawal visit as described in the schedules of assessments (SoAs; see Appendix 1A and Appendix 3A) and Section 4.6.2.3.

A safety follow-up telephone call approximately 30 days after the study completion/early withdrawal visit may be conducted, if applicable (see Section 4.6.2.4).

The patient's route through study completion, follow-up (if applicable) and access to risdiplam after completion are shown in Appendix 5.

For patients aged 2–60 years, the dose in this study will be 5 mg for patients with a BW ≥20 kg and 0.25 mg/kg for patients with a BW <20 kg, given orally once daily.

For patients aged 6 months to <2 years (infants), the dose will be 0.2 mg/kg. The PK in all infants will be regularly monitored by the Clinical Pharmacologist, and the dose of all or individual infants may be adjusted to ensure that infants are in the targeted exposure range and in compliance with the exposure cap.

As described above, the duration of the study for patients enrolled in this study will be divided as follows:

- Screening: Up to 30 days prior to the first dose of study drug
- Baseline: Day −1
- Treatment period: Up to *2 years*
- Thereafter, patients will be given the opportunity to enter the *OLE* phase of the study *for 3 years.*

3.1.2 Committees

3.1.2.1 Internal Monitoring Committee

The IMC will consist of selected Roche representatives: Clinical Pharmacologist, Clinical Science Leader, Safety Science Leader, Statistician, and Statistical Programmer. The IMC will be responsible for monitoring safety until the external iDMC for the confirmatory phase of the risdiplam program takes on the responsibility for monitoring the safety of Type 2 and Type 3 SMA patients. The members of the IMC for this study will be the same as for Study BP39055 to ensure consistency in the oversight of safety in Type 2 and Type 3 SMA patients.

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

3.1.2.2 Independent Data Monitoring Committee (iDMC)

An external iDMC has been established to monitor patient safety during the confirmatory phase of the risdiplam clinical development program. The responsibility for monitoring patient safety transitioned from the IMC to the iDMC when the iDMC took on the responsibility for monitoring the safety of Type 2 and Type 3 SMA patients within the program. The iDMC will meet on a regular basis during the course of the study (once it is formed) and may also meet on an ad-hoc basis as required, e.g., if any unexpected safety concerns arise. After meeting, the iDMC will make a recommendation to the Sponsor for study conduct including (but not limited to) continuation, halting or amending the protocol.

The roles, responsibilities, membership, scope of activities, time of meetings and communication plan for the iDMC will be documented in the Charter prior to the initiation

of the study. The iDMC will be chaired by a medically qualified individual with experience with SMA and will include at least one other Physician experienced in Neurology, a Clinical Pharmacologist, an Ophthalmologic Expert and a Biostatistician. No member of the iDMC will participate in the study as an Investigator or sub-Investigator.

3.1.2.3 Permanent Ventilation Adjudication Committee

Time to permanent ventilation will be determined by a central, independent Permanent Ventilation Adjudication Committee. The committee will review all pertinent data for patients aged 6 months to <2 years (infants) that may meet the definition of permanent ventilation (≥ 16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following, the resolution of an acute reversible event or tracheostomy).

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

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

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

The independent Permanent Ventilation Adjudication Committee will determine if this endpoint has been met and provide recommendations to the Sponsor.

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

3.1.3 End of Study

A patient 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 (see Section 4.6.2.3)*

- *A safety follow-up telephone call, if applicable (see Section 4.6.2.4 and Appendix 5). The safety follow-up telephone call is only for patients [a] who do not go on to receive risdiplam IMP through continued access or to receive risdiplam through commercial or post-trial access; or [b] who switch to another treatment for SMA within 30 days of stopping risdiplam*

The EOS is defined as the date *of* the last visit *or telephone call (whichever* occurs *later) of the last patient in the study. The EOS* is expected to occur approximately 5 years *and 1 month* after the last patient is enrolled (completion of *a 2 year* treatment phase*, a 3 year OLE* phase *plus 30-day follow-up if applicable).*

The study will continue until the EOS, the study is terminated per local regulation, or the Sponsor decides to terminate the study.

See Section 4.4.4 *for conditions regarding continued access to risdiplam until the EOS and Section* 4.4.5 for conditions regarding post-*study* access to risdiplam.

3.1.4 *Duration of Participation*

The total duration of study participation for an individual is expected to be approximately 5 years (2-year treatment phase and 3-year OLE phase) and 1 month (if 30-day follow-up applies).

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Dosage Selection

Given the severity and the high mortality and morbidity associated with SMA, the dose tested in this study aims to provide therapeutic benefit to patients upon chronic dosing.

Based on population PK modelling using available data in SMA patients from Study BP39055 Part 1, the selected dosing regimen of 5 mg for patients with a BW ≥20 kg and 0.25 mg/kg for patients with a BW <20 kg is predicted to result in a steady-state $AUC_{0\text{-}24h,ss}$ of 1690 ng•hr/mL in SMA Type 2 and 3 patients aged 2–25 years and is not expected to exceed the exposure cap (mean $AUC_{0\text{-}24h,ss}$ of 2000 ng•h/mL). On the basis of currently available data from Part 1 of Study BP39056, the selected dose of 0.2 mg/kg in patients aged 6 months to <2 years (infants) is predicted to result in a steady-state $AUC_{0\text{-}24h,ss}$ of 2020 ng•hr/mL. The predicted mean $AUC_{0\text{-}24h,ss}$ of 2020 ng•hr/mL is considered in compliance with the exposure cap of a mean $AUC_{0\text{-}24h,ss}$ of 2000 ng•hr/mL, since it is only numerically marginally greater and the PK will be monitored in all infants to ensure that the actual observed PK values are in compliance with the cap of a mean $AUC_{0\text{-}24h,ss}$ of 2000 ng•hr/mL. The dose of individual or all infants may be adjusted to ensure exposure in the right target range.

These doses and exposures are anticipated to be safe and well-tolerated based on the SAD data obtained in healthy subjects (single-dose administration of up to 18 mg), currently available data from Part 1 of Study BP39055 and BP39056 and the animal

toxicology studies. In Part 1 of Study BP39055, this dosing regimen resulted in a median increase in SMN protein of 151% in the age group of 12-25 years, and 96% in the age group of 2-11 years. In Part 1 of Study BP39056, a median 2-fold increase (range 1.0–5.4) in SMN protein in blood versus baseline was observed for infants with an exposure (AUC_{0-24}) ≤ 1000 ng•hr/mL, and a median 3.2 fold increase (range 1.6–6.5) was obtained in infants with an exposure (AUC_{0-24}) > 1000 ng•hr/mL.

SMN protein levels in SMA patients (Sumner et al 2006; Nguyen et al 2008) and data obtained in animal SMA models regarding efficacy and the associated SMN protein increase (Risdiplam Investigator's Brochure) suggest that a 100% increase in SMN protein levels could turn severe SMA phenotypes into milder forms, whereas further increase may provide even greater benefit. Therefore, the selected dose levels are expected to lead to a substantial clinical benefit in SMA patients by turning more severe phenotypes into milder forms.

The data summary from Part 1 of Study BP39055 and Study BP39056 supporting the rationale for the dose selection for this study can be found in the Risdiplam Investigator's Brochure.

3.2.2 Rationale for Study Population

This study is designed to assess the safety, tolerability, PK and PK/PD relationship of risdiplam following once daily oral administration in pediatric and adult patients with SMA who have been previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101, or olesoxime.

Risdiplam has been shown to be safe and well-tolerated after single dose administration in healthy adult volunteers (BP29840) and in Part 1 of Studies BP39055 and BP39056. It is currently being tested in treatment-naïve pediatric and adult patients with Type 2 and Type 3 SMA (BP39055) and infants with Type 1 SMA (BP39056). There is a need to study the safety, tolerability PK and PD profile of risdiplam in patients with SMA who have previously received other therapy for their disorder. Considering the different therapeutic agents currently approved or in development for SMA and the possibility that patients with a poor response to and/or lack of tolerability towards another agent may need alternative treatment options, it is important to evaluate the safety and PK/PD response to risdiplam in these patients compared to treatment-naïve patients. This information would be valuable for these patients in the event that they need to switch to risdiplam.

The risk-benefit of treatment with risdiplam in SMA patients previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101, or olesoxime is considered favorable given the potential it has to address the unmet medical needs of this population. With SMA being a progressive disease, the Sponsor perceives an ethical obligation to provide these patients with the opportunity to participate in this clinical study, particularly those previously enrolled in

BP29420 and those previously treated with olesoxime, as some of these patients may not have access to other treatment options. Appropriate inclusion and exclusion criteria, safety monitoring and stopping rules have been established to ensure the safety of the patients enrolled in this study.

3.2.3 Rationale for Biomarker Assessments

SMA is a heterogeneous disease presenting a spectrum of motor dysfunction (from not being able to sit up to not being able to walk) and variability in disease onset (from birth to the third decade of life). Due to the variability in SMA phenotypes, careful consideration is required when enrolling patients, when following the progression of the disease and measuring the response to study drug treatment.

The putative target tissues for SMA treatment are spinal cord and muscle, tissues that cannot be easily sampled multiple times to evaluate drug effects. As SMA is due to a lack of SMN protein, changes in *SMN* mRNA and SMN protein levels (relating to changes in the spinal cord and muscle) will be measured in blood.

As patients can have different *SMN2* copy numbers, which will affect SMN protein production, clinical genotyping for *SMN2* is important.

The following blood samples will be collected according to the SoAs and detailed tables (see Appendix 1 – ..... 4 for biomarker analyses:

- Clinical genotyping (Section 4.6.1.17).
- Blood samples for mandatory exploratory biomarker analyses (e.g., related to SMA disease and/or to treatment response).
- Upon optional consent, samples for Research Biosample Repository (RBR) as described in Section 4.6.1.23.

In addition, and as described in Section 4.6.1.14, the following blood samples will be collected according to the SoAs, in order to assess the PD effects of risdiplam as an *SMN2* splicing modifier:

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

For this study, a digital biomarker approach was developed. This is a sensor-based assessment approach for measuring motor abilities and strength using smartphones. Smartphones have high quality sensors that enable the remote, non-invasive, frequent and precise measurement of motor and non-motor symptoms. For this study, a sensor-based assessment approach using smartphones was developed, drawing on items assessed by the MFM (Bérard et al 2009).

A dedicated smartphone will be provided to each patient aged 6 years and older. The phone will prompt them to complete a selection of tests and surveys (Section 4.6.1.22).

Patients will do a subset of these tests each day, based on their ability and an automatic scheduler on the phone (see Appendix 1). *Digital biomarker assessments were performed under Protocol Versions 1-4, inclusive, but ceased to be performed during 2022.*

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) scale, Version 4.0 (see Section 5.3.3).
- Incidence of treatment discontinuations due to adverse events.
- Incidence of abnormal laboratory values.
- Incidence of abnormal ECG values.
- Incidence of abnormal vital signs (body temperature, systolic and diastolic blood pressure (DBP), heart rate, respiratory rate).
- Physical examination. For patients aged 9–17 years, physical examination will include formal Tanner staging for pubertal status.
- Neurological examination.
- Height, weight, and head and chest circumference.
- Incidence of emergence or worsening of symptoms as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS) (adult version for adults and adolescents, pediatric version for patients aged 6–11 years).
- Ophthalmological assessments as appropriate for age (for details, see Section 4.6.1.11). *This objective was in place in Protocol Versions 1-4 inclusive. Ophthalmological assessments have been removed starting in Protocol Version 5.*

Adverse events and concomitant medications will be monitored throughout the entire study.

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

3.3.2.1 Pharmacokinetic Outcome Measures

The PK evaluations for this study are as follows:

- Concentration per timepoint listed
- C_{max}
- AUC
- Concentration at the end of a dosing interval (C_{trough}) to assess steady-state
- Other PK parameters as appropriate

3.3.2.2 Pharmacodynamic Outcome Measures

The PD outcome measures for this study are as follows:

- *SMN* mRNA in blood: Blood samples will be collected at the times specified in the SoAs and detailed tables (see Appendices 1–4), to isolate mRNA and measure the relative amount of *SMN* mRNA and its splice forms. Housekeeping genes for the quantitative analysis of RNA will also be measured.
- SMN protein levels in blood.

3.3.3 Exploratory Outcome Measures

The exploratory outcome measures for this study are as follows:

- Disease-related adverse events
- MFM (32 item version)
- HFMSE
- RULM
- Gross Motor Scale of the Bayley Scales of Infant and Toddler development -Third Edition (BSID-III)
- Hammersmith Infant Neurological Examination Module 2 (HINE2)
- Six-minute walk test (6MWT) (for ambulant patients only)
- SNIP
- Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and peak cough flow (PCF)
- SMAIS
- Sensor data collected using smartphone-based monitoring as part of the digital biomarker approach. *(This objective was in place in Protocol Versions 1-4 inclusive; however, these assessments ceased to be performed during 2022).*
- Ventilation-free survival (i.e., without need for permanent ventilation, defined as ≥ 16 hours of noninvasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following, the resolution of an acute reversible event or tracheostomy)
- Ability to swallow

4. MATERIALS AND METHODS

4.1 CENTER

This is a multi-center study to be conducted globally in several countries. An additional site(s) may be included for back-up purposes and may be activated if needed.

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

4.2 STUDY POPULATION

This study will include both male and female patients with SMA aged 6 months to 60 years. Patients must meet all eligibility criteria in order to qualify for the study. Unless otherwise stated, inclusion and exclusion criteria refer to screening.

4.2.1 Recruitment Procedures

Patients will be recruited primarily from site/country clinical databases; however, in some cases, potential patients may be identified prior to consenting to take part in this study using pre-screening enrollment logs, Independent Ethics Committee (IEC/IRB) approved newspaper/radio advertisements and mailing lists. Additionally, patients previously enrolled in Study BP29420 or treated with olesoxime may be invited to participate in this study.

4.2.2 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Males and females 6 months to 60 years of age inclusive (at screening)
- Confirmed diagnosis of 5q-autosomal recessive SMA, including:
  - Genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the *SMN1* gene.
  - Clinical history, signs, or symptoms attributable to SMA.
- Previous enrollment in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previous treatment with any of the following:
  - Nusinersen (defined as having received ≥ 4 doses of nusinersen, provided that the last dose was received ≥ 90 days prior to screening)
  - Olesoxime (provided that the last dose was received ≤ 18 months and ≥ 90 days prior to screening)
  - AVXS-101 (provided that the time of treatment was ≥ 12 months prior to screening)
- Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonization (ICH) and local regulations. Alternatively, a legally authorized representative must be able to give consent for the patient according to ICH and local regulations and assent must be given whenever possible.
- Adequately recovered from any acute illness at the time of screening and considered well enough to participate in the opinion of the Investigator.
- For women of childbearing potential: negative blood pregnancy test at screening, agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs, as defined below:

- Women must remain abstinent (refrain from heterosexual intercourse) or use two adequate methods of contraception, including at least one method with a failure rate of $<1\%$ per year, during the treatment period and for at least 28 days after the final dose of study drug. Women must refrain from donating eggs during this same period.
- A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
- Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, established and proper use of hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  A vasectomy is a highly effective birth control method provided that the partner is the sole sexual partner of the woman of childbearing potential trial participant, and provided the vasectomized partner has received medical assessment of the surgical success.
- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception. If required per local guidelines or regulations, locally recognized acceptable methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
  - With a female partner of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of $<1\%$ per year during the treatment period and for at least 4 months after the final dose of study drug. Men must refrain from donating sperm during this same period. This period is required for small molecules with potential for genotoxic effect and includes the spermatogenic cycle duration and drug elimination process.
  - With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the final dose of study drug.
  - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

- For patients aged 2 years or younger at screening:
  - Receiving adequate nutrition and hydration (with or without gastrostomy) at the time of screening, in the opinion of the Investigator.
  - Medical care meets local accepted standard of care, in the opinion of the Investigator.
  - Would be able to complete all study procedures, measurements and visits, and the parent or caregiver of the patient has adequately supportive psychosocial circumstances, in the opinion of the Investigator.
  - Parent or caregiver of patient is willing to consider naso-gastric, naso-jejunal or gastrostomy tube placement, as recommended by the Investigator, during the study (if not already in place at the time of screening) to maintain safe hydration, nutrition and treatment delivery.
  - Parent or caregiver of patient is willing to consider the use of non-invasive ventilation, as recommended by the Investigator during the study (if not already in place at the time of screening).

4.2.3 Exclusion Criteria

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

- Inability to meet study requirements.
- Concomitant participation in any investigational drug or device study.
- With the exception of studies of olesoxime, AVXS-101, or nusinersen: Previous participation in any investigational drug or device study within 90 days prior to screening, or 5 half-lives of the drug, whichever is longer.
- Any history of gene or cell therapy, with the exception of AVXS-101.
- Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases as considered to be clinically significant by the Investigator.
- Inadequate venous or capillary blood access for the study procedures, in the opinion of the Investigator.
- For patients aged <2 years, hospitalization for a pulmonary event within 2 months prior to screening and pulmonary function not fully recovered at the time of screening.
- Lactating women.
- Suspicion of regular consumption of drugs of abuse.
- For adults and adolescents only, i.e., aged >12 years, positive urine test for drugs of abuse or alcohol at screening or Day -1 visit.
- Cardiovascular, blood pressure, and heart rate:
  - Adults: Sustained resting systolic blood pressure (SBP) >140 mmHg or <80 mmHg, and/or diastolic blood pressure (DBP) >90 mmHg or <40 mmHg; a resting heart rate <45 bpm or >100 bpm if considered to be clinically significant by the Investigator.

  - Adolescents (12–17 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate <50 bpm or >100 bpm if considered to be clinically significant by the Investigator.
  - Children (6–11 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate <60 bpm or >120 bpm, if considered to be clinically significant by the Investigator.
  - Children (2–5 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate <70 bpm or >140 bpm if considered to be clinically significant by the Investigator.
  - Children (6 months to <2 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate <70 bpm or >170 bpm, if considered to be clinically significant by the Investigator.
- Presence of clinically significant ECG abnormalities before study drug administration (e.g., second or third degree AV block, confirmed QTcF >460 msec for patients aged ≥ 10 years, or QTcB >460 ms for children up to age 10 years (Bazett's correction is more appropriate in young children) from the average of triplicate measurements, or cardiovascular disease (e.g., cardiac insufficiency, coronary artery disease, cardiomyopathy, congestive heart failure, family history of congenital long QT syndrome, family history of sudden death) indicating a safety risk for the patient as determined by the Investigator.
- History of malignancy if not considered cured.
- For patients aged >6 years, significant risk for suicidal behavior, in the opinion of the Investigator as assessed by the C-SSRS.
- Any major illness within 1 month before the screening examination or any febrile illness within 1 week prior to screening and up to first dose administration.
- Use of any OCT-2 and MATE substrates within 2 weeks before dosing (including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine) including the mother, if breastfeeding the patient.
- Use of the following medications within 90 days prior to enrollment: riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease muscle strength, agents with known or presumed histone deacetylase (HDAC) inhibitory effect, and medications with known phototoxicity liabilities (e.g., oral retinoids including over-the-counter formulations, amiodarone, phenothiazines and chronic use of minocycline). (Patients who are on inhaled corticosteroids, administered either through a nebulizer or an inhaler, will be allowed in the study.)
- Recently initiated treatment for SMA (within 6 weeks prior to enrollment) with oral salbutamol or another β2-adrenergic agonist taken orally is not allowed. Patients who have been on oral salbutamol (or another β2-adrenergic agonist) for ≥ 6 weeks before enrollment and have shown good tolerance are allowed. The dose of

β2-adrenergic agonist should remain stable as much as possible for the duration of the study. Use of inhaled β2-adrenergic agonists (e.g., for the treatment of asthma) is allowed.

- Any prior use of chloroquine, hydroxychloroquine, retigabin, vigabatrin or thioridazine, is not allowed. Use of other medications known to or suspected of causing retinal toxicity within one year prior to enrollment is not allowed.
- Clinically significant abnormalities in laboratory test results, e.g., ALT values exceeding 1.5-fold the upper limit of normal, unless the elevated ALT level is considered of muscular origin (i.e., in the absence of other evidence of liver disease) which is supported by elevated CK and LDH. Out of range CK 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.
- Donation or loss of blood 10% of blood volume within 3 months prior to screening.
- Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to risdiplam or to the constituents of its formulation (see Risdiplam Investigator's Brochure).
- Concomitant disease or condition that could interfere with, or treatment of which might interfere with, the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the patient in this study.
- Recent history (less than 1 year) of ophthalmological diseases (e.g., glaucoma not controlled by treatment, central serous retinopathy, inflammatory/infectious retinitis unless clearly inactive, retinal detachment, retinal surgery, intraocular trauma, retinal dystrophy or degeneration, optic neuropathy, or optic neuritis) that would interfere with the conduct of the study as assessed by an Ophthalmologist. Any other abnormalities detected at screening (e.g., retinal layer abnormalities, edema, cystic or atrophic changes) should be discussed with the investigator, the Ophthalmologist, and with the Sponsor, who will jointly make the decision if the patient may be enrolled in the study. Patients in whom SD-OCT measurement of sufficient quality cannot be obtained at screening will not be enrolled.
- Any prior use of an inhibitor or inducer of FMO1 or FMO3 taken within 2 weeks (or within 5 elimination half-lives, whichever is longer) prior to dosing.

4.3 METHOD OF TREATMENT ASSIGNMENT

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

An interactive voice or web-based response system (IxRS) will be used to manage patient screening, enrollment, and drug supply.

Patients that are newly screened in the study will be assigned a number allocated by the IxRS. Sites should call the IxRS to enter the subject into screening and to register a screening failure. Patient numbers will be allocated by IxRS and will be used in the clinical database and for recording data in the electronic Case Report Form (eCRF).

The enrollment call to the IxRS should occur after the patient's eligibility has been confirmed. The day of the enrollment call is considered as Day –1 of the trial.

4.4 STUDY TREATMENT

The investigational medicinal product (IMP) for this study is risdiplam. Appendix 6 identifies all investigational medicinal products for this study.

4.4.1 Formulation, Packaging, and Handling

4.4.1.1 One-Bottle Formulation (Powder for Oral Solution)

The IMP risdiplam one-bottle clinical formulation is a powder for constitution to an oral solution. Each bottle contains 60 mg of risdiplam substance with excipients. The powder is constituted with purified water to yield an oral solution containing 0.75 mg/mL of risdiplam.

The excipients used in the one-bottle clinical formulation of risdiplam are the same as for the two-bottle formulation (powder and solvent for oral solution), except for isomalt added as an additional diluent.

Patients that are already enrolled in the study shall continue to use the risdiplam two-bottle clinical formulation until availability of the one-bottle formulation. Patients that are newly enrolled in the study will only receive the risdiplam one-bottle formulation throughout their participation in the study.

Note: the two-bottle formulation is no longer used in this study.

4.4.1.2 Packaging and Handling

Study medication will be constituted at each site by qualified pharmaceutical personnel, with the exact dosing volume to be administered by an oral/enteral dispenser. Detailed instructions for the constitution procedure of the respective formulations will be provided in a separate pharmacy manual. The bottles containing the constituted oral solution will be inserted into a labeled carton provided by Roche Clinical Trials Supplies department. The clinical study site will provide oral/enteral dispensers to the patient/caregiver for administering the solution. A diary will be provided to the patient/caregiver with instructions on study drug administration at home.

For each patient and on all instances of study drug dispensing, the formulation used (i.e., one-bottle with 0.75 mg/mL; or two-bottle with 0.25 mg/mL or 1.5 mg/mL solution of risdiplam *[when used earlier in the study])* must be recorded by the pharmacist or an authorized personnel.

Study drug packaging will be overseen by the Roche Clinical Trial Supplies department and will bear a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labelling of the study medication and excipient will be in accordance to Roche standards and local regulations. The qualified

individual responsible for dispensing the study drug will prepare the correct drug product according to the individual specific dose allocated to the individual patient. This individual will also record study drug batch number received by each patient during the study.

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

For further details, see the Risdiplam Investigator's Brochure and BP39054 Pharmacy Manual.

4.4.2 Dosage, Administration and Compliance

The qualified individual responsible for dispensing the study drug will prepare the correct dose. This individual will write the date dispensed and patient number and initials on the study drug bottle label and on the Drug Accountability Record. This individual will also record the MEDNO/study drug batch number received by each patient during the study. Throughout the study duration, the study medication should be taken once daily in the morning with the patient's regular morning meal, except when site visits are planned and study medication will be administered at the clinical site (see Appendix 1A, Appendix 1B, Appendix 3A and Appendix 3B). On these days, patients should have their regular morning meal at home before coming to the site; should there be a long time interval between this meal and arrival at the site, a snack will be given by the site to the patient prior to study medication administration. Patients receiving the study medication orally should always follow this by rinsing their mouth with water and swallowing.

Patients who are unable to swallow the study medication and who have a naso-gastric or gastrostomy tube in situ should receive the study medication by bolus via the tube. This should always be followed by a bolus flush of water through the tube. The study medication should be administered only with the supplied colored dispensers. A patient diary will be required that will capture information related to drug administration for all doses throughout the study.

If breastfeeding, the patient should be fed and burped prior to dosing. For infants able to swallow, study drug will be administered with a syringe inserted between infant's gum and cheek as described in the study drug administration instructions for use (see patient diary). Thereafter, water (approximately 10–20 mL) should be administered with a baby's bottle to prevent prolonged contact of study drug with buccal mucosa. Similarly, the peribuccal area of the SMA infant should be washed with water in the event of drug drooling or spitting. Breastfeeding should be avoided within 1 hour after study drug

administration. Women breastfeeding will be advised to rinse their breasts with water if breastfeeding occurs shortly after (i.e., $<$1 hour) study drug administration.

If a dose is not administered by 12:00 (noon) local time, it will be considered a missed dose and patients, parents or caregivers will be instructed to not administer study drug for that day, administer the regular amount (i.e., not double the dose) at the next scheduled time on the subsequent day, and report the event in the medication diary.

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

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

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 5.2.3.

4.4.3 Investigational Medicinal Product Accountability

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

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

The Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the patient to whom the study drug was dispensed (for example patient initials and date of birth). The date(s), quantity of the study drug dispensed to the patient.
- The date(s) and quantity of the study drug returned by the patient.

All records and drug supplies must be available for inspection by the Roche Monitor at every monitoring visit.

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

destroyed and provided that adequate storage and integrity of the drug has been confirmed.

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

Written documentation of IMP destruction must contain the following:

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

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

4.4.4 *Treatment with Risdiplam Until End of Study (Continued Access to Risdiplam)*

Patients completing 5 years of study treatment (2-year treatment period and 3-year OLE) and with no access to commercial risdiplam are eligible to continue to receive risdiplam IMP until the EOS (defined as the last patient's last visit or telephone call, see Section 3.1.3).

These patients continuing to receive risdiplam IMP until the study end are not required to perform additional study visits. Risdiplam IMP will be provided as per current study procedures. Only adverse events must continue to be reported to maintain minimum study safety reporting requirements (Section 4.6.2.5).

Once a patient gains access to commercial risdiplam or another treatment for SMA or post-trial access to risdiplam, the patient will leave the study.

The patient's route through study completion, access to risdiplam prior to EOS, and access to post-trial risdiplam are shown in Appendix 5.

4.4.5 *Post-Trial Access to Risdiplam*

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

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

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

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

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

In these situations the investigator and local health care system will transition the study patient to an alternative therapy, unless stated differently in the local regulation.

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

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

The patient's route through study completion and access to post-trial risdiplam (as applicable) are shown in Appendix 5.

4.5 CONCOMITANT THERAPY AND FOOD

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

4.5.1 Permitted Therapy

Concomitant therapy includes any medication, e.g., prescription drugs, over-the-counter drugs (OTCs), approved dietary and herbal supplements, nutritional supplements and any non-medication interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, physical therapy and rehabilitative therapy) used by a patient within 30 days of study screening until the study completion/early withdrawal

visit. All concomitant medications should be reported to the Investigator and recorded on the eCRF.

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

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

Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use, which should be recorded.

Dosing should always be used in the dose-range according to the approved local prescribing information.

Unless specified differently below, for any chronic treatment (defined as a minimum of 8 weeks of treatment), patients should be on a stable regimen for 6 weeks prior to screening and should remain on a stable regimen throughout the study.

Examples of allowed medications include the following, except those that are OCT-2 or MATE substrates (see Section 4.5.2):

- *Topical medications, including the topical form of all medications listed as prohibited therapy in Section 4.5.2*
- Chronic treatment with oral salbutamol or another β2-adrenergic agonist taken orally is allowed as long as treatment has been introduced for at least 6 weeks before enrollment and the patient has shown good tolerance.
- Use of inhaled β2-adrenergic agonists (e.g., for the treatment of asthma) is also allowed.
- Inhaled corticosteroids.
- Other inhaled drugs for obstructive airways diseases (e.g., anticholinergics and anti-allergic agents).
- Other systemic drugs for obstructive airways diseases (e.g., leukotriene receptor antagonists).
- Laxatives and other drugs for functional gastrointestinal disorders.
- Analgesics, including opioids (e.g., hydromorphone or codeine).
- Antibiotics with the exceptions mentioned in Section 4.5.2.
- Antihistamines.
- Proton pump inhibitors.

4.5.2 Prohibited Therapy

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

The following medications are explicitly prohibited for patients and mothers of patients if breastfeeding the patient for 2 weeks prior to dosing and throughout the study:

- Any OCT-2 and MATE substrates, e.g., amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine.
- Any inhibitor or inducer of FMO1 or FMO3.

Use of the following therapies are prohibited during the study and for at least 90 days prior to enrollment:

Medications intended for the treatment of SMA

- Nusinersen
- Riluzole
- Valproic acid
- Hydroxyurea
- Sodium phenylbutyrate
- Butyrate derivatives
- Creatine
- Carnitine
- Growth hormone
- Anabolic steroids
- Probenecid
- Chronic oral or parenteral use of corticosteroids (inhaled corticosteroid use is allowed)
- Agents anticipated to increase or decrease muscle strength or agents with known or presumed HDAC inhibition activity

Medications with Known *Phototoxicity* Liabilities

- Amiodarone, phenothiazines, and chronic use of minocycline.

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

All examinations listed below will be performed according to the SoAs outlined in Appendices 1–4.

Prioritization of blood samples is described in Section 4.6.3.

Follow-up phone calls are planned in this study. Patients (or caregivers of patients, as appropriate) will be called by the Investigator or designee to monitor safety and tolerability when not attending the clinic. Assessments will include adverse events, concomitant medication review, and significant life events (including but not limited to changes in school or employment status, marriage, death of parent or spouse, if male becoming a parent, etc.). A *final* follow-up *telephone* call *may* be made *approximately* 30 days after the study completion/early withdrawal visit to collect any adverse events*, if applicable (see Section 4.6.2.4).*

Monthly pregnancy tests are planned in this study for women of childbearing potential. On months without a site visit, the pregnancy test may be conducted at home either by the patient or by a health care provider (see Appendix 1). Drug dispensation, return of used and unused study drug bottles and supplies will occur at scheduled site visits, ad hoc re-supply site visits, or delivery to the patient's home if necessary. If considered necessary by the investigator and delegated by him/her, a qualified health care provider may also visit the patient's home. The following could be performed during home visits: blood sample collection, vital signs check, weight, collection of adverse events, concomitant medications, and significant life events or other information, as appropriate.

The exact timing of all study assessments (e.g., PK or PD blood sampling) may be shifted depending on emergent data, but the total number of assessments will not change, unless required to ensure the safety of a patient (e.g., after a dose change).

Unless otherwise stated, the age at screening determines which assessments will be conducted throughout the entire study period (e.g., MFM, RULM and HFMSE in patients $\geq$2 years vs. BSID-III and HINE in patients $<$2 years).

4.6.1.1 Medical History and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, use of alcohol and drugs of abuse, all medications (e.g., prescription drugs, OTCs, herbal or homeopathic remedies, nutritional supplements) and physical/occupational/exercise therapy used by the patient within 30 days prior to the screening visit.

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

4.6.1.2 Spinal Muscular Atrophy History

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

- SMA type.

- Age of onset.
- *SMN2* copy number (if available; it will be measured in any case during this study by clinical genotyping).
- Previous score on functional motor scale (e.g., MFM, ULM/RULM, HFSME, BSID-III), and/or disability scale (e.g., Brooke, Vignos).
- Current level of function and highest motor function achieved (i.e., sitting without support, rolling, crawling, standing, walking).
- History of previous enrollment in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101, or olesoxime (e.g., compound, duration).
- History of scoliosis or hip surgery (if applicable).

4.6.1.3 Anthropometric Measurements

Anthropometric measurements will be performed at the timepoints specified in the SoAs as described below:

- For patients aged 6 months to <2 years (infants), body weight will be measured to the nearest 100 g using an appropriate scale. For patients aged 2–11 years, body weight will be measured to the nearest 100 g. For patients aged 12–60 years, body weight will be measured to the nearest kilogram.
- For wheelchair-bound patients, weight of the patient and the wheelchair will be obtained with a wheelchair balance scale with the patient in the wheelchair. Then, the wheelchair will be weighed by itself and subtracted from the total weight. For lighter patients, the caregiver may carry the patient and their combined weight measured, followed by the caregiver being weighed and subtracted from the total weight.
- Patients able to stand will be weighed directly on a standard scale.

The patient's height will be measured or derived from ulna length to the nearest centimeter as follows:

- For all patients who are able to stand, height will be measured while standing using a stadiometer, with at least three independent measurements, which will be averaged.
- For patients unable to stand for the duration of the measurement e.g., have too many contractures, height will be derived from the measurement of ulna length.
  - Ulna length (from the tip of the olecranon process to that of the styloid process) will be measured using an anthropometer with the patient in sitting position, the left forearm resting comfortably on a table, elbow bent 90° to 110°, palm facing downwards and fingers extended but together.
- For very young children, height will be measured with the child in lying position using an inflexible length board with fixed headboard and moveable footboard.
  - When a patient's height can no longer be assessed by a fixed board and the patient is unable to stand (e.g., because the patient is longer than the fixed

board or due to scoliosis/contractures), the patient's height will be derived from ulna length to the nearest centimeter as described above.

- The method of height measurement should be kept consistent for as long as possible.

Body mass index (BMI) will be derived. See the SoAs for timepoints (Appendix 1A, Appendix 1B, Appendix 3A and Appendix 3B).

For patients aged < 5 years only, head circumference will be measured to the nearest 0.1 cm using a flexible, non-stretchable tape. The head circumference (or occipital-frontal circumference) is measured around the widest part of the head from the most prominent point on the back of the head (occiput) to the most prominent part of the forehead between the eyebrows. The measuring tape should remain above the ears and fully compress any hair (hair ornaments should be removed and large plaits or braids loosened). The measurement should be taken to the nearest millimeter and repeated three times with the largest measurement being recorded.

For patients aged < 2 years only, chest circumference will be measured to the nearest 0.1 cm using a flexible, non-stretchable tape with the patient lying on the back, under the axilla and over the nipple line. The measurement should be taken to the nearest millimeter and repeated three times with the largest measurement being recorded.

Head to chest circumference ratio will be derived throughout the study for children aged 6 months to < 2 years (see Section 6.6).

4.6.1.4 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, throat, neck and lymph nodes, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. The physical examination will NOT include pelvic, rectal or breast exams except for Tanner staging, if needed.

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

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.6.1.5 Neurological Examination

A detailed neurological examination focusing on mental status, behavioral and cognitive assessments will be performed in all patients at the timepoints specified in the SoAs (Appendix 1A, Appendix 1B, Appendix 3A and Appendix 3B).

The examination will be performed by asking questions to the patient and/or the patient's caregiver as well as observing the behavior of the patient in general and while performing certain tasks. Questions and tasks will be adapted to the age and motor ability of the patient and may include the following:

- For very young patients, according to the Investigator's discretion: observing reaction to a sound, speech development, shifting attention to a newly introduced toy, observing the patient interact with the parent/caregiver
- For older patients: examination of social interaction (school, friends, activities, or job, as appropriate), memory (e.g., with short word recall), reasoning and language, drawing skills, etc.

4.6.1.6 Tanner Staging

Tanner staging will be determined at the baseline, Month 12 and subsequent yearly visits in all patients aged from 9–17 years of age at screening or following their 9th birthday if enrolled prior to age 9. Once a patient reaches stage 5, Tanner staging no longer needs to be performed.

Tanner staging criteria will be provided to the sites prior to study start.

4.6.1.7 Menstrual Status

For female patients, menstrual status during the study will be collected as appropriate. Once menstruation is confirmed, the patient must undergo pregnancy testing as outlined in Appendix 1.

4.6.1.8 Vital Signs

Blood pressure (BP), pulse rate, respiratory rate and body temperature (oral or tympanic) will be recorded at the timepoints specified in the SoAs.

Vital signs will be obtained while the patient is in a semi-supine/supine position after the patient has been resting for approximately 5 minutes. Vital signs should be measured prior to blood draw or at least 10 minutes after the last blood draw.

BP, pulse rate and respiratory rate should be obtained in a quiet room at a comfortable temperature, with the patient's arm unconstrained by clothing or other material. The patient should be asked to remove all clothing that covers the location of cuff placement. All measurements will be obtained from the same arm and, with the appropriate cuff size, using a well-calibrated automatic instrument with a digital readout, throughout the study (the “ideal” cuff should have a bladder length that is 80% and a width that is at least 40% of arm circumference [a length-to-width ratio of 2:1]). The individual should be comfortably in a semi-supine/supine position, with the legs uncrossed.

In pediatric patients (aged 17 years and below), at screening and at every BP assessment throughout the study, SBP and DBP percentiles for age should be

determined using the Centers for Disease Control and Prevention (CDC) tables, which require to first determine patient's percentile for stature using the CDC growth charts.

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

4.6.1.9 Electrocardiograms

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

To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. The timing of 12-lead ECG recordings and mealtimes should be consistent throughout all study visits with multiple ECG recordings (e.g., Day −1 and Weeks 4 and 13). In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

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

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction; Phan et al 2015), QTcF (Fridericia's correction) and RR will be calculated by the Sponsor in the eCRF. Both corrections of QTc will be tabulated and analyzed; although, in children, Bazett's formula appears to provide a better correction of the QT interval. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF, additionally as an adverse event as appropriate. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal.

4.6.1.10 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at timepoints specified in the SoAs (Appendix 1A, Appendix 1B, Appendix 3A and Appendix 3B).

At any time and as described in Section 4.6.3, safety laboratory samples (i.e., hematology, blood chemistry, coagulation) will be given priority over any other sample, such that the volume of blood taken at any single timepoint will not exceed 1 mL/kg (patients aged 2–60 years) or 1.5 mL/kg (patients aged 6 months to <2 years), and the volume collected over any 8-week period throughout the study will not exceed 4 mL/kg (patients aged 2–60 years) or 4.5 mL/kg (patients aged 6 months to <2 years). For infants only, use of microcollection method to collect safety laboratory samples should always be favored to limit the amount of blood collected.

Additional blood or urine 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's safety.

Where the clinical significance of abnormal laboratory results is considered uncertain, screening laboratory tests may be repeated before enrollment to confirm eligibility. If there is an alternative explanation for a positive urine test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

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

Samples for the following blood and urine laboratory tests will be collected as specified in the SoAs (Appendix 1A, Appendix 1B, Appendix 3A and Appendix 3B) and sent to the laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments. Through the duration of the study, safety laboratory assessments will be performed at the local laboratory for patients aged <2 years at screening and at the central laboratory for patients aged ≥ 2 years at screening.

- Hematology: Hemoglobin, hematocrit, erythrocytes (RBC), platelets, leukocytes (WBC), differentials (counts): neutrophils, eosinophils, lymphocytes, monocytes, basophils, reticulocyte count.
- Coagulation: prothrombin time (expressed as INR) and activated partial thromboplastin time (aPTT). Venous blood collection is required for coagulation. Coagulation should not be assessed for a given visit if venous blood cannot be drawn after two attempts.

- Blood chemistry:

  Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and conjugated bilirubin, alkaline phosphatase (ALP), gamma-glutamyl-transferase (γ-GT), creatine phosphokinase (CPK), albumin, creatinine, urea nitrogen, total protein, sodium, chloride, calcium, bicarbonate, phosphate, potassium, triglycerides, total cholesterol, glucose, C-reactive protein (CRP), amylase, lipase.
- Thyroid hormones (free T4 and thyroid stimulating hormone [TSH]; at the time of blood chemistry sampling at selected timepoints, see Appendix 1A and Appendix 1B) (for patients aged 2–60 years)
- Hormone: estradiol, follicle-stimulating hormone, luteinizing hormone in female patients of childbearing potential
- Pregnancy test

  All women of childbearing potential (including those who have had a tubal ligation) will have blood or urine pregnancy tests at the timepoints specified in the SoAs. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination, if clinically significant positive results from the dipstick (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria) (for patients aged ≥2 years at time of assessment).
- Drugs of abuse will be measured in urine: cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, phencyclidine, tricyclic antidepressants, and barbiturates (for patients aged 12–60 years).
- Alcohol will be measured in urine (for patients aged 12–60 years).

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

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

4.6.1.11 Ophthalmological Assessments and Examination

Ophthalmological assessments are no longer performed starting with Protocol Version 5. Assessments performed under Protocol Versions 1-4 inclusive are described below.

Ophthalmological assessments will be performed at timepoints specified *(refer to Appendix 5 in Protocol Version 4)*. Based on the review and assessment of the

cumulative safety data of all patients in clinical trials for risdiplam, the type and frequency of ophthalmology assessments have been modified once the Week 52 visit has been completed. Details of the changes to the ophthalmological assessments are described in this section. The details of the visual tests will be included in a separate Central Reading Center manual. An Ophthalmologist or other similarly trained person, trained and certified to perform the study-specific ophthalmological assessments will perform the ophthalmological assessments in all patients.

Central Reading

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

For Adults and Children Aged ≥ 10 Years

Ophthalmological assessments include slit lamp examination for assessment of the anterior and posterior segment including the cornea, anterior chamber, lens and the fundus (indirect ophthalmoscopy with e.g., 60 and 90 diopter lenses to examine the macula, optic nerve, mid- and peripheral areas). During selected visits, the intraocular pressure will be measured using standard techniques such as Goldmann tonometry or non-contact tonometry. The frequency of intraocular pressure measurement has been reduced to occur only at Screening and Week 52 visits. Once the Week 52 visit has been completed, measurement of intraocular pressure and fundus photography will no longer be performed. The remaining ophthalmology assessments will be performed every 6 months following the Week 52 visit. The method of assessment must remain constant for each patient throughout the study.

Fundus Photography (up to and including Week 52)

Seven-field or wide-field fundus photography (FP) will be performed at the study sites by trained and Central Reading Center-certified personnel. Where both 7-field and wide-field devices are available, wide-field FP should be performed. After a first unsuccessful attempt, an image of the fundus may be captured during funduscopy if possible.

Visual Acuity Tests

Best corrected visual acuity (BCVA)

BCVA will be measured using the ETDRS or equivalent charts at a distance of 4 meters. The eye chart has a series of letters, with the largest at the top. As the person being tested reads down the chart, the letters gradually become smaller. The chart will be

standing, at 4 meters from the patient's eyes. These sheets will be considered source data and scores from these sheets will be transcribed on the eCRF.

Visual Field Test - Automated Static Threshold Perimetry

Visual fields will be measured using automated perimetry (e.g., Humphrey Field Test Analyzer) with the 24-2 SITA fast program. Each visual field will be assessed centrally. In case of any clinically relevant abnormality, the patient should be further examined by an ophthalmological specialist. Visual field data will be printed out and stored. After a first unsuccessful attempt, threshold perimetry may be replaced by simple visual field testing such as easier perimetry protocols or, as a last resort, confrontation visual field testing if perimetry is not possible.

SD-OCT

Spectral domain-optical coherence tomography provides both qualitative (morphology and reflectivity) and quantitative (thickness, mapping and volume) analyses of the examined tissues in real time. Each SD-OCT will be graded as normal, or abnormal. If abnormal, the character of the abnormality will be noted (e.g., changes in retinal thickness, edema, cystoid or atrophic changes, detection of fluid within the retinal layers, macular holes, vitreo-macular traction) and the degree of abnormality. Additionally, every attempt should be made to capture additional images after up, down, left, and right gaze.

For Children Aged ≥2 to<10 Years

Examinations will be carried out by an experienced pediatric ophthalmology specialist, a pediatric ophthalmologist, or neuro-ophthalmologist. The frequency of intraocular pressure measurement has been reduced to occur only at Screening and Week 52 visits. Once the Week 52 visit has been completed, measurement of intraocular pressure and fundus photography (FP) will no longer performed. The remaining ophthalmology assessments will be performed every 6 months following the Week 52 visit. Ophthalmic examinations include the following:

- Bruckner Test.
- Red reflex.
- Fix and follow test.
- Cover-uncover test.
- Simple visual field test.
- Intraocular pressure (tonometry or digital palpation of globes) (Screening and Week 52 only).
- Visual acuity (adapted based on age and neurological development).
- Retinal examination (dilated or not) including slit lamp examination/ophthalmoscopy (including anterior and posterior segment, fundus, optic nerve).

- Imaging: SD-OCT (including up, down, left, and right gaze images whenever possible) and FP (after a first unsuccessful attempt, an image of the fundus may be captured during funduscopy if possible). Fundus photography up to and including Week 52 only.

For Children Aged <2 Years

Examinations will be carried out by a pediatric ophthalmologist or neuro-ophthalmologist with the support of a pediatric ophthalmology imaging specialist. Once the Week 52 visit has been completed, FP will no longer performed. The remaining ophthalmology assessments will be performed every 6 months following the Week 52 visit. Ophthalmologic examination and retinal imaging include:

- Visual Development.
- Red reflex: Performed with an ophthalmoscope or retinoscope from approximately 30 cm / 1 foot in a semi-darkened room, examination will assess brightness of pupil reflex (color and homogeneity, symmetry of the findings, absence, white, opacified).
- External Ocular Examination: including but not limited to eyelids, conjunctiva, sclera, cornea light reflex.
- Pupillary Response: Using a bright light, pupillary response of each eye will be assessed for direct and consensual response and when achievable accommodative response will be tested.
- Fix and follow test: Failure to fix and follow will be assessed in the context of the patient's medical conditions and age.
- Ocular examination under magnification (including slit lamp / ophthalmoscope of anterior and posterior segments including assessment (with or without dilation) of the retina and optic nerve).
- OCT imaging will be recorded with the Envisu hand-held device from Bioptigen Inc. (or other handheld OCT device available and approved by the central ophthalmic laboratory), alternative method may include the use of a Spectralis (Heidelberg Engineering) converted to a hand-held system for supine imaging. Every attempt should be made to capture additional images after up, down, left and right gaze.
- Color FP (up to and including Week 52 only).

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

4.6.1.12 Nutritional Check

Nutritional assessment will be performed for all patients at the timepoints indicated in Appendix 1A, Appendix 1B, Appendix 3A and Appendix 3B and will include:

- Determination of BMI, from body weight and height or head to chest circumference ratio from anthropometric measurements (Section 4.6.1.3).

- Nutritional status interview of the patient or caregiver (as appropriate), including questions about ability to swallow, type of food swallowed, and level of solid food intake.

Based on this assessment, specific nutritional advice may be given individually to the patients by the Investigator or Nutritionist.

4.6.1.13 Pharmacokinetic Assessments

Blood for determination of plasma concentrations of risdiplam, and its metabolite(s) as applicable, will be collected as detailed in Appendix 2 and Appendix 4.

Plasma concentrations of risdiplam will be measured by a specific validated LC-MS/MS assay. Metabolites may be measured by a specific validated LC-MS/MS assay, or other methods as appropriate, and PK samples may also be used for exploratory metabolite identification or measurement of olesoxime concentration in patients previously treated with olesoxime, if deemed necessary.

PK sampling must be attempted first utilizing venous blood collection. If venous blood cannot be drawn after two attempts, capillary blood collection may be attempted as a secondary option upon agreement with the Sponsor.

PK samples will be destroyed no later than 5 years after the date of the final Clinical Study Report.

4.6.1.14 Plasma Protein Binding

A venous blood sample will be collected at screening from patients aged < 1 year to measure plasma protein binding, i.e., to measure the free fraction of the study drug. Results for a patient must be available and checked by the Sponsor before any study drug is administered to the patient.

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

The measurement of plasma protein binding may be stopped during the study, if judged as no longer necessary on the basis of accumulated data from this and other ongoing studies.

4.6.1.15 Fluid Pharmacodynamic Assessments

The following fluid PD assessments will be performed as detailed in SoAs (see Appendices 1–4).

However, should the total blood volume to be collected at any timepoint according to these SoAs exceed 1 mL/kg (patients aged 2–60 years) or 1.5 mL/kg (patients aged 6 months to < 2 years), or the volume collected over any 8-week period throughout the study exceeds 4 mL/kg (patients aged 2–60 years) or 4.5 mL/kg (patients aged 6 months

to <2 years) the blood sample prioritization described in Section 4.6.3 should be followed.

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

  Whole blood samples will be taken from every patient at the timepoints specified in the SoAs (see Appendices 1–4) to measure in vivo splicing modification of SMN1, SMN2 FL, and SMNΔ7 mRNA during the course of the study. In addition, housekeeping genes for the quantitative analysis of RNA will be measured. Additional mRNA may be used for exploratory analysis/assay development related to SMA, including, but not limited to, pathways related to SMN function and treatment response.

- SMN protein levels

  Blood for SMN protein analysis will be collected from every patient.

- Mandatory exploratory biomarkers assessing treatment response (for patients aged 12–60 years)

  Serum for the analysis of exploratory biomarkers related to SMA or to the response from treatment (e.g., muscle damage or IGF system) will be collected from patients aged 12–60 years at the timepoints specified in the SoA (Appendix 1).

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

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

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

4.6.1.16 Digital Biomarker Assessment

Digital biomarker assessments ceased to be performed during 2022 (see amendment rationale). Assessments performed under Protocol Versions 1-4 inclusive are described in Protocol Version 4.

4.6.1.17 Clinical Genotyping Sample

A single mandatory whole blood sample will be taken for DNA extraction from every patient, at the timepoint indicated in the SoAs (Appendix 1A, Appendix 1B, Appendix 3A and Appendix 3B). The DNA will be used to determine the copy number of *SMN2* and may also be used to confirm the *SMN1* mutation, deletion or any other modifications of the SMN genes.

The clinical genotyping samples may be used for additional exploratory analysis/assay development related to SMA including, but not limited to, mitochondrial DNA and to genes related to drug metabolizing pathways, SMN function, severity of the disease or treatment response. These samples will be destroyed no later than 5 years after the date of the final clinical study report. Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4. For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.6.1.18 Functional Motor and Motor Development Assessments

Functional motor and motor development assessments will be performed as detailed in the SoAs (see Appendix 1A, Appendix 1B, Appendix 3A and Appendix 3B). The MFM, RULM, HFMSE, BSID-III, and HINE may be video recorded for quality assessment by trainers. These recordings will not be part of the clinical database. These videos may be anonymized and accessible by the Sponsor and Health Authorities. The MFM, RULM and HFMSE will be conducted in patients aged $\geq$2 years. The BSID-III and HINE will be conducted in patients aged 6 months to $<$2 years.

Patients who are unable to perform or complete one or several of the functional motor and motor development assessments may still participate in the study.

Motor Function Measure

The MFM (Bérard et al 2005) is an ordinal scale constructed for use in patients with neuromuscular disorders.

The scale comprises 32 items that evaluate physical function in three dimensions:

- D1 (13 items) evaluates functions related to standing and transfer.
- D2 (12 items) evaluates axial and proximal function in supine and sitting position on mat and chair (3/12 items evaluate arm function with the patient seated on a chair).
- D3 (7 items) evaluates distal motor function.

The scoring of each task uses a 4-point Likert scale based on the patient's maximal abilities without assistance:

- 0: cannot initiate the task or maintain the starting position
- 1: performs the task partially
- 2: performs the task incompletely or imperfectly (with compensatory/uncontrolled movements or slowness)
- 3: performs the task fully and "normally."

The 32 scores are summed and then transformed onto a 0-100 scale to yield a total score expressed as the percentage of the maximum possible score (the one obtained with no physical impairment); the lower the total score, the more severe the impairment.

Strong evidence of reliability (intra-class correlation coefficients ranging from 0.96-0.99 for the total and dimension scores for both intra-rater and inter-rater reliability) and validity (Spearman rank order correlation coefficients ranging from 0.85 to 0.91 with other functional measures including Vignos grade and Brooke grade) has previously been demonstrated (Bérard et al 2005).

The MFM is free, available in several languages including English, German, Italian, French, and Dutch. Users' manual and scoring sheet will be provided to the sites prior to study start.

The full MFM-32 will be administered to all patients aged ≥ 2 years. The scale will be administered by a trained Physiotherapist or other suitably qualified professional who has received training on the administration of the MFM, following the instructions in the MFM users' manual. If possible, the same assessor should follow the patient throughout the study. Scores will be recorded on the scoring sheet and on the eCRF and maximal score will be derived.

Revised Upper Limb Module

The RULM is a scale that assesses specifically the motor performance of the upper limbs in SMA patients. It consists of twenty items that test proximal and distal motor functions of the arm in patients with SMA. It is easy to use, measures functions related to everyday life and is applicable to children starting from 30 months of age.

The first entry item is scored from 0 (no useful function of hands) to 6 (can adduct both arms simultaneously in a full circle until they touch above the head). This item serves as a functional class identification but does not contribute to the total score.

Eighteen of the tasks in the RULM are scored, with:

- 0: cannot complete task independently
- 1: modified method but can complete task independently
- 2: completes task without any assistance

The remaining task is scored as a can/ cannot score with 1 as the highest score. The scores for all tasks, except the first entry item, are summed and can range from 0 (no tasks completed) to 37 (all tasks independently completed).

A users' manual and scoring sheet will be provided to the sites prior to study start. The scale will be administered by a trained Physiotherapist or other suitably qualified professional who has received training on the administration of the RULM according to the users' manual; scores will be recorded on the scoring sheet and on the eCRF and the total score will be derived.

The Hammersmith Functional Motor Scale Expanded

The HFMSE was developed to assess the motor function ability of individuals aged two years or older, with Type 2 and 3 SMA (O'Hagen et al 2007). The scale contains 33 items, which are scored on a 3-point Likert scale (0-2) and summed to derive the total score, with lower scores indicating greater impairment. Similar to the MFM, the HFMSE contains a series of assessments designed to assess important functional abilities, including standing, transfers, ambulation, and proximal and axial function. The original Hammersmith Functional Motor Scale (HFMS) contained 20 items and was developed primarily to assess a SMA Type 2 population. Thirteen items, adapted from the Gross Motor Function Measure (GMFM), were added to improve the sensitivity of the scale, particularly for measuring motor function ability in Type 3 SMA patients. The HFMS and HFMSE have been used in previous and ongoing clinical trials for SMA, including as a primary endpoint (ClinicalTrials.gov Identifiers NCT02292537, NCT01302600; Chiriboga et al 2016).

The intra-rater reliability of the HFMSE was assessed in a sample of 38 Type 2 and 3 SMA patients using data at baseline and 2 months, with strong evidence demonstrated: intra-class correlation coefficient = 0.99 (O'Hagen et al 2007). The validity of the HFMSE was assessed in a sample of 70 individuals with Type 2 and 3 SMA (Glanzman et al 2011). Convergent validity was demonstrated by strong correlations with the GMFM ($r = 0.98$), FVC (percentage of predicted normal; $r = 0.87$), functional rating ($r = 0.92$), measures of extension and flexion ($r = 0.74$-0.77). The HFMSE also demonstrated an ability to differentiate between groups defined by *SMN2* copy number, bi-level positive airway pressure use, ambulatory status, and SMA type. In this sample, time of administration averaged 12 minutes.

A users' manual and scoring sheet will be provided to the sites prior to study start. The scale will be administered by a trained Physiotherapist or other suitably qualified professional who has received training on the administration of the HFMSE according to the users' manual; scores will be recorded on the scoring sheet and on the eCRF and the total score will be derived.

Bayley Scales of Infant and Toddler Development–Third Edition

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

BSID data reflect the U.S. population in terms of race, ethnicity, infant gender, education level of parents, and demographic location of the infant. The BSID was standardized in

1,700 infants, toddlers, and preschoolers between 1 and 42 months of age. A supplemental study has also demonstrated strong measurement properties for the BSID-III in 221 infants in the United Kingdom and Ireland. The normed-scores derived from the BSID-III are used in clinical practice to detect infants with developmental delays, as well as to evaluate developmental progress and the impact of therapeutic interventions. In addition, the generated T-scores and percentiles for developmental achievement allow direct clinical comparison of any stabilization of decline or improvement against normally developing children.

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

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

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

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

- Head control:
  - Item 9 – Controls head while upright, 15 seconds
- Rolling:
  - Item 14 – Rolls from side to back
  - Item 20 – Rolls from back to side
- Sitting:
  - Item 16 – Sits with support briefly
  - Item 19 – Sits with support 30 seconds
  - Item 22 – Sits without support 5 seconds
  - Item 26 – Sits without support 30 seconds

- Standing
  - Item 33 – Supports weight
  - Item 40 – Stands alone
- Walking
  - Item 37 – Walks with support
  - Item 42 – Walks alone

Hammersmith Infant Neurological Examination – Module 2

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

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

4.6.1.19 Six-Minute Walk Test (6MWT; ambulant patients only)

The 6MWT is an objective evaluation of functional exercise capacity that measures the maximum distance a person can walk in 6 minutes over a 25-meter linear course. Originally developed for chronic respiratory disease and heart failure, the test has since then been widely used as a performance-based measure of functional exercise capacity in many other populations and diseases, and normative data are available for adults and children.

In particular, the 6MWT has been widely used as an outcome measure in clinical trials in neuromuscular diseases, including Duchenne muscular dystrophy, Becker muscular dystrophy, and SMA.

In addition to providing a clinically relevant measure of the patient's walking ability that has a direct impact on autonomy, the 6MWT was shown to detect physiological fatigue in ambulatory SMA patients as demonstrated by a 17% decrease in gait velocity from the first minute to the last (Montes et al 2010).

In this study, the 6MWT will be administered by a trained Physiotherapist or other suitably qualified professional who has received training on the administration of the 6MWT, assisted by an additional follower to ensure patient safety during the tests. Patients must be aged $\geq$6 years and must be able to walk unassisted (i.e. without braces, crutches or calipers, or person [e.g., hand-held] assistance) for at least 10 m in order to complete this test. It will be performed with minimum verbal encouragement, according to the American Thoracic Society (ATS) guidelines (ATS 2002). The

evaluator and follower keep the patient on course, let the patient know how long they have left to walk, and ensure the patient chooses his or her own pace for the whole duration of the test. The course is a 25-m linear course in a quiet corridor at least 30-m long. It is marked with a horizontal line at the beginning, the end, and at each intervening meter. A cone is placed at each end. Participants will be instructed that the test aims to see how far they can walk over a 6-minute period going around the cones. They must not run or jog. The use of assisted devices, such as ankle foot orthoses, crutches, walkers, or canes, will not permitted during the assessment. However, suitable shoes and socks are to be worn. Patients will be permitted to rest against the wall, without sitting, if necessary. The total distance walked is recorded as well as how far they walk in each minute of the test.

Falls, if any, will also be recorded.

4.6.1.20 Pulmonary Function Testing

Pulmonary testing will be performed as detailed in the SoA (see Appendix 1).

Spirometry

For patients aged ≥6 years, hand-held spirometry will be performed according to the manual of operations. The test will be performed a minimum of three times while the patient is in a sitting position.

If the patient reaches 6 years of age at any time during the 30-day screening period, the patient should have spirometry performed during the screening visit.

Spirometry data will be electronically transferred from the investigational sites to Morgan Scientific where the data will be verified for quality. The spirometry data, including the following measures, will then be electronically loaded in to the study database:

- FVC
- FEV1
- PCF

Patients who are unable to perform or complete the pulmonary function testing assessments may still participate in the study.

Sniff Nasal Inspiratory Pressure

The SNIP is a volitional, non-invasive test of inspiratory muscle strength that has been successfully applied to children >2 years of age. Advantages include the simplicity of the maneuver and the absence of a mouthpiece, which is particularly helpful for patients with SMA, who may have bulbar weakness. SNIP also has the advantage of measuring inspiratory pressure during a natural maneuver that is easily performed even by young children with neuromuscular disorders. Based on the shape of the normal pressure–volume curve, a loss of respiratory muscle strength is expected before a fall in volume capacity and other lung volumes. SNIP has been shown to decline in both SMA

Type 2 and 3 patients, with an annual decline of 5.4 ± 6.3% and 6.4 ± 8.0%, respectively (Khirani et al 2013). It is therefore plausible that SNIP measurement may detect the respiratory muscle strength decrease earlier in the disease or in younger children than would other respiratory function tests.

The SNIP test is performed according to the manual of operations.

At least three valid measurements must be obtained from each patient aged ≥ 2 years. SNIP data will be electronically transferred from the investigational sites to a third party vendor where the data will be verified for quality. The SNIP data will then be electronically loaded in to the study database.

4.6.1.21 Columbia-Suicide Severity Rating Scale

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a clinical-rated tool used to assess the lifetime suicidality of a patient (C-SSRS baseline/screening) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality. A modified and reduced pediatric version exists that has been successfully applied in children with various psychiatric disorders that do not involve cognitive impairment (Food and Drug Administration [FDA] 2012). The suggested age range for this pediatric version is from middle childhood (typically, around age 7) through onset of adolescence (typically, through age 11).

In this study, the C-SSRS will be collected at baseline and at the timepoints indicated in the SoA in patients aged ≥ 6 years at time of assessment, using the appropriate version according to the patient's age. It will be completed by a member of the site staff who has received appropriate training after an interview with the patient and additionally for children, with the parent attending the visit.

4.6.1.22 SMA Independence Scale (SMAIS)

The SMAIS was developed specifically for SMA in order to assess function-related independence. The SMAIS contains 29 items, assessing the amount of assistance required from another individual to perform daily activities such as eating, or transferring to/from their wheelchair. Each item is scored on a 0–4 scale (with an additional option to indicate that an item is non-applicable). Item scores are summed to create the total score. Lower scores indicate greater dependence on another individual. The SMAIS will be completed by patients aged ≥ 12 years.

A parent, or caregiver, if no parent is available, should complete the caregiver-reported version of the SMAIS about the patient's level of independence, where possible for patients aged ≥ 2 years. This questionnaire assesses the same content as the patient-reported version described above. The same caregiver should complete the measure throughout the study.

4.6.1.23 Samples for Research Biosample Repository

Overview of the Research Biosample Repository

The Roche Research Biosample Repository (RBR) is a centrally administered group of facilities for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage and analysis of these specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Specimens (blood samples) will be collected from patients who give specific consent, and assent if applicable, to participate in this optional RBR. Only patients aged 12–60 years will be invited to participate. Collected specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression.
- To increase knowledge and understanding of disease biology.
- To study drug response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

Approval by the Institutional Review Board or Ethics Committee

Sampling for the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's Institutional Review Board or Ethics Committee (IRB/EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol will not be applicable at that site.

Sample Collection

The following samples will be collected at the timepoints specified in the SoAs for identification of dynamic (non-inherited) biomarkers:

- Blood for samples plasma isolation.
- Blood samples will be collected for RNA analysis.

The following samples will be collected for identification of genetic (inherited) biomarkers:

- Blood sample for DNA extraction for genetic biomarker (inherited) discovery and validation.

The sample collected for DNA extraction may be used for whole genome sequencing (WGS) and other genetic analysis and may be sent to one or more laboratories for analysis.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS provides a comprehensive characterization of the genome and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analyzed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For all samples, dates of consent and specimen collection should be recorded on the associated RBR page of the eCRF. For sampling procedures, storage conditions, and shipment instructions, see the separate laboratory manual.

RBR specimens will be stored and used until no longer needed or until they are exhausted. The RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., Health Authority requirements).

The repository specimens will be subject to the confidentiality standards described in Section 8.4.

Confidentiality

Data generated from RBR specimens must be available for inspection upon request by representatives of national and local Health Authorities, and Roche Monitors, representatives, and collaborators, as appropriate.

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

Data derived from RBR specimen analysis on individual patients will generally not be provided to study Investigators unless a request for research use is granted. The aggregate results of any conducted research will be available in accordance with the effective Roche policy on study data publication.

Genetic research data and associated clinical data may be shared with researchers who are not participating in the study or submitted to government or other health research databases for broad sharing with other researchers. Patients will not be identified by name or any other personally identifying information. Given the complexity and exploratory nature of these analyses, genetic data and analyses will not be shared with Investigators or patients unless required by law.

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

Consent to Participate in the Research Biosample Repository

The Informed Consent and Assent Form will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each patient, and their parent/caregiver if applicable, the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

The Investigator should document whether or not the patient, or their parent/caregiver if applicable, has given consent/assent to participate by completing the RBR Sample Informed Consent eCRF.

In the event of death or loss of competence of a patient who is participating in the Research, the participant's specimens and data will continue to be used as part of the RBR.

Withdrawal from the Research Biosample Repository

Patients or their parent/caregiver if applicable, who give consent to provide specimens for the RBR have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient or their parent/caregiver if applicable, wishes to withdraw consent to the testing of his or her specimens during the study, the Investigator must inform the Medical Monitor in writing of the patient's wishes through the use of the appropriate RBR Subject Withdrawal Form and, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the Investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from Study BP39054 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study BP39054.

Monitoring and Oversight

Specimens collected for the Research Biosample Repository will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche

monitors and auditors will have direct access to appropriate parts of records relating to patient participation in Research Biosample Repository for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the samples.

4.6.2 Timing of Study Assessments

4.6.2.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

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

An Eligibility Screening Form documenting the Investigator's assessment of each screened patient with regard to the protocol's inclusion and exclusion criteria is to be completed by the Investigator and kept at the investigational site.

Screening and pre-treatment assessments will be performed between 2 to 30 days prior to Day 1 (according to the SoAs, see Appendix 1A and Appendix 3A). An abbreviated rescreening (written informed consent, medical history, physical examination, RULM [patients aged ≥2 years], HFMSE [patients aged ≥2 years], body weight, safety laboratory tests, pregnancy test [females of childbearing potential only], urine analysis [patients aged ≥2 years] and inclusion/exclusion criteria) may be allowed under circumstances where the patient has passed screening but could not be enrolled within the 30-day screening window due to a study halt, logistical, personal, or technical reasons. At no time should the duration between the original screening visit and the abbreviated rescreening visit exceed 3 months. An abbreviated rescreening will only be permitted in cases where this poses no safety risk to the patient.

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

For patients aged ≥2 years: Due to the high number of assessments, including multiple 12-lead ECG recordings (for patients aged 12–60 years only), pulmonary testing and the MFM, it is important that the order of assessments be maintained on Day −1 to minimize variability, as follows: adverse events, previous/concomitant medications, confirmation of eligibility, enrollment, 1st ECG recording, 2nd ECG recording, 3rd ECG recording,

physical examination, Tanner staging, vital signs, 4th ECG recording, patient/caregiver-reported outcomes, pulmonary testing, MFM, 6MWT and blood samples. Flexibility is given to the site whether to perform the physical examination, Tanner staging, vital signs, patient/caregiver-reported outcomes assessment, pulmonary testing, MFM, and blood samples after the 3rd or 4th ECG recording. To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. If pulmonary testing, MFM, or blood samples are done prior to the 4h ECG recording, the following ECG recording should be preceded by a break of at least 20 minutes. The timing of 12-lead ECG recordings and mealtimes should be consistent throughout all study visits with multiple ECG recordings (e.g., Day −1 and Weeks 4 and 13). The pulmonary testing, the MFM and the 6MWT should be preceded by a break of at least 15 minutes. Additional breaks are recommended at any other times as appropriate for each patient.

4.6.2.2 Assessments During Treatment

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

The study visits when efficacy assessments are performed (see SoAs for timepoints, Appendix 1A, Appendix 1B, Appendix 3A and Appendix 3B) will be the most extensive visits, including all efficacy assessments in addition to PK, PD, full physical examination, and safety assessments.

For patients aged ≥2 years, these visits will be conducted over 2 days but can also be conducted over 3 days if preferred by the patient (e.g., the *physical examination)* may be conducted on the morning of the day preceding Block 1 or the day after Block 3. For these visits, three blocks of assessments have been identified that must be conducted in the order described in Table 2, with Blocks 1 and 2 to be performed on Day 1 and Block 3 on Day 2. Flexibility is given to the site for the order of tests within each of these blocks. It is critical that the MFM, the HFMSE, the RULM and the 6MWT are always preceded by a break of at least 15 minutes. Additional breaks are recommended at any other time as appropriate for each patient.

For patients aged 6 months to <2 years, these visits may be conducted either as one day visit or over 2 days, whichever is preferred by the parents or caregiver and possible for the clinical site. Table 3 provides guidance for the order in which the assessments should be conducted. Flexibility is given to the site for the order of tests. However, it is critical that the BSID-III is always preceded by a break of at least 15 minutes. Additional breaks, which can include nursing/feeding of the patient (if applicable), are recommended at any other time as appropriate for each patient.

It is also recommended that for a single patient, assessments be conducted in the same order throughout the trial.

Motor function and motor milestone assessments may be delayed to another time or day within the visit window if, in the opinion of the investigator or physiotherapist, the patient is uncooperative.

Table 2 Order and Blocks of Assessments for Patients Aged ≥2 Years at Study Visits when Efficacy Measurements are Performed

Day 1	
Block 1	• Collection of adverse events and concomitant therapies • Pulmonary testing including SNIP **BREAK** • MFM (32 item) **BREAK**
Block 2	• ECGs, vital signs • Physical examination • C-SSRS
Day 2	
Block 3	• Blood samples or insertion of catheter for blood sampling **BREAK** • SMAIS **BREAK** • HFMSE **BREAK** • RULM **BREAK** • Ambulant patients: 6MWT

Note: If possible, blood samples should not be scheduled to take place during the HFMSE and RULM assessments. However, if this is not possible, the blood sample should be obtained and the patient allowed a break if required, before resuming the assessment.

Patients already enrolled in this study prior to the implementation of the 6MWT, the SMAIS and the digital biomarker will complete those assessments for the first time at their next visit with the respective assessments being scheduled.

Table 3 Order of Assessments for Patients aged < 2 Years at Visits When Efficacy Measurements Are Performed

Block 1	• ECG, vital signs, physical examination (including weight) **BREAK** • BSID-III **BREAK** • HINE-2 **BREAK** • Blood sample (or insertion of catheter) • Dose administration

4.6.2.3 Assessments at Study Completion/Early Withdrawal Visit

Patients who complete the study or discontinue study drug early will be asked to return to the clinic for a study completion/early withdrawal visit as shown in the SoA (Appendix 1B and Appendix 3B). *For patients who reach Week 260 (Year 5), a study completion visit will be performed in place of the Week 260 visit.*

4.6.2.4 Follow-Up

A follow-up *telephone* call should occur *approximately* 30 days after the study completion/early withdrawal visit, to collect information on adverse events as outlined in Sections 5.5, 5.6, and SoAs (Appendix 1B and Appendix 3B).

A follow-up telephone call is required for:

- *Patients who stop study treatment and do not receive risdiplam IMP through continued access (Section 4.4.4) or to receive risdiplam through commercial access or post-trial access;*
- *Patients who stop study treatment and who switch to another treatment for SMA within 30 days of stopping risdiplam. If a patient switches to another SMA treatment during the 30 day follow-up period, a telephone call should be performed to collect information up to the time that the patient begins the new treatment.*

A follow-up telephone call is not required for:

- *Patients who continue on risdiplam (through continued access as defined in Section 4.4.4, or through commercial access or post-trial access*
- *Patients who switch to another treatment for SMA immediately after stopping risdiplam treatment*

4.6.2.5 *Assessments During Continued Access*

If risdiplam is not commercially available to the patient at the time of the Week 260 (study completion) visit, the patient can continue to receive risdiplam in the study until risdiplam is commercially available to the patient or until the patient is eligible for post-trial access or until EOS (whichever occurs first) (Section 4.4.4; Appendix 5).

Any patients continuing to receive risdiplam beyond their Week 260 (study completion) visit until the EOS are not required to perform additional study visits. Risdiplam will be provided as per current study procedures. Only adverse events must continue to be reported to maintain minimum study safety reporting requirements. Therefore, investigators should proactively contact those patients every 13 weeks to ensure adverse events are reported in the eCRF and document this contact in the patient's notes. The eCRF should be updated with adverse events and any concomitant medications given for the adverse event only.

Patients with a body weight <20 kg should continue to be weighed to ensure patients receive the correct dose for their weight. Study sites should ensure that weight is measured on calibrated scales appropriate for the patient.

4.6.2.6 Assessments at Unscheduled Visits

Assessments as listed in Appendix 1A and Appendix 3A as deemed necessary by the Investigator and/or Sponsor and/or iDMC in particular for safety, will be performed at unscheduled visits.

4.6.3 Prioritization Order for Blood Samples

Timepoints for blood samples are indicated in Appendices 1–4. However, should the total blood volume to be collected at any timepoint according to the SoAs exceed 1 mL/kg (patients aged 2–60 years) or 1.5 mL/kg (patients aged 6 months to <2 years), or the volume collected over any 8-week period throughout the study exceed 4 mL/kg(patients aged 2–60 years) or 4.5 mL/kg (patients aged 6 months to <2 years) the prioritization order indicated in Table 4 below should be followed.

Table 4 Prioritization Order for Blood Samples

Order	Samples
1	Any safety laboratory samples (scheduled or unscheduled and performed at the discretion of the Investigator)
2	PK samples
3	Samples for SMN protein levels
4	Samples for in vivo splicing modification of *SMN2* mRNA
5	Clinical genotyping
6	Samples for exploratory biomarkers (patients aged ≥ 12 years only)
7	RBR samples (optional, upon specific consent, patients aged ≥ 12 years only)

4.7 PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

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

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

4.7.1.1 Discontinuation from Study Drug

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

- Pregnancy.
- Events, as described in Section 5.2.3
- Unable to continue to comply with study requirements.

Patients discontinuing study drug prematurely will be asked to return to the clinic for a study completion/early withdrawal visit (Section 4.6.2.3) and will be followed with a *telephone* call from the site *approximately* 30 days after this last visit (Section 4.6.2.4). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

During the study a patient may need to stop administration of study drug, e.g., due to immediate need for surgery, required treatment with a drug known to or suspected to have an interaction with risdiplam, etc. The Investigator must discuss these situations with the Sponsor to determine if the patient should withdraw from the study or temporarily discontinue study drug.

4.7.1.2 Withdrawal from Study

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

Patients will not be followed for any reason after consent from participation in the study has been withdrawn.

When a patient voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the patient specifically requests for these to be discarded or local laws require their immediate destruction. A patient's withdrawal from Study BP39054 does not, by itself, constitute withdrawal of specimens donated to the Research Biosample Repository.

Patients who withdraw from the study, whether for safety or other reasons, will not be replaced.

4.7.2 Study and Site Discontinuation

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

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

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

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the ICH guideline for Good Clinical Practice

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

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

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.1.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10).
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

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

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

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

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

Non-serious adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4 for reporting instructions). Adverse events of special interest for this study include the following:

- Cases of an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined in Section 5.3.5.6.
- Suspected transmission of an infectious agent by the study drug, as defined below:

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is

considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2 SAFETY PLAN

The Safety Plan considers observations made in nonclinical investigations, including Good Laboratory Practice toxicology studies in rat and cynomolgus monkey, and the observations made in clinical trials. Hypothetical considerations are included in the interpretation of nonclinical and clinical data.

The exposure cap of a mean $AUC_{0\text{-}24h,ss}$ 2000 ng•hr/mL corresponds to the NOAEL in the 39-week toxicology study in cynomolgus monkey, i.e., the exposure level at which no adverse events were observed. This exposure cap also corresponds to the NOAEL observed for toxicities caused in adult and juvenile rats. Only effects on testes, i.e., on male fertility, were observed at exposure levels below those observed in another study in juvenile/young rats. Male patients and/or their parents or caregivers will be informed accordingly about this potential adverse consequence of treatment with the study drug. In humans, the pachytene stage of meiosis is completed towards the end of fetal development. In this study, effects on the oocyte are not expected because premature infants will not be included. In juvenile and adult rat toxicity studies and in monkey toxicity studies, there was no effect on female reproductive organs or female fertility. Any effects on meiosis and oocyte maturation will be further investigated in a pre-postnatal toxicity study in rats (see Risdiplam Investigator's Brochure).

5.2.1 Safety Precautions

Safety precautions and monitoring measures have been implemented to maximize the safeguards for the patients enrolled in this study. The stopping rules for individuals detailed in Section 5.2.3 will be applied in case of specific adverse events.

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

- Male fertility:

  Inform male patients and/or their parents or caregivers about the risk to fertility.

  In circumstances where male patients exposed to study drug desire future conception, they will be informed about the time required to recover from potential changes in semen parameters based on the duration of a spermatogenic cycle.

- Possible chromosome damage:

  Strict contraception for female patients and male patients with female partners of childbearing potential (Section 4.2.2).

Male patients will also be reminded of the necessity to respect a minimum period of 4 months before trying to conceive or before donating sperm (see also contraception requirements in Section 4.2.2).

- Effects on bone marrow/hematology: Assessment of hematological parameters is part of the routine monitoring and will be performed throughout the study.
- Effects on the developing embryo:

  Studies in animals have shown that risdiplam is teratogenic and fetotoxic. Hence, strict contraception is required (Section 4.2.2; see Section 5.4.3 for pregnancy reporting requirements).

5.2.2 Safety Monitoring

Based on observed toxicity in nonclinical studies (risdiplam Investigator's Brochure for details), the following safety monitoring plan will be conducted in this study:

- The study will include frequent triplicate 12-lead ECGs. ECGs will be time-matched with PK samples, on selected PK days to allow PK/QTc analyses and modelling in patients aged ≥ 12 years.
- Follow-up *telephone* calls (as per the timepoints in Appendix 1A and Appendix 3A):
  - Patients (or caregivers of patients, as appropriate) will be called by the Investigator or designee to monitor safety and tolerability when not attending the clinic. Assessments will include adverse events, concomitant medication review and significant life events.

5.2.3 Stopping Rules

While the Investigators, the Roche Clinical Science Leader, the Roche Safety Science Leader, the IMC and the iDMC (and any other professional(s) considered necessary to consult) will review available data for the individual patients on an ongoing basis, the following specific stopping rules for an individual patient are defined a priori:

- Patients with any elevated ALT or aspartate aminotransferase (AST) of $> 3 \times$ upper limit of normal (ULN), ALP $< 2 \times$ ULN, and associated with an increase in bilirubin ($\geq 2 \times$ ULN) (i.e., a suspected "Hy's law" which indicates risk of severe/serious liver impairment) in the absence of a different explanation.
- Significant and clinically relevant changes in laboratory parameters, ECG or vital signs which pose an unacceptable risk for the patient.
  - NB: Although no cardiovascular signal emerged from safety pharmacology studies in animals, or in the clinical study in healthy subjects, a prolongation of the QTcF exceeding 500 msec with a repeat ECG within 2 hours confirming the QTc abnormality should be promptly reviewed by a cardiologist on the same day and before subsequent dosing to evaluate if treatment discontinuation is warranted.
- Other findings such as a serious adverse event or any other severe adverse event that indicate that dosing should be halted.

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

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all adverse events (see Section 5.1.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4 to 5.5.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until *the final follow-up telephone call (if applicable, per Section 4.6.2.4) or until final dose of IMP.*

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used to assess adverse event severity. Table 5 below will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [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]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events. Based on the NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to 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 one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

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

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

5.3.4 Assessment of Causality of Adverse Events

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events Occurring Secondary to Other Events

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

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

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

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

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

5.3.5.5 Abnormal Vital Sign Values

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

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

- Clinically significant in the Investigator's judgment.

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

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

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

5.3.5.6 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$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. Therefore, Investigators must report as an adverse event the occurrence of either of the following:

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

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

5.3.5.7 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). This includes death attributed to progression of SMA.

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

be replaced by the established cause of death. The term "**sudden death**" should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

If the death is attributed to progression of SMA disease and/or associated complications or comorbidities, “SMA progression or complication/comorbidity” should be recorded on the Death Attributed to Progressive Disease eCRF.

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

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Spinal Muscular Atrophy

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.1.2), except as outlined below.

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

- Hospitalization for respite care.
- Planned hospitalization required by the protocol (e.g., for study drug administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease. The patient has not suffered an adverse event.

- The patient has not experienced an adverse event

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

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

5.3.5.11 Overdoses

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

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

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

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

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO or caregiver-reported outcome data by the Sponsor, and safety analyses will not be performed using these data. However, if any PRO or caregiver-reported outcome responses suggestive of a possible adverse event are identified during site review of these data, the Investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

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

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

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

5.4.1 Emergency Medical Contacts

Investigators will be provided with contact information for the Medical *Monitor. 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.*

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

For reports of serious adverse events and non-serious adverse events of special interest (see Sections 5.1.2 and 5.1.3), Investigators should record all case details that can be gathered on the *Clinical Trial* Adverse *Event/Special Situations* Reporting Form and forward this form to the Serious Adverse Event Responsible (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Studies in animals have shown that risdiplam is teratogenic and fetotoxic. Female patients of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 28 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

5.4.3.2 Pregnancies in Female Partners of Male Subjects

Risdiplam is known to affect male germ cells in their development. This is likely based on an interaction with cell cycle genes. In animals, this effect with the *SMN2* splicing modifier, risdiplam, has been demonstrated to be reversible. Thus, male patients are advised to not father a child while on treatment and for up to 4 months after cessation of treatment. Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 4 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

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

All pregnancies reported during the study should be followed until pregnancy outcome and reported according to the instructions provided in Section 5.4.3.

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

The Investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 30 days after the last dose of study medication). If the Investigator becomes aware of any other serious adverse event occurring after the end of the adverse event reporting period, if the event is believed to be related to prior study drug treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the *Clinical Trial* Adverse Event*/Special Situations* Reporting Form using the fax number or email address provided to Investigators.

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

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

The Sponsor has a legal responsibility to notify regulatory authorities about the safety of a study treatment under clinical investigation. The Sponsor will comply with regulatory requirements for expedited safety reporting to regulatory authorities (which includes the use of applicable systems, such as EudraVigilance), IRBs, ECs, and investigators.

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

- Risdiplam Investigator's Brochure

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

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

An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to Health Authorities.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The primary objective of the study is to assess the safety, tolerability, PK, and PD of risdiplam in patients previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101, or olesoxime. All efficacy endpoints are regarded as exploratory.

A database lock for the analyses of the 12-month safety and exploratory efficacy endpoints will occur once the last patient enrolled has either completed his/her 12-month assessments or has been withdrawn. All available safety data will also be reported.

An additional database lock will occur once the last patient enrolled has either completed his/her 24-month assessments or has been withdrawn.

A database lock will also occur for an interim analysis to perform safety and exploratory efficacy analyses of the data to support initial filing and registration of risdiplam.

Additional database locks may occur in order to perform exploratory efficacy and safety analyses of the data in response to information that may emerge during the course of the study. Data from this study will be used to complement the safety information contained in the regulatory dossier, and as part of a safety update if requested by Health Authorities.

Final database lock will occur at the study end.

Full details of the statistical methods will be described within the Data Analysis Plan (DAP).

6.1 DETERMINATION OF SAMPLE SIZE

The sample size was determined by practical considerations and not based on statistical power calculations.

The target sample size is up to 180 SMA patients previously enrolled in Study BP29420 (Moonfish) or previously treated with nusinersen, AVXS-101, or olesoxime. With 180 patients exposed to risdiplam, there is a 92% chance to detect an adverse event in at least one patient, assuming that the true underlying adverse event rate is 1.4%.

Approximately 80 patients who previously received treatment with nusinersen or AVXS-101 will be enrolled. This will enable an initial evaluation of whether the switch from nusinersen or AVXS-101 to risdiplam is well-tolerated and will generate initial safety, PK, and PD (SMN protein) data for the comparison between treatment-naïve patients and patients who previously received nusinersen or AVXS-101.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who were enrolled, discontinued, continuing treatment at the time of analysis or completed the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

All patients who received at least one dose of risdiplam, whether prematurely withdrawn from the study or not, will be included in the safety population.

6.3.2 Pharmacokinetic and Pharmacodynamic Analysis Populations

All patients with at least one timepoint with a measurable drug concentration or PD marker will be included in the respective analysis data sets. Patients will only be excluded from the analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol or if data are unavailable or incomplete which may influence the PK or PD analysis. Excluded cases will be

documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

6.3.3 Intent-To-Treat/ Exploratory Efficacy Analysis Population

The Intent-To-Treat (ITT) population is defined as all enrolled patients, regardless of whether they receive risdiplam or not. The ITT population will be the primary population for all exploratory efficacy analyses.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and other baseline characteristics will be summarized for the ITT population using descriptive statistics, means, standard deviations, medians, interquartile range and ranges for continuous variables and number and percentages for categorical variables, as appropriate. Baseline will be defined as the last measurement prior to enrollment unless specified otherwise in the DAP. Summaries will be presented overall and by previous treatment: RO6885247, nusinersen, AVXS-101, or olesoxime.

6.5 SAFETY ANALYSES

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

- Incidence of adverse events (overall, by severity and by relationship to study medication).
- Incidence of serious adverse events.
- Incidence of treatment discontinuations due to adverse events.
- Incidence of laboratory abnormalities.
- Incidence of ECG abnormalities.
- Incidence of vital sign abnormalities.
- Incidence of suicidal ideation or behavior (C-SSRS).
- Incidence of clinically significant findings on ophthalmological examination *performed under Protocol Versions 1-4 inclusive*.
- Incidence of clinically significant findings on neurological examination.
- Anthropometric examination including weight, height, head and chest circumference.

All safety analyses will be based on the safety analysis population. Safety data collected from each of the endpoints will be summarized descriptively for the first 12-month period (i.e., 12-month data for each individual patient) at the time of the 12-month analysis reporting event and for all available safety data collected at the time of the analysis.

Safety data may also be summarized overall and by previous treatment: RO6885247, nusinersen, AVXS-101, or olesoxime, as appropriate.

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

6.5.1 Adverse Events

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

6.5.2 Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Data will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing.

Laboratory data will be listed for patients with laboratory abnormalities or values outside the normal ranges. In addition, tabular summaries including shift tables to compare the status at baseline to each timepoint post-baseline and overall will be used, as appropriate.

6.5.2.1 Definition of Laboratory Abnormalities

Laboratory values falling outside the normal range will be labeled "H" for high or "L" for low in patient listings of laboratory data.

6.5.3 Vital Signs

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

6.5.4 ECG Data Analysis

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

Additionally, a time-matched QT profile assessment will be performed in patients aged $\geq$ 12 years.

Categorical summaries by timepoint (predose, 1h, 2h, and 4h) and 'week' (Weeks 4 and 13) of absolute and time-matched change from baseline in QT, QTcF, and QTcB will be presented, as well as, summaries for maximum post-dose absolute and time-matched changes from baseline in QTcF.

For the analysis of time-matched change from baseline in QTcF, all subjects in the safety population with at least one non-missing value will be included in the analysis. The main statistical analysis is a mixed-effects ANOVA model with ΔQTcF, the

time-matched change from baseline in QTcF, as dependent variable, the fixed effects ‘timepoint’ (predose, 1h, 2h, and 4h) and ‘week’ (Weeks 4 and 13) and the random effects ‘subject’ and ‘subject × week’, the interaction between ‘subject’ and the fixed effect ‘week’.

In addition, time-matched QTcF values and PK data from this study will be pooled with time-matched QTcF and corresponding PK values from other risdiplam studies in healthy volunteers (Entry-in-Human and PK ethnicity studies) and in patients treated with risdiplam to explore the relationship between risdiplam plasma concentrations and QTc interval. This will be performed by fitting a mixed-effects model using all the data across the entire range of plasma concentrations to improve the precision of the estimation of the QTc effect.

6.5.5 Concomitant Medications

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

6.6 EXPLORATORY EFFICACY ANALYSES

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

For all patients

- Proportion of patients who experience at least one disease-related adverse event by Month 12 and Month 24.
- Number of disease-related adverse events per patient-year at Month 12 and Month 24.

For patients aged 12–60 years

- Change from baseline in the total score of the patient-reported SMAIS at Month 12 and Month 24.

For patients aged 6–60 years old

- Change from baseline in FVC at Month 12 and Month 24
- Change from baseline in FEV1 at Month 12 and Month 24
- Change from baseline in PCF at Month 12 and Month 24
- Change from baseline in the 6MWT distance (for ambulant patients only) at Month 12 and Month 24
- Change from baseline in the percentage change in distance walked in the first versus the last minute of the 6MWT (for ambulant patients only) at Month 12 and Month 24.

For patients aged 2–60 years

- Change from baseline in the Total MFM score and its domain scores of D1, D2, D3 and the total combined score of (D1++D2) at Month12 and Month 24
- Proportion of patients who achieve stabilization or improvement (i.e., a change from the study baseline ≥ 0) on the Total MFM score by Month 12 and Month 24
- Change from baseline in the Total score of HFMSE at Month 12 and Month 24
- Change from baseline in the Total score of the RULM at Month 12 and Month 24
- Change from baseline in the best SNIP (expressed as a percentage of the predicted value) at Month 12 and Month 24
- Change from baseline in the total score of the caregiver-reported SMAIS at Month 12 and Month 24.

For patients aged 6 months to < 2 years

- Proportion of infants who achieve relevant motor milestones as assessed by BSID-III gross motor scale at Month 12 and Month 24.
- Change from baseline in the total raw score of the BSID-III gross motor scale at Month 12 and Month 24.
- Proportion of infants who achieve the relevant attainment levels of the motor milestones as assessed by HINE-2 at Month 12 and Month 24.
- Proportion of motor milestone responders as assessed by HINE-2 at Month 12 and Month 24.
- Time to death (from enrollment).
- Time to permanent ventilation (from enrollment).
- Time to death or permanent ventilation (from enrollment).
- Proportion of infants without permanent ventilation at Month 12 and Month 24.
- Proportion of infants with the ability to swallow at Month 12 and Month 24.

All exploratory efficacy analysis will be based on the ITT population. Efficacy data collected from each of the exploratory efficacy endpoints will be summarized descriptively by timepoint and by previous treatment: RO6885247, nusinersen, AVXS-10, or olesoxime, as appropriate.

Details of the statistical methods, definitions and analyses for all exploratory efficacy endpoints will be fully specified in the DAP.

6.7 PHARMACOKINETIC ANALYSES

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

Non-linear mixed effects modeling (NONMEM® software) will be used to analyze the sparse samples of concentration–time data of risdiplam (and its metabolites if deemed necessary). Population and individual PK parameters will be estimated and the influence of various covariates (such as age, gender and body weight, or previous treatment with nusinersen, AVXS-101, or olesoxime) on these parameters will be investigated in an exploratory manner. Data may be pooled with data from other studies with risdiplam in order to improve the parameter estimates from the model. Secondary PK parameters (such as C_{max} and AUC) may be derived from the model for each individual included in the PK analysis and will be presented descriptively.

Additional exploratory analyses on exposure and safety/efficacy relationship may be conducted if deemed necessary. The details of the modelling and exploratory analyses may be reported in a document separate from the clinical study report.

Additional PK analyses will be conducted as appropriate.

6.8 PHARMACODYNAMIC ANALYSES

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

6.9 DIGITAL BIOMARKER ANALYSES

Digital biomarker assessments were in place in Protocol Versions 1-4, inclusive (analysis detailed below), but ceased to be performed during 2022.

Smartphone sensor data collected as part of the digital biomarker approach will be analyzed. Participant adherence will be evaluated. After sensor data quality checks and pre-processing throughout the study, features will be developed for each smartphone-based test and correlated with the MFM and other clinical endpoints. Further exploratory analyses may be conducted.

The results will be reported separately from the clinical study report.

6.10 INTERIM ANALYSES

The IMC or iDMC will be requested to review all available safety data in an ongoing basis, in accordance with the associated IMC and iDMC Charter.

An interim analysis of all available safety and efficacy data will be performed to support the initial filing and registration of risdiplam. The interim analysis will be performed by the Sponsor and the results presented to the external iDMC. The study will not be stopped early based on the results of the efficacy analysis.

Given the exploratory nature of this non-comparative and open-label study, the Sponsor may choose to conduct additional interim efficacy or safety analyses. The decision to conduct additional interim analysis and the timing of the analysis will be documented in

the Sponsor's trial master file prior to the conduct of the interim analysis. These interim analyses will also be performed by the Sponsor and results presented to the IMC or iDMC.

The final analysis will occur after all patients have completed the study.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

The Sponsor will produce a Data Handling Manual and a Data Management Plan that describes the quality checking to be performed on the data. Laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period of

time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) application will comply with U.S. Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the E.U./EEA will comply with the E.U. Clinical Trial Directive (2001/20/EC) or Clinical Trials Regulation (536/2014) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Assent or Caregiver's Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the “Consent Forms”) before IRB/EC submission.

The final IRB/EC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements.

In this study, caregiver specific information will be collected to evaluate caregiver burden requiring that a separate written informed consent be obtained from the caregiver.

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.5).

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

8.4 CONFIDENTIALITY

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.

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

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

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

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

An IMC and iDMC will be responsible for reviewing safety, PK and PD data. The scope and responsibility of these committees will be detailed in a specific Charter.

An IxRS system will be used for drug allocation.

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

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

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and/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 made available 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/

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

American Thoracic Society. ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166:111–17.

Bérard C, Payan C, Hodgkinson I, et al. and the MFM Collaborative Study Group. A motor function measure scale for neuromuscular diseases. Construction and validation study. Neuromuscul Disord. 2005;15:463–70.

Bérard C, Girardot F, Payan C. Motor Function Measure in Neuromuscular Diseases: User's Manual MFM-32 and MFM-20. Second Edition. 2009.

Bussel II, Wollstein G, Schuman JS. OCT for glaucoma diagnosis, screening and detection of glaucoma progression. Br J Ophthalmol. 2014;98(2):ii15–ii19.

Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN_{RX}) in children with spinal muscular atrophy. Neurology. 2016;86:890–7.

Cho S, Dreyfuss G. A degron created by SMN2 exon 7 skipping is a principal contributor to spinal muscular atrophy severity. Genes Dev. 2010; 24(5):438–42.

Crawford TO, Pardo CA. The neurobiology of childhood spinal muscular atrophy. Neurobiol Dis. 1996;3:97–110.

d'Ydewalle C, Sumner C. Spinal muscular atrophy therapeutics: Where do we stand? Neurotherapeutics. 2015; 12(2):303–16.

[FDA] U.S. Food and Drug Administration. Guidance for industry: suicidal ideation and behavior: prospective assessment of occurrence in clinical trials [resource on the Internet]. 2012 [cited June 2018]. Available from: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm315156.htm.

Glanzman AM, O'Hagen JM, McDermott MP, et al. Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. J Child Neurol. 2011;26:1499–1507.

Hua Y, Sahashi K, Rigo F, et al. Peripheral SMN restoration is essential for long-term rescue of a severe spinal muscular atrophy mouse model. Nature. 2011;478:123–6.

Khirani S, Colella M, Caldarelli V, et al. Longitudinal course of lung function and respiratory muscle strength in spinal muscular atrophy type 2 and 3. Eur J Paediatr Neurol. 2013;17(6):552–60.

Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. Arch Neurol. 2011;68(8):979–84.

Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995;80:155–65.

Lewelt A, Newcomb TM, Swoboda KJ. New therapeutic approaches to spinal muscular atrophy. Curr Neurol Neurosci Rep. 2012;12(1):42–53.

Lorson CL, Hahnen E, Androphy E J, et al. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. Proc Natl Acad Sci USA. 1999;96:6307–11.

Lunn MR, Wang CH. Spinal muscular atrophy. Lancet. 2008;371:2120–33.

Mao J, Tay S, Khojasteh CS, et al. Evaluation of Time Dependent Inhibition Assays for Marketed Oncology Drugs: Comparison of Human Hepatocytes and Liver Microsomes in the Presence and Absence of Human Plasma. Pharm Res. 2016;33:1204-19.

Montes J, McDermott MP, Martens WB, et al. Six-minute walk test demonstrates motor fatigue in spinal muscular atrophy. Neurology. 2010;74:833–8.

Munsat TL, Davies KE. International SMA Consortium Meeting (26-28 June 1992, Bonn, Germany). Neuromuscul Disord. 1992;2(5-6):423–8.

Nguyen TM, Humphrey E, Lam LT, et al. A two-site ELISA can quantify upregulation of SMN protein by drugs for spinal muscular atrophy. Neurology. 2008; 71:1757–63.

Nurputra DK, Lai PS, Haraha NIF, et al. Spinal muscular atrophy: from gene discovery to clinical trials. Ann Hum Genet. 2013;77:435–63.

O'Hagen JM, Glanzman AM, McDermott MP, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord. 2007;17:693–7.

Passini MA, Bu J, Richards AM, et al. Antisense oligonucleotides delivered to the mouse CNS ameliorate symptoms of severe spinal muscular atrophy. Sci Transl Med. 2011; 3(72):72ra18.

Phan DQ, Silka MJ, Lan YT, et al. Comparison of formulas for calculation of the corrected QT interval in infants and young children. J Pediatr. 2015;166:960–4.

Porensky PN, Mithpant C, McGovern VL, et al. A single administration of morpholino antisense oligomer rescues spinal muscular atrophy in mouse. Hum Mol Genet. 2012;21(7):1625–38.

Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet. 2012;20:27–32.

Sumner CJ, Kolb SJ, Harmison GG, et al. SMN mRNA and protein levels in peripheral blood: biomarkers for SMA clinical trials. Neurology. 2006;66:1067–73.

Appendix 1A
Schedule of Assessments for Patients Aged 2–60 Years: Screening through Week 52

Week	Screening [a] D –30 to D –2		Baseline	Week 1	Week 2	Week 4	Week 13	Week 26 [a]		Week 39	Week 52 [a]	
Day	SD 1	SD 2	D –1 [b]	D 1	D 14	D 28	D 91	D 182	D 183	D 273	D 364	D 365
(Visit window, days)					(±1)	(±3)	(±7)	(±7)		(±7)	(±7)	
Site visit	x	x	x	x	x	x	x	x		x	x	
Follow-up phone call			x [c]									
Informed consent	x											
Demography	x											
Medical history, including SMA history	x											
Physical examination [d]	x		x		x	x	x	x		x	x	
Neurological examination	x							x			x	
Vital signs	x		x	x [e]	x	x [e]	x [e]	x		x	x [e]	
Plasma PK sample [f, g]				x	x	x	x		x	x		x
ECG-12 lead [g]	x		x	x	x	x	x	x		x	x	
Substance use [h]		x	x									
Significant life events			x		x	x	x	x		x	x	
Hematology [e] and blood chemistry [e]		x			x	x	x		x			x
Coagulation [e]		x				x	x		x			x
Urinalysis [e]		x				x	x		x			x

Appendix 1A
Schedule of Assessments for Patients Aged 2–60 Years: Screening through Week 52 (cont.)

Week	Screening [a] D –30 to D –2		Baseline	Week 1	Week 2	Week 4	Week 13	Week 26 [a]		Week 39	Week 52 [a]	
Day	SD 1	SD 2	D –1 [b]	D 1	D 14	D 28	D 91	D 182	D 183	D 273	D 364	D 365
(Visit window, days)					(±1)	(±3)	(±7)	(±7)		(±7)	(±7)	
Hormone panel [i,e]		x					x					
Pregnancy test blood [j]		x				x	x		x			x
Pregnancy test urine– site [j]			x							x		
Pregnancy test urine– home [j, k]							x [k]					
Ophthalmological assessments [l]												
Tanner staging [m]			x								x	
In vivo mRNA [f]			x	x		x	x		x			x
SMN protein [f]			x			x	x		x			x
MFM [n]	x		x					x			x	
Pulmonary testing [o]	x		x					x			x	
6MWT (for ambulant patients) [p, q]		x	x						x			x
RULM/HFMSE [n]		x							x			x
C-SSRS [q]	x		x					x			x	
Nutritional check		x	x			x	x		x	x		x
Serum biomarkers [e, h]			x									x
Digital biomarker– in clinic [p, r]												
Digital biomarker– remote [p, r]												
Blood sample for RBR (optional) [e,s]			x									

Appendix 1A
Schedule of Assessments for Patients Aged 2–60 Years: Screening through Week 52 (cont.)

Week	Screening [a] D –30 to D –2		Baseline	Week 1	Week 2	Week 4	Week 13	Week 26 [a]		Week 39	Week 52 [a]	
Day	SD 1	SD 2	D –1 [b]	D 1	D 14	D 28	D 91	D 182	D 183	D 273	D 364	D 365
(Visit window, days)					(±1)	(±3)	(±7)	(±7)		(±7)	(±7)	
Clinical genotyping				x [t]								
SMAIS [p]			x						x			x
Study medication dispensation/return				x [u]								
Daily administration of study medication				Daily								
Daily diary				Daily								
Adverse events	x [v]		x [v]	x								
Previous and concomitant treatments	x		x	x								

6MWT = Six-Minute Walk Test; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; MFM = motor function measure; PK = pharmacokinetic; RBR = Research Biosample Repository; RULM/HFMSE = Revised Upper limb module/ Hammersmith functional motor scale expanded; SD = screening day; SMA = spinal muscular atrophy; SMAIS = Spinal Muscular Atrophy Independence Scale; SMN = survival of motor neuron; TSH = thyroid stimulating hormone.

For footnotes, see Appendix 1B that follows.

Appendix 1B
Schedule of Assessments for Patients Aged 2–60 Years: Year 2 through End of Study

Week	Week 65	Week 78 [a]		Week 91	Week 104 [a]		OLE Phase [a]			Comp/EW [a]		Follow-Up Phone call [z]
Day	D 456	D 546	D 547	D 637	D 728	D 729	Every 13 weeks [y]	Every 26 weeks D 1	Every 26 weeks D 2	D 1	D 2	Comp/EW + *approx.* 30 days
(Visit window, days)	(±7)	(±7)		(±7)	(±7)		(±14)	(±14)				(±7)
Site visit	x	x		x	x		x	x		x		
Physical examination [d]	x	x		x	x		x	x		x		
Neurological examination		x			x			x		x		
Vital signs	x			x [e]	x			x		x		
Plasma PK sample [f, g]	x			x		x					x	
ECG-12 lead [g]	x			x	x			x		x		
Substance use [h]												
Significant life events	x	x		x	x			x		x		
Hematology [e] and blood chemistry [e]			x			x			x		x	
Coagulation [e]			x			x			x		x	
Urinalysis [e]						x			x		x	
Hormone panel [i, e]						x						
Pregnancy test blood [j]			x			x			x		x	
Pregnancy test urine–site [j]	x			x								
Pregnancy test urine–home [j, k]	x											
Ophthalmological assessments [l]												
Tanner staging [m]					x					x		

Appendix 1B
Schedule of Assessments for Patients Aged 2–60 Years: Year 2 through End of Study (cont.)

Week	Week 65	Week 78 [a]		Week 91	Week 104 [a]		OLE Phase [a]			Comp/EW [a]		Follow-Up Phone call [z]
Day	D 456	D 546	D 547	D 637	D 728	D 729	Every 13 weeks [y]	Every 26 weeks D 1	Every 26 weeks D 2	D 1	D 2	Comp/EW + *approx.* 30 days
(Visit window, days)	(±7)	(±7)		(±7)	(±7)		(±14)	(±14)				(±7)
In vivo mRNA [f]						x					x	
SMN protein [f]						x					x	
MFM [n]		x			x			x		x		
Pulmonary testing [o]		x			x			x		x		
6MWT (for ambulant patients) [p, q]			x			x			x		x	
RULM/HFMSE [n]			x			x			x		x	
C-SSRS [q]		x			x			x		x		
Nutritional check	x		x	x		x			x		x	
Serum biomarkers [e, h]						x					x	
Digital biomarker–in clinic [p, r]												
Digital biomarker–remote [p, r]												
Blood sample for RBR (optional) [e, s]						x					x	
Clinical genotyping												
SMAIS [p]			x			x			x		x	
Study medication dispensation/return	x [u]									x [w, ‡]		
Daily administration of study medication	Daily									*x* [‡]		
Daily diary	Daily									x		
Adverse events	x [§]											x
Previous and concomitant treatments	x											

Appendix 1B
Schedule of Assessments for Patients Aged 2–60 Years: Year 2 through End of Study (cont.)

Week	Week 65	Week 78 [a]		Week 91	Week 104 [a]		OLE Phase [a]			Comp/EW [a]		Follow-Up Phone call [z]
Day	D 456	D 546	D 547	D 637	D 728	D 729	Every 13 weeks [y]	Every 26 weeks D 1	Every 26 weeks D 2	D 1	D 2	Comp/EW + *approx.* 30 days
(Visit window, days)	(±7)	(±7)		(±7)	(±7)		(±14)	(±14)				(±7)

6MWT = Six-Minute Walk Test; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; Comp/EW = Completion/Early Withdrawal; MFM = motor function measure; OLE = open-label extension; PK = pharmacokinetic; Q13W = every 13 weeks; RBR = Research Biosample Repository; RULM/HFMSE = Revised Upper limb module/ Hammersmith functional motor scale expanded; SD = screening day; SMA = spinal muscular atrophy; SMAIS = Spinal Muscular Atrophy Independence Scale; SMN = survival of motor neuron; TSH = thyroid stimulating hormone.

[a] See Section 4.6.2.2, Table 2 and Table 3 for order of assessments, it is recommended that these assessments be conducted over two days.

[b] Assessments should be performed in the following order: adverse events, previous/concomitant medications, confirmation of eligibility, enrollment, 1st ECG recording, 2nd ECG recording, 3rd ECG recording, physical examination, Tanner staging, vital signs, 4th ECG recording, patient/caregiver-reported outcomes, pulmonary testing, MFM, 6MWT and blood samples. Flexibility is given to the site whether to perform the physical examination, Tanner staging, vital signs, patient/caregiver-reported outcomes assessment, pulmonary testing, MFM, and blood samples after the third or fourth ECG recording. The 6MWT should only be performed after the fourth ECG recording. In case the pulmonary testing, the MFM or blood samples are done prior to the fourth ECG recording, the following ECG recording should be preceded by a break of at least 20 minutes. The pulmonary testing, MFM and 6MWT should be preceded by a break of at least 15 minutes.

[c] Mandatory follow-up phone calls on Days 4, 11, 19, 33, 49, 63 and 77. It is at the discretion of the Investigator to perform the follow-up phone calls at the most appropriate time (day) between the site visits. After Week 12, additional follow-up phone calls are per Investigator's decision.

[d] At Weeks 65, 91, and every 13 weeks during the OLE phase, only body weight will be measured. At all other visits (including every 26 weeks during the OLE phase) a full physical examination needs to be done, including the head circumference in children below 5 years. Height (measured or derived from ulna length) at Screening, Weeks 13, 39, 52, 78, and 104 in patients 2–17 years of age. In patients >17 years of age, height at screening, Week 52 and Week 104 only. Body Mass Index (BMI) will be derived from the height recorded at screening in patients >17 years of age, and from the last known height in patients 2–17 years of age.

[e] Predose.

[f] Predose except for those outlined in Appendix 2.

[g] Timing and number of samples as outlined in Appendix 2.

[h] Only patients of ≥12 years of age.

[i] Thyroid hormones (free T4 and TSH) in all patients; estradiol, follicle-stimulating hormone and luteinizing hormone in female patients of child-bearing potential.

[j] Pregnancy tests in females of child-bearing potential only. Pregnancy tests may be repeated at the discretion of the Investigator at any time. Positive urine pregnancy tests results must be confirmed with a blood pregnancy test.

Appendix 1B
Schedule of Assessments for Patients Aged 2–60 Years: Year 2 through End of Study (cont.)

Week	Week 65	Week 78 [a]		Week 91	Week 104 [a]		OLE Phase [a]			Comp/EW [a]		Follow-Up Phone call [z]
							Every 13 weeks [y]	Every 26 weeks				
Day	D 456	D 546	D 547	D 637	D 728	D 729		D 1	D 2	D 1	D 2	Comp/EW + *approx.* 30 days
(Visit window, days)	(±7)	(±7)		(±7)	(±7)		(±14)	(±14)				(±7)

[k] The home pregnancy test must be performed every 4 weeks following the latest clinic visit. The urine pregnancy test kit will be dispensed to patients to perform at home and the Investigator will arrange to perform a phone call to obtain the results of the pregnancy test. Alternatively, a home visit at the required time will be performed to administer and obtain the results of the urine pregnancy test, unless the patient has agreed to return to the clinic site at the required time.

[l] Ophthalmological assessments were performed under Protocol Versions 1-4, inclusive, but are no longer to be performed starting with Protocol Version 5.

[m] Tanner staging will be determined at baseline, Month 12 and subsequent yearly visits in all patients who are 9–17 years of age at time of enrollment or following their 9th birthday, if they enrolled in the study before age 9. Once a patient reaches stage 5, Tanner staging no longer needs to be performed.

[n] Due to fatigue, motor function assessments should be performed over 2 days it is very important that the MFM is performed on Day 1 and the HFMSE is performed on Day 2 of the visit.

[o] SNIP in patients 2 years of age and older; Spirometry (FVC, FEV1, and PCF) in patients 6 years of age and older.

[p] For patients already enrolled in this study prior to the implementation of the 6MWT, the SMAIS and the digital biomarker: These assessments will be completed for the first time at the next visit with the respective assessments being scheduled. Digital biomarker assessments were performed under Protocol Versions 1-4, inclusive, but ceased to be performed during 2022.

[q] Only patients of ≥6 years of age.

[r] Digital biomarker assessments were performed under Protocol Versions 1-4, inclusive, but ceased to be performed during 2022.

[s] Only in patients ≥12 years of age. RBR sampling is optional, requiring additional consent. RBR DNA samples will be collected once on

Appendix 1B
Schedule of Assessments for Patients Aged 2–60 Years: Year 2 through End of Study (cont.)

Week	Week 65	Week 78 [a]		Week 91	Week 104 [a]		OLE Phase [a]			Comp/EW [a]		Follow-Up Phone call [z]
Day	D 456	D 546	D 547	D 637	D 728	D 729	Every 13 weeks [y]	Every 26 weeks D 1	Every 26 weeks D 2	D 1	D 2	Comp/EW + *approx.* 30 days
(Visit window, days)	(±7)	(±7)		(±7)	(±7)		(±14)	(±14)				(±7)

Day −1, RBR plasma and RNA samples on Day −1 and on week 104/Early Withdrawal.

[t] Blood sample for clinical genotyping may be collected once at any time after dosing (at the time of collection of other samples).

[u] Starting at Week 6, drug delivery and return of unused drug and supplies at the patient's home may be scheduled as appropriate depending on the formulation (two-bottle or one-bottle, respectively) the patient is receiving, unless the patient has agreed or is scheduled to visit the clinic at these times.

[v] Only serious adverse events caused by a protocol-mandated intervention.

[w] No dispensation of study medication except for patients who will continue on risdiplam IMP (Section 4.4.4) until EOS.

[y] The Q13W assessments in the OLE phase may be performed remotely (e.g. by telephone) at the Investigator's discretion.

[z] Follow-up telephone call, if applicable (see Section 4.6.2.4 and Appendix 5), approximately 30 days after the study completion/early withdrawal visit. The follow-up call will only be conducted for patients [a] who do not go on to receive risdiplam IMP through continued access or to receive risdiplam through commercial or post-trial access; or [b] who switch to another treatment for SMA within 30 days of stopping risdiplam. If a patient switches to another SMA treatment during the 30-day follow-up period, a telephone call should be performed to collect information up to the time that the patient begins the new treatment.

[‡] Study medication administration only for patients who will continue on risdiplam treatment (Section 4.4.4) until EOS.

[§] For patients receiving risdiplam IMP (Section 4.4.4) until EOS , investigators should proactively contact those patients every 13 weeks to ensure adverse events are reported in the eCRF and document this contact in the patient notes.

Appendix 2
Detailed Schedule of Pharmacokinetic and Biomarker Samples: Patients Aged 2–60 Years

Week	Day	Scheduled Time (hr)	ECG-12 Lead	PK Sample	In vivo mRNA	SMN Protein	Serum Biomarkers	RBR Sample (optional) [a]
Screening	Day −30 to −2		x					
Baseline	Day −1	0 hr	x		x [b]	x [b]	x [b]	x [b]
		+1 hr	x [c]					
		+2 hr	x [c]					
		+4 hr	x [c]					
Week 1	Day 1	Predose	x					
		+1 hr		x				
		+2 hr		x				
		+4 hr		x	x			
		+6 hr		x				
Week 2	Day 14	Predose	x	x				
Week 4	Day 28 [c]	Predose	x	x				
		+1 hr	x	x				
		+2 hr	x	x				
		+4 hr	x	x	x	x		
		+6 hr		x				
Week 13	Day 91 [c]	Predose	x	x	x	x		
		+1 hr	x	x				
		+2 hr	x	x				

Appendix 2
Detailed Schedule of Pharmacokinetic and Biomarker Samples: Patients Aged 2–60 Years (cont.)

Week	Day	Scheduled Time (hr)	ECG-12 Lead	PK Sample	In vivo mRNA	SMN Protein	Serum Biomarkers	RBR Sample (optional) [a]
		+4 hr	x	x				
		+6 hr		x				
Week 26	Day 182	Predose	x					
	Day 183	Predose		x	x	x		
Week 39	Day 273	Predose	x	x				
Week 52	Day 364	Predose	x					
	Day 365	Predose		x			x	
		+1 hr		x				
		+2 hr		x				
		+4 hr		x	x	x		
		+6 hr		x				
Week 65	Day 456	Predose	x	x				
Week 91	Day 637 [c]	Predose	x	x				
		+1 hr		x				
		+2 hr		x				
		+4 hr		x				
		+6 hr		x				
Week 104	Day 728	Predose	x					
	Day 729	0 hr		x	x	x	x	x
OLE Phase			x [d]					
Completion/Early Withdrawal	Day 1		x					
	Day 2			x	x	x	x	x

Appendix 2
Detailed Schedule of Pharmacokinetic and Biomarker Samples: Patients Aged 2–60 Years (cont.)

OLE = *open-label extension*; PK = pharmacokinetic; RBR = Research Biosample Repository; SMN = survival of motor neuron.

[a] Only in patients ≥ 12 years of age. RBR sampling is optional, requiring additional consent. RBR DNA samples will be collected once on Day −1, RBR plasma and RNA samples on Day −1 and on Week 104/Early Withdrawal.

[b] Blood samples should be taken after the 12-lead ECG recordings and all other assessments scheduled on Day −1 as indicated in Section 4.6.2.1.

[c] Matched ECG and PK samples only in patients ≥ 12 years of age. In patients < 12 years of age, only a predose ECG is to be obtained; no post-dose ECGs are required unless the Investigator deems them necessary for safety.

[d] ECG every 26 weeks during OLE phase.

Appendix 3A
Schedule of Assessments for Patients Aged 6 Months to < 2 Years: Screening through Week 52

Week	Screening	Baseline	Week 1	Week 2	Week 4	Week 13	Week 26	Week 39	Week 52
Day	D −30 to D −2	D −1 [a]	D 1	D 14	D 28	D 91	D 182	D273	D364
(Visit window, days)				(±1)	(±3)	(±7)	(±7)	(±7)	(±7)
Site visit	x	x	x	x	x	x	x	x	x
Follow-up phone call			x [b]						
Informed consent	x								
Demography	x								
Medical history, including SMA history	x								
Physical examination [c]	x	x		x	x	x	x	x	x
Neurological examination	x	x		x	x	x	x	x	x
Vital signs	x	x	x(4 hr) [d]	x	x	x	x	x	x
Protein binding sample [e]	x								
Plasma PK sample [f,g]			x	x	x	x	x	x	x
ECG-12 lead [g]	x	x	x	x	x	x	x	x	x
Significant life events (including family)		x		x	x	x	x	x	x
Hematology [f] and blood chemistry [h]	x			x		x	x		x
Coagulation [h]	x			x		x	x		x
Urinalysis [h, i]				x		x	x		x
Ophthalmological assessments [j]									
In vivo mRNA [f]			x		x (4 hr) [d]		x		x
SMN protein [f]			x		x (4 hr) [d]		x		x

Appendix 3A
Schedule of Assessments for Patients Aged 6 Months to < 2 Years: Screening through Week 52 (cont.)

Week	Screening	Baseline	Week 1	Week 2	Week 4	Week 13	Week 26	Week 39	Week 52
Day	D −30 to D −2	D −1 [a]	D 1	D 14	D 28	D 91	D 182	D273	D364
(Visit window, days)				(±1)	(±3)	(±7)	(±7)	(±7)	(±7)
BSID-III-gross motor score		x					x		x
HINE2		x					x		x
Level of respiratory support	x	x		x	x	x	x	x	x
Nutritional check [k]	x	x			x	x	x	x	x
Clinical genotyping						x [l]			
Study medication dispensation/return			x [m]						
Daily administration of study medication			Daily						
Daily diary			Daily						
Adverse events	x [n]	x [n]	x						
Previous and concomitant treatments	x								

Appendix 3B
Schedule of Assessments for Patients Aged 6 Months to < 2 Years: Year 2 through End of Study

Week	Week 65	Week 78	Week 91	Week 104	OLE Phase		Comp/EW	Follow-up phone call [r]
Day	Day 456	Day 546	Day 637	Day 728	Every 13 weeks [q]	Every 26 weeks		Comp/EW $+approx.$ 30 days
(Visit window, days)	($\pm$7)	($\pm$7)	($\pm$7)	($\pm$7)	($\pm$14)	($\pm$14)		($\pm$7)
Site visit	x	x	x	x	x	x		
Physical examination [c]	x	x	x	x	x [o]		x	
Neurological examination	x	x	x	x		x	x	
Vital signs	x	x	x	x		x	x	
Protein binding sample [e]								
Plasma PK sample [f,g]	x	x	x	x		x	x	
ECG-12 lead [g]	x	x	x	x		x	x	
Significant life events (including family)	x	x	x	x		x	x	
Hematology [h] and blood chemistry [h]		x		x		x	x	
Coagulation [h]		x		x		x	x	
Urinalysis [h, i]				x		x	x	
Ophthalmological assessments [j]								
In vivo mRNA [f]				x			x	
SMN protein [f]				x			x	
BSID-III-gross motor score		x		x		x	x	
HINE-2		x		x		x	x	

Appendix 3B
Schedule of Assessments for Patients Aged 6 Months to < 2 Years: Year 2 through End of Study (cont.)

Week	Week 65	Week 78	Week 91	Week 104	*OLE* Phase		Comp/EW	Follow-up phone call [r]
Day	Day 456	Day 546	Day 637	Day 728	Every 13 weeks [q]	Every 26 weeks		Comp/EW +*approx.* 30 days
(Visit window, days)	(±7)	(±7)	(±7)	(±7)	(±14)	(±14)		(±7)
Level of respiratory support	x	x	x	x		x	x	
Nutritional check [k]	x	x	x	x		x	x	
Clinical genotyping								
Study medication dispensation/return	x [m]						x [p, s]	
Daily administration of study medication	Daily						x [s]	
Daily diary	Daily							
Adverse events	X [t]							x
Previous and concomitant treatments	x							

BSID-III = Bayley Scales of Infant and Toddler development – Third Edition; Comp/EW = Completion/Early Withdrawal; HINE2 = Hammersmith Infant Neurological Examination Module 2; *OLE* = *open-label extension*; PK = pharmacokinetic; *Q13W* = *every 13 weeks;* RBR = Research Biosample Repository; SMA = spinal muscular atrophy; SMN = survival of motor neuron.

[a] Assessments should be performed in the following order: adverse events, previous/concomitant medications, and confirmation of eligibility, followed by the other scheduled assessments.

[b] Mandatory follow-up phone calls on Days 4, 11, 19, 33, 49, 63, and 77. It is at the discretion of the Investigator to perform the follow-up phone calls at the most appropriate time (day) between the site visits. After Week 12, additional follow-up phone calls are per Investigator's decision. If a patient withdraws from the study and *if the follow-up telephone call is applicable (see Section 4.6.2.4)*, follow-up phone calls should occur every 2 weeks after the early withdrawal visit until the Follow-Up *telephone call if the parent(s) guardian(s) agree* to collect information on adverse events and use of respiratory support.

[c] Physical examination will include weight, height, and head and chest circumference (until patients turn 2 years of age) at every visit.

[d] Assessment to be performed 4 hours after dose administration.

[e] Only required in patients aged < 1 years.

[f] Predose except for those outlined in Appendix 4.

[g] Timing and number of samples as outlined in Appendix 4.

Appendix 3B
Schedule of Assessments for Patients Aged 6 Months to < 2 Years: Year 2 through End of Study (cont.)

[h] Predose.

[i] For patients aged ≥ 2 years at time of assessment only.

[j] *Ophthalmological assessments were performed under Protocol Versions 1-4, inclusive, but are no longer performed starting with Protocol Version 5.*

[k] A detailed interview will be performed at Day −1 and at Weeks 26, 52, 78, and 104.

[l] Blood sample for clinical genotyping may be collected once at any time after dosing (at the time of collection of other samples).

[m] Starting at Week 6, drug delivery and return of unused drug and supplies at the patient's home may be scheduled as appropriate, unless the patient has agreed or is scheduled to visit the clinic at these times.

[n] Only serious adverse events caused by a protocol-mandated intervention.

[o] Collection of body weight only.

[p] *Study medication administration only for patients who will continue on risdiplam IMP (Section 4.4.4) until EOS.*

[q] *The Q13W assessments in the OLE phase may be performed remotely (e.g. by telephone) at the Investigator's discretion.*

[r] *Follow-up telephone call, if applicable (see Section 4.6.2.4 and Appendix 5), approximately 30 days after the study completion/early withdrawal visit. The follow-up call will only be conducted for patients [a] who do not go on to receive risdiplam IMP through continued access or to receive risdiplam through commercial or post-trial access, or [b] who switch to another treatment for SMA within 30 days of stopping risdiplam. If a patient switches to another SMA treatment during the 30-day follow-up period, a telephone call should be performed to collect information up to the time that the patient begins the new treatment.*

[s] *Study medication administration only for patients who will continue on risdiplam treatment (Section 4.4.4) until EOS.*

[t] *For patients receiving risdiplam IMP (Section 4.4.4) until EOS , investigators should proactively contact those patients every 13 weeks to ensure adverse events are reported in the eCRF and document this contact in the patient notes.*

Appendix 4
Detailed Schedule of Pharmacokinetic and Biomarker Samples: Patients Aged 6 Months to < 2 Years

Week	Day	Scheduled Time (hr)	PK Sample [a]	ECG	In vivo mRNA	SMN Protein
Screening	Day −30 to −2			x		
Baseline	Day −1			x		
Week 1	Day 1	Predose		x	x	x
		+ 2 hr	x	x		
		+ 4 hr	x			
		+ 6 hr	x			
Week 2	Day 14	Predose	x	x		
Week 4	Day 28	Predose	x	x		
		+ 2 hr	x	x		
		+ 4 hr	x		x	x
		+ 6 hr	x			
Week 13	Day 91	Predose	x	x		
		+ 2 hr	x	x		
		+ 4 hr	x			
		+ 6 hr	x			
Week 26	Day 182	Predose	x	x	x	x
		+ 2 hr	x	x		
		+ 4 hr	x			
		+ 6 hr	x			
Week 39	Day 273	Predose	x	x		
		+ 2 hr	x			
		+ 4 hr	x			
		+ 6 hr	x			
Week 52	Day 364	Predose	x	x	x	x
Week 65	Day 456	Predose	x	x		
Week 78	Day 546	Predose	x	x		
		+ 2 hr	x			
		+ 4 hr	x			
		+ 6 hr	x			
Week 91	Day 637	Predose	x	x		
		+ 2 hr	x			
		+ 4 hr	x			

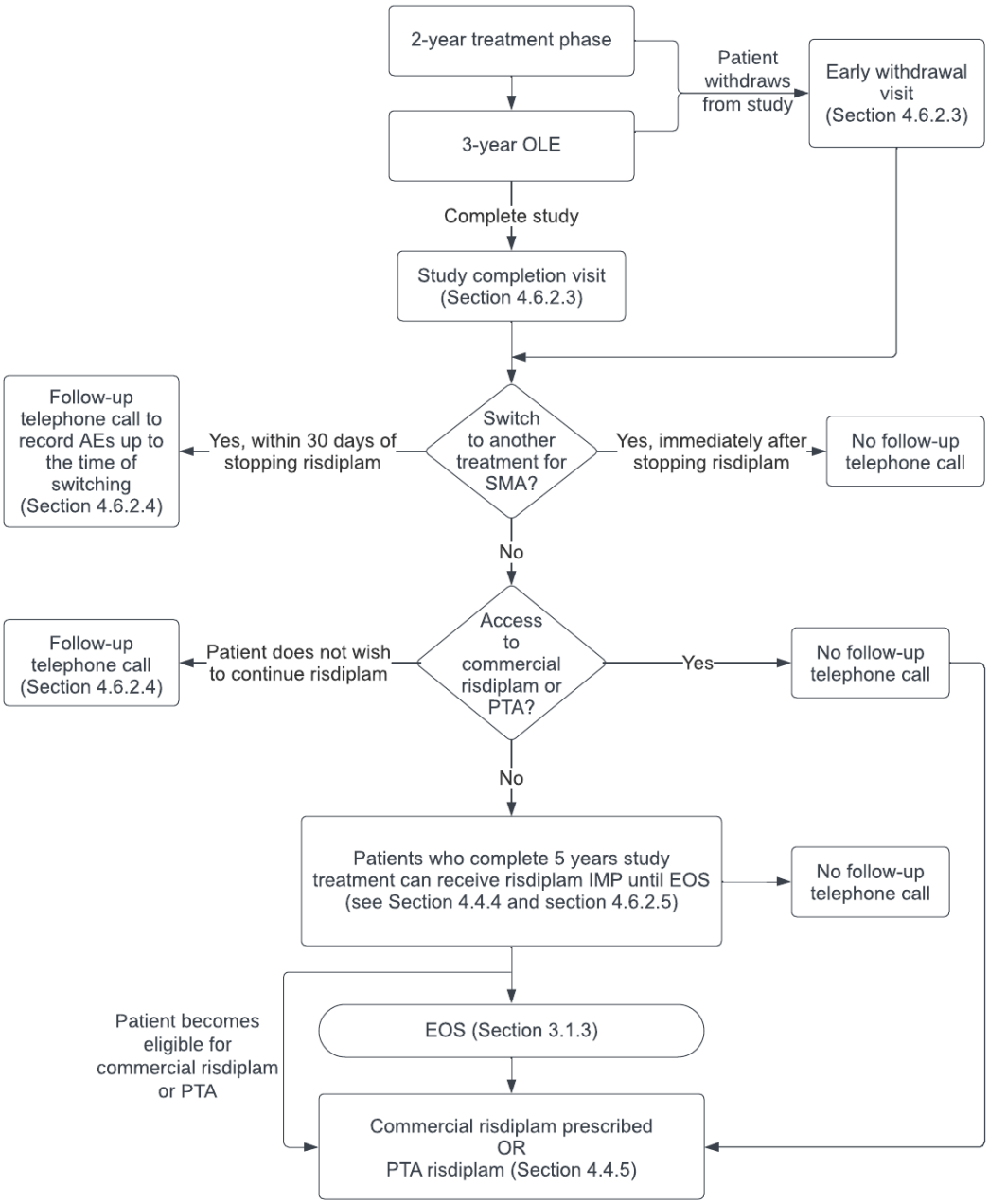
Appendix 4
Detailed Schedule of Pharmacokinetic and Biomarker Samples: Patients Aged 6 Months to <2 Years (cont.)

Week	Day	Scheduled Time (hr)	PK Sample [a]	ECG	In vivo mRNA	SMN Protein
		+ 6 hr	x			
Week 104	Day 728	Predose	x	x	x	x
OLE Phase		Predose	x [a]	x		
Completion/Early Withdrawal			x	x	x	x

OLE = *open-label extension*; PK = pharmacokinetic; RBR = Research Biosample Repository; SMN = survival of motor neuron.

[a] Additional PK samples collected predose at additional visits every 26 weeks during the *OLE* phase.

Appendix 5
Treatment Flow Chart



AE = adverse event; EOS = end of study; IMP = investigational medicinal product; OLE = open-label extension; PTA = post-trial access; SMA = spinal muscular atrophy.

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

Investigational Authorized Auxiliary, and Unauthorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	IMP/AxMP Designation	Marketing Authorization Status in EEA	Used within Marketing Authorization
Risdiplam (RO7034067)	IMP (test product)	Authorized	Yes

AxMP = auxiliary medicinal product; EEA = European Economic Area; IMP = investigational medicinal product.

Signature Page for Protocol - BP39054 - (Jewelfish) - risdiplam - v5 - Publishe
System identifier: RIM-CLIN-520756

Approval Task	[redacted] Company Signatory 08-Feb-2024 15:10:47 GMT+0000