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

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STATISTICAL ANALYSIS PLAN

TITLE: **AN OPEN–LABEL STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS/PHARMACODYNAMICS OF RISDIPLAM IN ADULT AND PEDIATRIC PATIENTS WITH SPINAL MUSCULAR ATROPHY**

PROTOCOL NUMBER: BP39054

STUDY DRUG: Risdiplam

VERSION NUMBER: 3

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SPONSOR: F. Hoffmann-La Roche Ltd

PLAN PREPARED BY: [redacted], MMath

DATE FINAL: Version 1: 31 March 2020

DATES AMENDED: Version 2: 04 March 2021
Version 3: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
21-Mar-2022 14:17:12	Company Signatory	[redacted]

CONFIDENTIAL

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) Version 3 for Study BP39054 has been amended to incorporate the following changes:

- The subgroup analyses in later onset spinal muscular atrophy have been removed due to the small sample size in the subgroups and the heterogeneous population.

- Additional corona virus disease 2019 outputs have been added in line with current guidance.

- Two additional adverse event (AE) summaries (AE and serious AEs [SAEs] rates adjusted for patient years at risk by 6-monthly intervals) were added to present longitudinal time trends.

- The text to describe the summary of previous and concomitant procedures as well as medical history was corrected. For these outputs, the Medical Dictionary for Regulatory Activities (MedDRA) will be used to assign standardized terms (not the WHO Drug Global B3 Format Dictionary).

- Due to a gap in the WHO growth reference data for those aged between 19 and 20 years, additional text has been added to explain how BMI-for-age and length-for-age percentiles will be calculated for patients in this age range.

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

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GLOSSARY OF ABBREVIATIONS

6MWT	six-minute walk test
AE	adverse event
AEBC	Annesley Eye Brain Center
AEGT	adverse event grouped terms
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration–time curve
BMI	body mass index
BiPAP	bilevel positive airway pressure
BCVA	best corrected visual acuity
BSID-III	Bayley Scales of Infant and Toddler Development Third Edition
BW	body weight
C_{max}	Maximum concentration observed
COVID-19	Coronavirus Disease 2019
CNT	cannot test
C-SSRS	Columbia Suicide Severity Rating Scale
C_{trough}	concentration at the end of a dosing interval
DBP	diastolic blood pressure
ETDRS	early treatment diabetic retinopathy study
EW	early withdrawal
FAF	fundus auto fluorescence
FEV_1	forced expiratory volume in one second
FP	fundus photography,
FU	follow-up
FVC	forced vital capacity
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE-2	Hammersmith Infant Neurological Examination Module 2
iDMC	independent data monitoring committee
ITT	intent-to-treat
LPLV	last patient last visit
MFM	motor function measurement
mRNA	messenger ribonucleic acid
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NEC	not elsewhere classified

OLE	open label extension
PCF	peak cough flow
PD	pharmacodynamics
PK	pharmacokinetic
PT	preferred term
RULM	Revised Upper Limb Module
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SD-OCT	spectral domain-optical coherence tomography
SMAIS	SMA Independence Scale upper limb total score
SMN	survival of motor neuron
SNIP	sniff nasal inspiratory pressure
SOC	system organ class
ULN	upper level of normal

1. INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of the summaries and analyses to be performed to report the results of the Study BP39054. The following documents were used:

- Study Protocol, Version 4.0, 23 June 2020
- Electronic Case Report Form (eCRF), Version 9.0, 4 June 2021
- Study specific Rave site user guide, Version 5.0, 29 December 2021

2. STUDY DESIGN

This is a multi-center, exploratory, non-comparative and open–label study to investigate the safety, tolerability, pharmacokinetic (PK), and PK/pharmacodynamics (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.

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 OBJECTIVES

The secondary objective for this study is as follows:

- To investigate the PK-PD relationship of risdiplam. The PD investigations will include analyses of survival of motor neuron (SMN) messenger ribonucleic acid (mRNA) splice forms and SMN protein.

2.3 EXPLORATORY OBJECTIVES

The exploratory objectives for this study are as follows:

- To evaluate the efficacy of treatment with risdiplam in terms of the proportion of patients who experience a pre-specified disease-related adverse event (AE).
- 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 one 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) upper limb total score (patients aged 2-60 years)
- To assess time to death (patients aged 6 months to <2 years)
- To assess time to permanent ventilation (patients aged 6 months to <2 years)

2.4 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 and children and infants with SMA previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247, previously treated with nusinersen, AVXS–101 (adeno–associated virus 9 based gene therapeutic that delivers a normal copy of the SMN1 gene), or olesoxime.

For patients aged 2–60 years, the starting dose for patients, enrolled under protocol Version 1, was 3 mg. Their dose was switched to 5 mg for patients with a body weight (BW) ≥20 kg and 0.25 mg/kg for patients with a BW <20 kg, given orally once daily as soon as the updated protocol was available.

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.

2.5 STUDY DURATION

The duration of the 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 104 weeks
- Thereafter, patients will be given the opportunity to enter the extension phase of the study (additional three years with monitoring of safety, tolerability and efficacy)
- Follow-up period:
  - Under protocol version 3.0: If a patient is withdrawn from the study treatment, completes the extension phase, or does not participate in the extension phase, the patient will be requested to attend follow-up visits over a 52−week period
  - Under protocol version 4.0: If a patient completes or withdraws early from study treatment, the patient will be requested to attend a study completion/early withdrawal visit and then followed with a phone call from the site 30 days after the study completion/early withdrawal visit

2.6 NUMBER OF CENTERS AND PATIENTS

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

2.7 DETERMINATION OF SAMPLE SIZE

The target 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) treated with RO6885247 or previously treated with nusinersen, AVXS−101, or olesoxime. With 180 patients exposed to risdiplam, there is a 92% chance to detect an AE in at least one patient, assuming that the true underlying AE 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-naive patients and patients who previously received nusinersen or AVXS−101.

2.8 TREATMENT ASSIGNMENT

Blinding not applicable since the study is open-label. 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.

2.8.1 Previous Treatment

The following rules will be used for the reporting:

- RO6885247 group: include patients who have only ever received RO6885247
- Olesoxime group: include patients who have only ever received olesoxime

- Nusinersen group: include patients who have received nusinersen, or who have received both olesoxime and nusinersen, regardless of the order in which the treatments were received
- AVXS−101 group: include patients who have received AVXS−101, or who have received both AVXS−101 and nusinersen

2.9 VISIT WINDOW

Efficacy Visit Time Window

For efficacy analysis (MFM32, HFMSE, RULM, 6MWT, SMAIS, HINE-2, BSID−III and pulmonary testing) the visits as scheduled will be included in the analysis. The following visits will be used for efficacy analysis: Baseline, Week 26, Week 52, Week 78, Week 104, extension visits (every 26 weeks) and the completion/early withdrawal visit. Follow-up visits performed under protocol version 3.0 will also be used for efficacy analysis for MFM32 and pulmonary testing. For efficacy analysis during the open label treatment period, the boundaries for the visit time windows are the midpoints between two consecutive efficacy visits. For example, the visit time window for the week 52 visit (day 364) is day 274 to day 455.

Safety Visit Time Window

For safety analysis, the visit as recorded will be used. The different protocol amendment Versions 1-4 will be shown in the following visit time window table (Table 1).

Table 1 Safety Visit Window for Analysis Visits

Actual Study Visit Label	Version 1	Version 2	Version 3	Version 4	Visits to be used for Time windowing
Baseline Day −1 to Week 1	x	x	x	x	Baseline to Day −1
Day 1 to Week 1	x	X	x	x	Day 1 (1 to 3 days)
Day 7 to Week 1	x				Day 7 (4 to 10 days)
Day 14 (±1day) to Week 2	x	X	x	x	Week 2 (11 to 21 days)
Day 28 (±3 days) to Week 4	x	X	x	x	Week 4 (22 to 42 days)
Day 56 (±3 days) to Week 8	x				Week 8 (43 to 73 days)
Day 91 (±7 days) to Week 13		X	x	x	Week 13 (74 to 105 days)
Day 119 (±7 days) to Week 17	x				Week 17 (106 to 150 days)
Day 182–183 (±7 days) to Week 26	x	X	x	x	Week 26 (151 to 213 days)
Day 245 (±7 days) to Week 35	x				Week 35 (214 to 259 days)
Day 273 (±7 days) to Week 39		x	x	x	Week 39 (260 to 287 days)
Day 301 (±7 days) to Week 43	x				Week 43 (288 to 332 days)
Day 364–365 (±7 days) to Week 52	x	x	x	x	Week 52 (333 to 395 days)
Day 427 (±7 days) to Week 61	x				Week 61 (396 to 441 days)
Day 456 (±7 days) to Week 65		x	x	x	Week 65 (442 to 473 days)

Table 1 Safety Visit Window for Analysis Visits (cont.)

Actual Study Visit Label	Version 1	Version 2	Version 3	Version 4	Visits to be used for Time windowing
Day 490 (±7 days) to Week 70	x				Week 70 (474 to 518 days)
Day 546-547 (±7 days) to Week 78	x	x	x	x	Week 78 (519 to 577 days)
Day 609 (±7 days) to Week 87	x				Week 87 (578 to 623 days)
Day 637(±7 days) to Week 91		x	x	x	Week 91 (624 to 654 days)
Day 672 (±7 days) to Week 96	x				Week 96 (655 to 700 days)
Day 728–729 (±7 days) to Week 104	x	x	x	x	Week 104 (701 to 773 days)
Extension phase (after 104 weeks every 13 weeks (±14 days) and every 26 weeks day 1–day 2 (±14 days)		x	x	x	Every 3 months after Week 104. That is Week 117, Week 130 etc. (+13 weeks). Every 6 months after Week 104. That is Week 130, Week 156, etc. (+26 weeks)
Early withdrawal / Completion / Unscheduled	x	x	X	x	To the closest visits of any of the above visits in this same column
Follow up phone call +30 days (± 7 days)				x	Follow-up
Follow up #1+ 8 weeks (±7 days)	X	x	X		Follow-up
Follow up #2 and #3+26 and+52 weeks (±14 days)	X	x	X		Follow-up

Visits which are affected due to the switch of the protocol visit schedule will be explained in footnotes. A listing of patients switching protocol visit schedule will be provided. A time window is defined for each visit, starting midway between that visit and the previous study visit, and ending midway between that visit and the next study visit (if applicable). Safety analyses will use the same visit windows defined in the visit window above. If multiple valid values for a variable are recorded in the same time window (including assessments performed at an unscheduled visit or an early treatment discontinuation visit), the last record will be selected for summary of the data, except for laboratory data, where the worst record will be selected for summary of the data.

2.10 END OF STUDY

This study includes an extension phase for all enrolled patients, it will continue until risdiplam is commercially available, the study will be terminated per local regulation, or the Sponsor will decide to terminate the study. The end of this study is defined as the date when the last patient last visit (LPLV) occurs. LPLV is expected to occur approximately 5 years after the last patient is enrolled.

3. ANALYSIS TIMING

3.1 DATA CUT DEFINITION OF ANALYSIS

A database lock for the analyses of the 12–month and 24–month safety and exploratory efficacy endpoints will occur once the last patient enrolled has either completed 12–month and 24–month assessment or has been withdrawn. All available safety and efficacy data will also be reported and a fixed clinical cut-off date will be applied to all patients.

Analysis period

- The first 12 and 24 months of risdiplam treatment for each individual
- Extension phase

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.

Analysis Timing:

- **Open-label first 12 months risdiplam treatment period (0 to ≤ 12 months)**: This is the first 12–month treatment period for all patients receiving risdiplam treatment. This is also an analysis period for the 12–month reporting event. The completion time of this period is before dose administration on the last day of the patient's Week 52 visit. Data will be summarized by previous treatment and overall

- **Open-label first 24 months risdiplam treatment period (0 to ≤ 24 months)**: This is the first 24–month treatment period for all patients receiving risdiplam treatment. This is also an analysis period for the 24–month reporting event. The completion time of this period is before dose administration on the final day of the patient's Week 104 visit. Data will be summarized by previous treatment and overall
- **Open-label second 12 months risdiplam treatment period (12 to ≤ 24 months):** This is the second 12-month treatment period for all patients receiving risdiplam treatment. The start time is defined as after dose administration on the last day of the patient's Week 52 visit. The completion time of this period is before dose administration on the last day of the patient's Week 104 visit.
- **Extension phase (> 24 months)**: This is the treatment period after each patient completes first 24 months of treatment. The start time is defined as after dose administration on the final day of patient's Week 104 visit. Data will be summarized by previous treatment and overall
- **Follow-up period:**
  - Under protocol version 3.0: This applies to all patients who discontinue treatment and/or withdraw from the study early at any time of the study or who reach the end of the 24 months treatment period and do not enter the extension phase and are requested to attend safety follow–up visits up to Week 52 after withdrawal/completion. The start day is one day after the date of withdrawal (Day 1 follow–up) and the completion date is Week 52 from the date of withdrawal. Data will be summarized by previous treatment prior to withdrawal.
  - Under protocol version 4.0: For all patients, the start time of this period is one day after the date of the study completion/early withdrawal visit. The end day is the date of the follow up phone call which should occur 30 days after the study completion/early withdrawal visit.
- **Whole treatment period**: For all patients, the start time of this period is when the first dose of study medication is administered to each patient. The end day of this period is the date of the corresponding clinical cutoff date. Safety data presented at each time point for this period will be summarized by previous treatment. Data presented for the whole treatment period will be summarized by previous treatment and overall. Whole treatment period includes also follow-up period.

3.2 DATA MONITORING

An external independent Data Monitoring Committee (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 Internal Monitoring Committee (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 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.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATION

4.1.1 Safety Population

All patients who receive at least one dose of risdiplam at any dose level whether prematurely withdrawn or not, will be included in the safety analysis population.

4.1.2 Efficacy Analysis Population

The intent–to–treat (ITT) population is defined as all enrolled patients, regardless of whether they received risdiplam or not. Unless otherwise stated, the ITT population will be the primary population for all exploratory efficacy analyses.

4.1.3 Pharmacokinetic Analysis Population

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

4.1.4 Pharmacodynamic Analysis Population

All patients with at least one time–point with a measurable PD marker will be included in the respective analysis data sets. Patients will only be excluded from the analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol or if data are unavailable, not plausible (e.g., suspected protein degeneration), or incomplete which may influence the PD analysis. Excluded cases will be documented together with the reason for exclusion.

4.2 ANALYSIS OF STUDY CONDUCT

4.2.1 Screening Failure

Screening failures (SF) will not be captured in Rave and no further analysis will be done.

4.2.2 Study Enrollment

The number of patients in the ITT and safety population will be summarized by previous treatment (RO6885247, olesoxime, nusinersen and AVXS-101) and overall for all enrolled patients. The number of patients excluded from each of the populations will be

summarized by reason for exclusion. The number and percentage of patients enrolled at each geographical region (Europe and North America), country and site will also be summarized by previous treatment and overall.

The patients excluded from the analysis populations will also be listed.

4.2.3 Patient Disposition

The number and percentage of patients enrolled, completed, ongoing and discontinued from the study will be summarized by previous treatment and overall for all patients. The number and percentage of patients entered, completed and discontinued early will be summarized for the first (0 to $\leq$12 months) and second (12 to $\leq$24 months) 12-month treatment periods, the extension phase and the follow–up (FU) periods. The number and percentage of patients who discontinued prior to the start of treatment will also be summarized.

The reason for early discontinuation during each of the periods will also be summarized and listed.

4.2.4 Protocol Deviations

The major protocol deviations will be identified according to the Management of Violations to Protocol Specifications document before database lock. The number and percentage of patients with major protocol violations categorized by protocol violation criteria will be summarized by previous treatment and overall for all patients up to the clinical cutoff date. Data will be presented overall and separately for the screening period, 0 to 12 months and 12 to 24 months of treatment period, the extension phase and follow-up period defined in protocol version 3.0.

Major protocol deviations will also be listed and evaluated for their potential effects on the interpretation of study results.

4.2.5 Previous Treatment

Summaries of previous treatment will be presented overall and by previous treatment. For those who were previously treated with nusinersen, the following will be summarized: time from last nusinersen treatment to first risdiplam treatment, dose frequency, total nusinersen treatment duration and reasons for subjects switching from nusinersen. For those who were previously treated with AVXS-101, the following will be summarized: time from AVXS-101 treatment to first risdiplam treatment, AVXS-101 dose level, route of administration and reasons for subjects participating in the current study after treatment with AVXS-101.

A listing of reasons for subjects switching from nusinersen and a listing of reasons for subjects participating in the current study after treatment with AVXS-101 will be provided.

A listing of information on previous SMA treatment will be presented by each previous treatment group.

4.2.6 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the ITT population using descriptive statistics, means, standard deviations, medians, interquartile range ($Q_{0.25}$; $Q_{0.75}$), minimum and maximum for continuous variables and numbers and percentages for categorical variables, as appropriate.

A listing of demographic and baseline characteristics will be provided.

Baseline is the patient's last observation prior to initiation of study medication. Data will be summarized by previous treatment and overall for all patients for the following:

- Age at enrollment (years)
- Age groups of 6 months to < 2 years old, 2–5, 6–11, 12–17, 18–25, 26–44, and 45–60 years old
- Gender
- Self/caregiver-reported race
- Self/caregiver reported ethnicity
- Height/length (in centimeters [cm])
- Height/length–for–age percentile 3rd, 5th, 10th, 25th, 50th and > 50th (up to 19 years old)
- Weight (in kilograms [kg])
- Weight-for-age percentile 3rd, 5th, 10th, 25th, 50th and > 50th (inclusively only up to 10 years old, as the World Health Organization (WHO) data reference data for weight–for–age is only up to 10 years old)
- Weight for lengths/height percentile 3rd, 5th, 10th, 25th, 50th and > 50th (inclusively only up to 10 years old)
- Body mass index (BMI)
- BMI category < 18.5: underweight, 18.5 to 24. 9: normal, 25.0 to 29.9: overweight, and ≥ 30: obese (≥ 20 years)
- BMI–for–age percentiles 3rd, 5th, 10th, 25th, 50th, and > 50th (up to 19 years old)
- Head circumference (in cm) (those aged less than 5 years at screening)
- Head circumference–for–age percentile 3rd, 5th, 10th, 25th, 50th, and > 50th (those aged less than 5 years old at screening)
- Chest circumference (in cm) (those aged less than 2 years at screening)
- Substance used (Yes/No), if yes classification (alcohol, drugs) for 2 to 60 years old

4.2.6.1 SMA Disease Characteristics at Baseline

All collected SMA disease characteristics at baseline will be presented in listings, and the following will be summarized by previous treatment and overall for all patients:

- Sleep results (Normal/Abnormal)
- SMN2 copy number from clinical genotyping
- Ambulatory/Non−ambulatory (for patients under the age of 2 years, ambulant will be defined as achieving 'walking independently' as assessed on item 8 of the HINE-2)
- SMA type (1, 2 and 3)
- Initial SMA Symptoms, best response
- Age at diagnosis (in months)
- Age at onset of initial SMA symptoms (in months)
- Time from onset of SMA symptoms to first start of risdiplam treatment (in months)

  (Date of first dose of study medication-Date of initial SMA symptom onset)/365×12
- Tracheostomy (Yes/No)
- Patient's current level of motor function
- Highest motor function achieved

<u>For patients aged 2 years or above</u>

- Respiratory device(s) used within 2 weeks prior
  - No Pulmonary Care (Non-Invasive or Invasive)
  - Cough Assist required- (Used Daily For Therapy, Not Illness Related or used with an illness)
  - Bilevel Positive Airway Pressure (BiPAP) Support (<16 or ≥ 16 Hours Per Day)
  - Airway clearance through cough assistance
- RULM entry item (Item A) score
- Motor function measure (MFM32) item 9 score
- Number of fractures (None, 1-2, 3-5, ≥ 6)
- Scoliosis (Yes/No). If yes, the degree of curve in degrees ($0-10$, $10-40$, >40)
- Scoliosis surgery before screening (Yes/No)
- Hip subluxation or dislocation (Yes/No)
- Hip surgery (Yes/No)
- Baseline total score HFMSE < 10

For patients aged 6 months to <2 years old

- Respiratory device(s) used within 2 weeks prior to study enrollment
  - Do not require Pulmonary Care (Non-Invasive or Invasive)
  - Cough Assist required (Used Daily For Therapy, Not Illness Related or used with an illness)
  - BiPAP Support (<16 or ≥ 16 Hours Per Day)
- Is ventilation provided prophylactically (Yes or No)
- BiPAP support been required for ≥ 16 hours per day for more than >21 consecutive days (Yes/No)
- Intubated for a period of ≥ 21 consecutive days since last visit (Yes/No)
- Attainment on the following HINE-2 motor milestones: head control, sitting, ability to kick (in supine), rolling, crawling, standing and walking

4.2.7 Previous and Concomitant Procedures

4.2.7.1 Previous and Concomitant SMA Related Surgeries and Procedures

For all SMA-related surgeries and procedures, the term entered by the investigator describing the condition (the 'verbatim term') will be assigned to a standardized term (the 'preferred term') and system organ class based on the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA). All analyses will be performed using these preferred terms and body systems and summarized by previous treatment and overall for all patients.

The number and the percentage of patients with any SMA–related surgeries and procedures will be summarized. Multiple occurrences of the same procedure for each individual patient (same coded term) will be counted only once. The number of patients who have undergone at least one procedure and the total number of procedures reported will also be presented.

Previous surgeries or procedures performed prior to the first dose date and for concomitant surgeries or procedures performed on or after the first dose date up to study withdrawal or completion will be summarized separately.

For the safety follow-up period under protocol version 3.0, surgeries or procedures performed on or after Day 1 and up to Week 52 after study withdrawal/completion will also be summarized similarly.

Listings of the results will be presented which include the investigator reported term and the corresponding terms by system organ class, preferred term and the lowest level term by previous treatment and by previous or concomitant.

4.2.7.2 Previous and Concomitant SMA Related Spinal/Tendon Release Surgeries and Procedures

For patients aged 2 years or above

The number and percentage of patients with at least one tendon release or spinal surgery and the total number of tendon release or spinal surgery reported will also be summarized.

For those with tendon release or spinal surgery, data categorized by the following will also be summarized:

- Spinal surgery
  - spinal fusion with segmental instrumentation
  - insertion of traditional growing rods
  - insertion of magnetically controlled growing rods
  - rod adjustment
  - other
- Tendon release
  - hip
  - knee
  - ankle
  - other

Listings of the results (tendon release or spinal surgery) will be presented which include the investigator reported term and the corresponding terms by system organ class, preferred term and the lowest level term and by previous treatment and by previous or concomitant.

4.2.8 Previous and Concurrent Medical History

For all conditions, the term entered by the investigator describing the condition (the 'verbatim term') will be assigned to a standardized term (the 'preferred term') and system organ class based on the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA). All analyses will be performed using these preferred terms and body systems and summarized by the previous treatment and overall for all patients.

All medical conditions present from 30 days prior to the screening visit will be reported:

- The number and percentage of patients with concurrent medical history i.e. with previous conditions present at baseline (starts prior to the first dose and with no end date or with an end date after the first dose)

- The number and percentage of patients with previous medical history i.e. with previous conditions no longer present at baseline (starts prior to the first dose and with an end date before the first dose)

Multiple occurrences of the same condition (same coded term) for an individual will be counted only once. The number of patients with at least one condition and the total number of conditions reported will also be presented.

Previous and concurrent medical history at baseline will be summarized separately.

Listings of the results will be presented by previous treatment.

4.2.9 Previous and Concomitant Medications

For all medications, the term entered by the investigator describing the medications (the "verbatim term") will be assigned to a standardized term (the "preferred term") and drug class on the basis of the investigator terms for medications and procedures have been encoded using the WHODrug Global B3 Format Dictionary. All analyses will be performed using these preferred terms and medication classes and summarized by previous treatment and overall for all patients.

All medications taken by the patients from 30 days prior to the screening visit will be reported:

- The number and percentage of patients with medications present at baseline (starts prior to the first dose and with no end date or with an end date after the first dose)
- The number and percentage of patients with previous medications i.e. with previous medications no longer present at baseline (starts prior to the first dose and with an end date before the first dose)
- The number and percentage of patients with concomitant medications (starts on or after the first dose date up to the date of study withdrawal/completion)

Multiple occurrences of the same medication (same coded term) for an individual will be counted only once. The number of patients taking at least one medication and the total number of medications taken will also be presented.

Previous medications, medications present at baseline, concomitant medications taken for adverse events, and concomitant medications not taken for adverse events will be summarized separately.

Medications with a start date from 1 day up to 52 weeks after study withdrawal/completion recorded under protocol version 3.0 will also be summarized separately.

Listings of the results will be presented separately by previous treatment.

4.2.10 Physiotherapy, Occupational Therapy, and Other Forms of Exercise Therapy (for Patients Aged 2 Years or above)

All therapies used by patients from 30 days prior to the screening visit are recorded and will be reported. The number and percentage of patients undergoing any physical/occupational/exercise therapy (marked as 'ongoing' or with no end/stop date) will be summarized by previous treatment and overall for all patients.

A listing of physical/occupational/exercise therapy will be presented by previous treatment.

4.3 EFFICACY ANALYSIS

All efficacy analyses are considered as exploratory and will be based on the ITT population and summarized by previous treatment and overall for all patients.

All available efficacy data up to the clinical cut-off date (if required) will be presented at the time for each reporting event.

Results for assessments that are conducted at unscheduled or withdrawal visits will be assigned to the appropriate scheduled study visit according to the visit window. If multiple valid values for a variable are recorded in the same time window, the assessment performed closest to the scheduled study day of the visit will be used for the summary of the data. If the closest assessments are equidistant from the scheduled study day, then the later of the assessments will be used.

Proportions will be calculated based on the number of patients with available results at each time-point. Missing results at each time-point or the number of available results will also be presented at each time-point.

4.3.1 Motor Function

4.3.1.1 Motor Function Measure (MFM) for Patients Aged 2 to 60 Years

The MFM (Bérard et al. 2005) is an ordinal scale constructed for use in patients with neuromuscular disorders. The scale comprises 32 items (MFM32) 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 score 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 MFM total score will be calculated according to the user manual. The 32 scores are summed and then transformed onto a 0 to 100 scale (i.e., sum of 32 items scores divided by 96 and multiplied by 100) to yield the MFM total score expressed as a percentage of the maximum score possible for the scale (the one obtained with no physical impairment). The lower the total score, the more severe the impairment is.

The full MFM32 will be administered to all patients (aged 2 years or above before screening) at screening, baseline, Week 26/52/78/104, extension (every 26 weeks), early withdrawal (EW) and follow-up under protocol version 3.0.

For items that are recorded as “Not Done” in the eCRF, these items are considered as missing with missing item scores. If the MFM has been administered at a visit but item scores are missing, the following rule will be applied to handle missing items.

Input from the holder of the MFM confirmed that score calculation by domain is only possible as follows. For the score calculation by domain, D1, D2, and D3, scores will only be calculated if there is less than 15% of missing data; i.e., for domain D1 and D2, scores will only be calculated if there is a maximum of two items missing in each domain; and for domain D3, a maximum of 1 item missing. In addition, total scores will only be calculated where there is a calculated score in all domains D1, D2, and D3. If there are only two missing items in either D1 or D2, and/or one missing item in D3, the missing items in D1, D2, and D3 will be imputed with “0” prior to the calculation of the total score. Missing MFM total scores will not be imputed. If possible, the same assessor should follow the patient throughout the study.

The total score and the change from baseline total score for the MFM32 will be summarized descriptively by previous treatment and overall for all patients at each time-point.

The total score and the change from baseline total score for the MFM32 Domain score D1, D2, D3, combined score $D1+D2$ and $D2+D3$ will be summarized descriptively by previous treatment and overall for all patients at each time-point.

Proportions will be calculated at each time point using the total number of patients with available results at each time-point as the denominator. Missing results at each time-point or the number of available results at each time-point will also be presented.

The proportion of patients who report a decline (<0) and stabilization or improvement (i.e., a change from the study baseline ≥ 0, 1, 2, 3, and 4) on the MFM32 total score will also be summarized at each time-point by previous treatment and overall for all patients.

The mean change from baseline in the MFM32 total score and the mean MFM32 total score and their corresponding 95% confidence interval at each time-point (Week 26, Week 52, Week 78, Week 104, and extension visit and follow-up completed under protocol version 3.0) will be summarized and presented graphically (mean plot) by previous treatment and overall for all patients.

A listing of the MFM32 will be presented by previous treatment.

4.3.1.2 Hammersmith Functional Motor Scale Expanded (HFMSE) for Patients aged 2 to 60 years

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 score on a 3-point Likert scale (0–2) and are summed to derive the total score, with lower scores indicating greater impairment. The HFMSE was designed to assess important functional abilities, including standing, transfer, ambulation, and proximal and axial function.

For items recorded as "Not Done" for both the HFMSE scale, these items are considered as missing with missing item scores.

For the HFMSE, if 6 or fewer items are missing, the missing items will be imputed to be "0" (unable to perform the task) prior to the calculation of the total score of HFMSE. If more than 6 items are missing at an assessment time-point, the total score of HFMSE at this assessment time-point will not be calculated.

The total score and the change from baseline total score for the HFMSE will be summarized descriptively by previous treatment and overall for all patients at each time-point.

Proportions will be calculated at each time point using the total number of patients with available results at each time-point as the denominator. Missing results at each time-point or the number of available results at each time-point will also be presented. The proportion of patients who report a decline (<0) and stabilization or improvement (i.e., a change from the study baseline ≥ 0, 1, 2, 3, and 4) on the HFMSE total score will also be summarized by previous treatment and overall for all patients at each time-point.

The mean change from baseline in the HFMSE total score and the mean HFMSE total score and their corresponding 95% confidence interval over each time-point will be presented in a mean plot by previous treatment and overall for all patients.

A listing of the HFMSE will be presented by previous treatment.

4.3.1.3 Revised Upper Limb Module for Patients Aged 2 to 60 Years

The revised upper limb module (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. 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).

Items recorded as “Not Done” are considered as missing with missing item scores.

For the RULM, a score will be collected for each item on both the left and right side; the highest score will be used in calculating the total RULM score. If 3 or fewer items are missing, the missing items will be imputed to be “0” (unable to perform the task) prior to the calculation of the total score of RULM. If more than 3 items are missing at an assessment time-point, the total score of RULM at this assessment time-point will not be calculated.

The total score and the change from baseline total score for the RULM will be summarized descriptively by previous treatment and overall for all patients at each time-point.

Proportions will be calculated at each time point using the total number of patients with available results at each time-point as the denominator. Missing results at each time-point or the number of available results at each time-point will also be presented. The proportion of patients who achieve a decline (<0), stabilization or improvement (i.e., a change from the study baseline ≥ 0, 1, 2, 3 and 4) on the RULM total score will also be summarized by previous treatment and overall for all patients at each time-point.

The mean change from baseline in the RULM total score and the mean RULM total score and their corresponding 95% confidence interval over each time-point will be presented graphically (mean plot) by previous treatment and overall for all patients.

A listing of the RULM will be presented by previous treatment.

4.3.1.4 Gross Motor Scale of the Bayley Scales of Infant and Toddler Development Third Edition for Infants aged 6 months to < 2 years

The Gross Motor scale of the Bayley Scales of Infant and Toddler Development–Third Edition (BSID-III) will be used as an outcome measure to assess attainment of motor milestones and 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.

The BSID consists of a core battery of five scales. Three scales (cognitive, motor, and language) are administered with child interaction and two scales (social-emotional adaptive behavior) are conducted with parent questionnaires.

Motor Milestones

The number and percentage of infants (1) sitting without support for 5 seconds (as assessed in item 22), (2) sitting without support for 30 seconds (defined as 'Sits without support for 30 seconds' as assessed in item 26 of the modified BSID-III gross motor scale), (3) standing (defined as 'Stands alone' as assessed in item 40 of the modified BSID-III gross motor scale), and (4) walking (defined as 'Walks alone' as assessed in item 42 of the modified BSID-III gross motor scale) at Month 12 and Month 24 will be presented with a two-sided 95% Clopper–Pearson (exact) confidence interval (CI) for the proportion by previous treatment and overall.

The proportion of responders will be calculated based on the number of infants with available results at each time-point. Missing results at each time-point or the number of available results will also be presented at each time-point.

The number and percentage of infants who achieved motor milestones (item 22, 26, 40, and 42) at each time-point and corresponding 95% CIs will be presented by previous treatment and overall for all infants. The same responder/non-responder definitions described above will be used for these analyses.

Total Raw Score

The gross motor scale consists of 72 items scored at 0 (unable to perform the activity) or 1 (criteria for item achieved). The total raw score is calculated by summing the item scores to give a maximum possible score of 72.

For the calculation of the modified BSID-III gross motor scale total raw score, if any individual item score contributing to the total score is missing or 'CNT' is recorded, then that item will be set to 0 if there is at least one non-missing item at the assessment. If all items are missing, then the total score will be set to missing

The raw total score and the change from baseline in the total raw score of the BSID–III gross motor scale will be summarized by previous treatment and overall for all infants at each time-point.

A listing of the BSID-III Score (including raw total score, change from baseline total raw score, score of item 22 (Sits without support for 5 seconds), item 26 (Sits without support for 30 seconds), item 40 (Stand Alone) and item 42 (Walks alone)) will be presented by previous treatment.

4.3.1.5 Hammersmith Infant Neurological Examination –Module 2 for Infants Aged 6 Months to < 2 Years

The Hammersmith Infant Neurological Examination (HINE) is a neurologic examination initially designed to evaluate infants between 6 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 HINE–2 evaluates 8 developmental milestones scored on a 3, 4, or 5-point scale, with 0 indicating inability to perform a task and a score of 2, 3, or 4 (depending on the task) indicating full milestone development. The total score is calculated by summing the item scores to give a maximum possible score of 26. If any individual item score contributing to the total score is missing or 'CNT' is recorded, then that item score will be set to 0 if there is at least one non-missing item at the assessment. If all items are missing, then the total score will be set to missing.

Motor Milestones

The number and percentage of infants within each attainment response category of the HINE–2 motor milestones at Month 12 and Month 24 (and all other time-points) will be presented by previous treatment and overall for all patients. CNT will be included as a separate response category for each milestone. Milestones include head control, sitting, voluntary grasp, ability to kick, rolling, crawling, standing, and walking. The number and percentage of infants with a missing HINE–2 assessments at a visit (including withdrawals) and the number and percentage of infants who had died by that visit will also be presented.

Motor Milestones Responder

The number and percentage of motor milestone responders (as assessed by HINE–2) at Month 12 and Month 24 will be summarized by previous treatment and overall. For the responder definition, an improvement in a motor milestone is defined as at least a 2-point increase in ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing or walking. Worsening is similarly defined as a 2-point decrease in ability to kick (or lowest score) or a 1–point decrease in head control, rolling, sitting, crawling, standing or walking. Voluntary grasp is excluded from the definition. An infant will be classified as a responder if more motor milestones show improvement than show worsening.

The proportion of milestone responders, that is the proportion who could achieve each of the 8 milestones, as assessed by HINE-2 will also be summarized at each time-point by previous treatment and overall of all infants. Proportions will be calculated at each time

point using the total number of infants with available results at each time-point as the denominator. Missing results at each time-point or the number of available results at each time-point will also be presented.

The number and percentage of motor milestone responders at each time-point and corresponding 95% CIs will be presented by previous treatment and overall of all infants. The same responder/non-responder definition described above will be used for these analyses.

The HINE−2 total score and change from baseline will be summarized by each time−point by previous treatment and overall of all infants.

A listing of the result for each motor function attainment level of HINE-2 will be provided.

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

4.3.1.6 Six Minute Walk Test (Ambulatory Patients Aged 6 to 60 Years)

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. 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).

Patients must be aged ≥ 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. The total distance walked in every minute is recorded.

The distance walked in every minute and the total distance walked will be summarized at each time-point by previous treatment and overall for all patients.

The change from baseline in the total distance walked in 6 minutes will be summarized overall and by previous treatment.

Fatigue will be assessed by the difference between the distance walked for the first minute and the distance walked for the sixth (last) minute and expressed in a percentage. The definition is given as follows.

(The sixth minute distance walked − the first minute distance walked)/the first minute distance walked) × 100

The change from baseline of percentage change in distance walking from first to last minute (fatigue) of the 6MWT will be summarized and at each time-point by previous treatment.

The total distance walked (m) over each time-point will be presented in a line plot for each individual patient.

4.3.2 Respiratory

4.3.2.1 Pulmonary Testing for Patients Aged 2 to 60 Years

The respiratory tests for the study include the Sniff Nasal Inspiratory Pressure (SNIP) and spirometry tests. The SNIP test will be performed for patients aged 2 years or above and the spirometry test will be performed in patients aged 6 years or above.

The respiratory measurements obtained will include the SNIP and spirometry tests (FVC, FEV1 and PCF).

Patients are allowed to perform each of the respiratory tests up to 5 consecutive maneuvers (times) at each scheduled assessment time-point. The highest (best) value out of all available maneuvers will be chosen for each of the respiratory measurements.

The best values and the best value expressed as a percentage of the predicted values (best percentage predicted values and absolute value in litre) for each of the respiratory measurements will be used for the analyses. All percentage predicted values will be derived by the external vendor based on individual's actual respiratory value, age, race, height, gender and weight. The Sponsor will utilize the percentage predicted values and absolute value in litre provided by the vendor for the analyses.

The best percentage predicted value and the change from baseline best percentage predicted value of the SNIP and spirometry tests (i.e. FVC, FEV1 and PCF) will be summarized at each time-point by previous treatment and overall for all patients, as well as being presented graphically (mean plot) over all time-points by previous treatment group and overall for all patients.

The absolute value and change from baseline absolute value of the SNIP (cmH_2O) and spirometry tests (i.e., FVC [litre], FEV1 [litre] and PCF [litre/second]) will be summarized at each time-point by previous treatment and overall for all patients, as well as being presented graphically (mean plot) over all time-points by previous treatment group and overall for all patients.

4.3.3 Survival, Permanent Ventilation and Ventilation Free Survival

4.3.3.1 Ventilation Free Survival (aged 6 months to < 2 years)

Time-to-death or permanent ventilation will be presented graphically using Kaplan-Meier curves. Permanent ventilation will be measured for infants aged 6 months to 2 years and are defined as:

- $\geq$16 hours of non-invasive ventilation (e.g., Bi-level Positive Airway Pressure) per day or intubation for$\geq$21 consecutive days in the absence of, or following the resolution of, an acute reversible event
- 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 median time to ventilation-free survival (and 95% CI) and the proportion of infants who are surviving without permanent ventilation at Month 12 and Month 24 of treatment will be estimated using Kaplan–Meier methodology, when possible. 95% CIs for the proportion of infants surviving without permanent ventilation at Month 12 and Month 24 will be presented by previous treatment and overall. CIs will be calculated using the complimentary log–log transformation for the estimated survivor function S(t), with standard errors computed via Greenwood's formula of Kaplan–Meier estimator.

Time-to-death or permanent ventilation is defined as the time in months from the date of enrollment into the study until the date of death from any cause or date of permanent ventilation, whichever event occurs first. The date of permanent ventilation will be the first of the > 21 days of non-invasive ventilation support or intubation to be confirmed, or the date of tracheostomy. Infants with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be alive and without permanent ventilation.

Individual listings will also be presented for the time-to-death or permanent ventilation (and the individual components) by previous treatment and overall.

Note: the date of enrollment occurs at least one day before the first study drug administration.

A partial event date will be replaced by the first day of the month (assuming the month and year are known), unless there is evidence that the infant was event–free within that month, in which case the date the infant was last known to be event-free within that month will be used as the event date. If the month is missing, the date the infant was last known to be event–free will be used.

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

enrollment up to the date of withdrawal will be included in the analysis. The patient diary will not be available to provide information about the use of non-invasive ventilation once an infant has been withdrawn from the study and is no longer receiving study drug.

If an infant has reached 16 hours of non-invasive ventilation support per day or has been intubated continuously within the last 21 days prior to withdrawal, he or she will be followed by telephone contact until the outcome is confirmed.

4.3.3.2 Survival (Aged 6 Months to <2 Years)

Time–to–death is defined as the time in months from the date of enrollment until the date of death from any cause. Infants with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be alive.

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

Time–to–death by previous treatment and overall will be presented graphically using Kaplan-Meier curves. The median time to death (and 95% CI) and the proportion of infants who are alive at Month 12 and Month 24 of treatment will be estimated using Kaplan–Meier methodology, when possible. 95% CIs for the proportion of infants who are without permanent ventilation at Month 12 and Month 24 will be presented by previous treatment and overall.

A listing of deaths will be provided.

4.3.3.3 Permanent Ventilation (aged 6 months to <2 years)

Time to permanent ventilation is defined as the time in months from the date of enrollment into the study until the date of permanent ventilation. Infants with no event reported prior to the analysis cutoff date will be censored at the latest date before the cutoff in which they were known to be without permanent ventilation. Infants who have been withdrawn from the study with no event reported prior to withdrawal will be censored at the date of withdrawal. For infants who have been withdrawn from the study and entered follow-up, all events reported from the date of enrollment up to the date of withdrawal will be included in the analysis by previous treatment and overall.

Time to permanent ventilation by previous treatment and overall will be presented graphically using Kaplan–Meier curves. The median time to permanent ventilation (and 95% CI) and the proportion of infants who are without permanent ventilation at Month 12 and Month 24 of treatment will be estimated using Kaplan–Meier methodology, when possible. 95% CIs for the proportion of infants who are without permanent ventilation at Month 12 and Month 24 will be presented by previous treatment and overall.

4.3.4 Swallowing and Nutrition Check-up

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

The nutrition check-up by age groups in detail as following:

Swallowing/Nutritional Status (aged 6 months to < 2 years)

- Nutritional Check-up:
  - Primary food intake type (Solid food, modified oral food intake, nasogastric food intake, 100% gastrostomy tube fed, oral fluid (milk) food intake, or mixed (fluid/puréed food) oral food intake)
- Prior swallowing assessment using an imaging modality (Yes/No). If yes, normal or abnormal
- How is the patient fed? (oral, tube feeding, combination of oral and tube feeding) If combination oral and tube feeding, specify approximate % of feeding with tube
- Number of times fed during the day
- If 'oral feeding' is selected the length of time required to reach satiety
- The number and percentage of infants who can swallow:
  - Water
  - Nectar
  - Rice pudding
  - Purees
  - Solid food

A summary of feeding route and ability to swallow different food types at each time-point will be presented by previous treatment and overall for all patients.

The following rule will be used to define 'ability to swallow' in patient narratives: 'able to swallow' is defined as the ability to swallow at least one of the following: water, nectar, rice pudding, purees or solid food. If the response to all five items (can the patient swallow: water, nectar, rice pudding, purees or solid food) is recorded as 'no' then the patient is 'unable to swallow.'

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

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

Nutrition check (aged 2–60 years)

- Nutritional Checkup:
  - Primary food intake type (Solid food, modified oral food intake, nasogastric food intake, 100% gastrostomy tube fed, oral fluid (milk) food intake, or mixed (fluid/puréed food) oral food intake)

The number and percentage of patients for primary food intake type will be summarized at each time-point by previous treatment and overall for all patients.

4.3.5 Disease Related Adverse Event

For all patients

The disease–related AEs and the disease–related AE rate adjusted for patient years (AE rate per 100 patient–years) will be presented. The analysis of disease-related AEs will be based on the safety population.

Disease-related AEs will be collected through the AE reporting of the study and events will be identified by applying two different types of baskets to the AE dataset:

- Narrow prospectively defined baskets of MedDRA lowest level terms suggestive of SMA related AEs. This basket was defined based on a group of CDC terms selected from an age and gender matched case control study comparing CDC code rates observed in patients with and without SMA using commercially available insurance claim data (CLAIMS and Market scan data). These selected ICD9 codes were then manually linked to the corresponding MedDRA lowest level terms and grouped by medical concepts in different baskets, using the latest version of MedDRA

- Broad baskets with events suggestive of SMA related events selected at MedDRA preferred term level from all AEs reported in all ongoing risdiplam clinical trials up to January 2019 i.e., prior to unblinding of Part 2 of Study BP39055 (SUNFISH).

For both wide and narrow baskets, terms have been defined for each of the following disease related medical concepts:

- Overall disease related AEs basket consisting of all terms of the following 7 medical concepts baskets:
  - gastro-intestinal disorders
  - lower respiratory tract infections
  - respiratory impairment disorders
  - neuro-musculo–skeletal and connective tissues disorders
  - nutrition and growth disorders
  - cardiac not elsewhere classified (NEC) disorders
  - other NEC SMA related disorders

Note: the same lowest level term or preferred term may be applicable to more than one medical concept and will therefore be included in more than one basket.

The number and percentage of patients who have experienced at least one disease–related AE, and the number of disease-related AEs will be summarized descriptively for each basket and by previous treatment and overall for all patients. Percentages will be based on the number in the safety population.

The proportion of patients with at least one disease-related AE will be analyzed using log binomial model including previous treatment.

The rate of disease–related AEs by medical concept and overall adjusted for patient years for all occurrences will also be summarized. The disease–related AE rate per 100 patient-years, which is also the average number of events per 100 patient-years, is calculated by:

- Disease-related AE rate = (number of disease related AEs observed ÷ total patient–years at risk) × 100

where, the total patient-years at risk is defined as:

– Total patient-years at risk = sum across all patients of the time interval in the years between the start of study medication and up to study withdrawal/completion or the clinical data cutoff date

The 95% confidence interval of the disease-related AE rate (average number of events) per 100 patient–years will also be presented and will be calculated based on the exact method of a Poisson distribution for the disease-related AE rate.

4.3.6 SMA Independent Scale (SMAIS)

4.3.6.1 SMAIS patient-reported (aged 12–60 years)

The SMAIS was developed specifically for SMA in order to assess function–related independence. The SMAIS contains 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) which is transformed to a 0–2 scale. Lower scores indicate greater dependence on another individual. Calculation of the total score will follow the scoring manual and create an upper limb total score comprising of 22 items. The SMAIS will be completed by patients aged ≥ 12 years.

4.3.6.2 SMAIS caregiver-reported (aged 2–60 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 and is scored in the same way, as per the

scoring manual. The same caregiver should complete the measure throughout the study.

4.3.6.3 Analysis of the SMAIS (patient- and caregiver-reported)

Missing data will be handled according to the scoring manual (including the minimum number of completed items required for calculation of a total score). If the SMAIS has been completed at a visit but item scores are missing, these items will be set to 0 (i.e., "He/she cannot do this at all without help [caregiver/parent]"; "I cannot do this at all without help [patient]) prior to the calculation of the total score. Not applicable response for an item will also be set to 0 prior to the total score calculation. Missing data at the form level, that is when all items are missing at a scheduled assessment time-point, will not be imputed.

The actual value and the change from baseline value for the patient–reported and the caregiver–reported total SMAIS scores will be summarized by previous treatment and overall for all patients at each time-point.

Proportions will be calculated at each time point using the total number of patients with available results at each time-point as the denominator. Missing results at each time-point or the number of available results at each time-point will also be presented.

The proportion of patients who report a decline (<0) and stabilization or improvement (i.e., a change from the study baseline ≥ 0, 1, 2, 3, and 4) on the patient-reported and caregiver-reported SMAIS upper limb 22-item total score will also be summarized at each time-point by previous treatment.

4.4 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSIS

4.4.1 Pharmacokinetic Analysis

Pharmacokinetic (PK) parameters will be assessed (if possible, based on the available data):

- Concentration per time-point listed
- Maximum concentration observed (C_{max})
- Area under the concentration–time curve (AUC)
- Concentration at the end of a dosing interval (C_{trough}) to assess steady–state
- Other PK parameters as appropriate.

The PK samples are collected as per the Schedule of Assessment in the protocol (Appendix 7).

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

Nonlinear mixed effects modeling (software NONMEM) will be used to analyze the sparse concentration-time data of risdiplam (and its metabolite(s) if deemed necessary).

Population and individual PK parameters will be estimated and the influence of various covariates (such as age, gender, body weight, or previous treatment) on these parameters will be investigated in an exploratory way. Data may be pooled with data from other studies with risdiplam in order to improve the parameter estimates from the model. Secondary PK parameters (such as C_{max} and AUC) may be derived from the model for each individual included in the PK analysis and will be presented descriptively.

Additional exploratory analyses on exposure and safety/efficacy relationship may be conducted if deemed necessary.

The details and results of the PK analyses may be reported in a document separate from the clinical study report.

4.4.2 Pharmacodynamic Analysis

The PD parameters include SMN mRNA and SMN protein in blood. The PD samples are collected as per the Schedule of Assessment in the protocol.

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

Exploratory analyses on PD parameters versus selected efficacy parameters may also be performed as deemed necessary.

The details and results of the PD analyses may be reported in a document separate from the clinical study report.

4.5 DIGITAL BIOMARKER ASSESSMENT

The results of digital biomarker and exploratory analyses will be reported separately from the clinical study report.

4.6 SAFETY ANALYSIS

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 death
- Incidence of treatment discontinuations due to adverse events
- Incidence of laboratory abnormalities
- Incidence of electrocardiogram (ECG) abnormalities

- Incidence of vital sign abnormalities
- Incidence of suicidal ideation or behavior (C-SSRS)
- Incidence of clinically significant findings on ophthalmological examination
- Incidence of clinically significant findings on neurological examination
- Anthropometric examination including weight, height, head and chest circumference

Safety data will be summarized descriptively using the safety population. All available safety data up to the clinical cutoff date will be presented by previous treatment at the time of each reporting event. Safety data will be summarized for the whole treatment period and by period (open label treatment period, extension period and follow-up period), if specified.

4.6.1 Exposure of Study Medication

The extent of exposure of study medication (risdiplam) will be summarized by previous treatment and overall for all patients and include the following:

Duration of study medication will be calculated from the first day of study medication to the last day of study medication:

Duration of study medication in days = date of last dose − date of first dose + 1

- Duration of study medication for the 24-month period will be calculated from the first day of study medication to the last day of the 24-month period:

Duration of 24-month study medication in days = date of last dose (24−month period) − date of first dose + 1

- Duration of study medication for the 12-month period will be calculated from the first day of study medication to the last day of the 12-month period:

Duration of 12-month study medication in days = date of last dose (12−month period) − date of first dose + 1

- Number and percentage of patients with duration of study medication grouped by time unit for every 6 months (0 to ≤ 6 months, > 6 to ≤ 12 months, > 12 to ≤ 18 months, > 18 to ≤ 24 months, etc.)
- Number of dose(s) taken
- Number of dose(s) missed
- The number and percentage of patients with 0, ≥1, 1–5, 6–10, 11–15, ≥16 missed doses
- Number of Partial dose(s) taken (Partial dose taken is as defined as actual volume administered <90% of planned volume administered)
- The number and percentage of patients with 0, 1, 2, 3, ≥4 partial doses
- Number of overdose(s) taken (Over dose taken is defined as the actual volume administered ≥110% of the planned volume administered)
- The number and percentage of patients with 0, 1, 2, 3, ≥4 overdoses

- Dose intensity in percentage, calculated by

Dose intensity % = (number of non-missing doses taken ÷ number of doses expected to be taken) × 100

- The number and percentage of patients with dose intensity < 80% and ≥ 80%
- Route of administration
- Number of dose adjustments
- Cumulative dose, defined as the sum of all doses actually received by the patient in milligrams

A listing of study treatment exposure and a listing of study treatment duration will be provided. All available study medication exposure data will be reported at each clinical cutoff date. If dose administration is ongoing at the time of the clinical cutoff date, the last dose date will be replaced by the clinical cutoff date for the analysis. All dose records with a start date on or before the clinical cutoff date will be included in each data cut-off date.

4.6.2 Adverse Events

For each AE recorded, the term entered by the investigator describing the event (the "verbatim term") will be assigned to a standardized term (the "preferred term") based on the most up-to-date version of MedDRA. All data displays of AEs will be performed using the system organ class (SOC) and preferred terms (PT) and summarized by previous treatment and overall for all patients.

The following AEs of special interest as defined in protocol version 4.0 will be summarized:

- Cases of potential drug induced liver injury that includes an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 × Upper Limit of Normal [ULN]) in combination with either an elevated total bilirubin > 2 × ULN or clinical jaundice as defined by Hy's law.
- Suspected transmission of an infectious agent by the study drug

  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.

In addition, the following AEs of special interest as defined in protocol version 1.0 will be summarized:

- Skin or subcutaneous reaction, pharyngeal/laryngeal or mucosal reaction (Grade 2, CTCAE V4.03).

- Clinically relevant retinal abnormalities on OCT/FAF/fundus photography confirmed by an Ophthalmologist

For summaries of AE incidences, patients who experienced the same event on more than one occasion will be counted once in the calculation of the event frequency at the highest intensity reported. The total number of AEs (events) and the total number of patients with at least one observed AE will be presented in each summary table.

An overview summary of AEs and serious adverse events (SAEs), AEs by SOC and PT, AE by greatest intensity/severity according to National Cancer Institute-Common Terminology Criteria for Adverse Event (NCI-CTCAE) grade, AEs related to study drug, AEs leading to any study medication adjustment (dose increased, dose reduced, drug interrupted), AEs leading to withdrawal of study treatment/drug and AEs resulting in death will be summarized. The AEs resulting in death will also be summarized by cause of death (AE as primary cause of death vs progressive disease specified as primary cause of death).

The most common AEs reported in $\geq 5\%$ of patients in the nusinersen and olesoxime previous treatment groups and in $\geq 10\%$ of patients in the RO6885247 and AVXS-101 previous treatment groups will be summarized by PT. For AEs, the outcomes of 1) Fatal, 2) Not recovered/not resolved, 3) recovered/resolved, including those recovered/resolved with sequelae and recovering/resolving, 4) unknown; will also be summarized by PT. For this outcome table, the number of events, not the number of patients will be reported.

The AE and SAE rate overall, by SOC, and by SOC and preferred term adjusted for patient years for all occurrences will be summarized for the whole treatment period as well as by 6-month intervals. The AE/SAE rate per 100 patient–years, which is also the average number of events per 100 patient-years is calculated by

- AE/SAE rate $=$ (number of AEs/SAEs observed $\div$ total patient years at risk) $\times 100$.

where the total patient–years at risk is defined as

– Total patient-years at risk $=$ the sum of all patients across the time interval in years between the start of study medication and up to study withdrawal/completion or the clinical data cutoff date.

The 95% confidence interval of the AE/SAE rate (average number of events) per 100 patient-years will also be presented and will be calculated based on the exact method of a Poisson distribution for the AE rate.

All AEs above will be summarized for the first 12 and 24 month treatment periods, as well as for the whole treatment period. An overview summary of AEs and SAEs for the second 12-month treatment period (12 to ≤24 months) will be provided at the Month 24 reporting event. The AE/SAE results will be presented by 6 month periods (e.g.,

0 to ≤ 6 months (Day 0 to 183), > 6 to ≤ 12 months (Day 184 to 365), > 12 to ≤ 18 months (Day 366-548) and for the whole corresponding treatment period up to the clinical cutoff date. The AE/SAE results for the 0 to ≤ 12 months period and the > 12 to ≤ 24 months period will also be presented.

- **First 12-month treatment period** (0 to ≤ 12 months). This will include the AEs with
  - Onset date on or after the first day of administration of study drug
  - Onset date prior to the first dose day of study drug, is unresolved, and the most extreme intensity is worse than the initial intensity;

  and up to the earliest date of study withdrawal during the first 12 months of treatment period or before dose administration on the final day of their Week 52 visit for each individual.

- **First 24-month treatment period** (0 to ≤24 months). This will include the AEs with
  - Onset date on or after the first day of administration of study drug
  - Onset date prior to the first dose day of study drug, is unresolved, and the most extreme intensity is worse than the initial intensity;

  and up to the earliest date of study withdrawal during the first 24 months of treatment period or before dose administration on the final day of their Week 104 visit for each individual.
- **Second 12-month treatment period** (12 to ≤24 months). This will include the AEs with
  - Onset date after dose administration on the last day of their Week 52 visit
  - Onset date prior to dose administration on the last day of their week 52 visit, is unresolved, and the most extreme intensity is worse than the initial intensity;

  and up to the earliest date of study withdrawal during the second 12 months of treatment period or before dose administration on the final day of their week 104 visit for each individual.

- **Whole treatment period** This will include AEs with
  - Onset date on or after first dose day of study medication
  - Onset date before the first risdiplam dose, is unresolved and the most extreme intensity is greater than the initial intensity;
  - AEs reported during the follow up period will be included in the whole treatment period

All listings will be based on the whole treatment period.

Individual patient listings will also be presented for AEs, SAEs, AEs/SAEs leading to withdrawal of study treatment, AEs leading to dose modification or interruption, AEs

related to study medication, AEs by intensity, AEs resulting in death and AEs of special interest, by previous treatment for each patient.

All AEs results recorded during the follow-up periods defined in protocol versions 3.0 and 4.0 will be listed by previous treatment for each patient.

In addition, non-treatment emergent AEs, including the SAEs caused by a protocol-mandated intervention (e.g., SAEs related to invasive procedures such as biopsies), for which the onset date is before the date of the start of study medication (after informed consent has been obtained but prior to initiation of study drug), will be listed.

The following rules will be applied for AEs with missing onset and/or end dates:

- Events that are missing both onset and end dates will be considered treatment emergent, given that a patient had at least one dose of study drug.
- If the onset date is missing and the end date is on or after the first dosing date, then the event will be considered treatment emergent.
- If the end date is missing and the onset date is on or after the first dosing date, then the event will be considered treatment emergent.
- If the end date is missing and the extreme intensity is worse than the initial intensity, and the onset date is prior to the first dosing date, then the event will be considered treatment emergent.
- The duration will be set to missing.

All available data up to the clinical cut-off date will be presented at the time of each reporting event. All AE records with a start date on or before the clinical cutoff date will be included in the data cut.

4.6.3 Deaths

Individual patient listings will be presented with all the details for patients who died at any time during the study and up to 52 weeks after study withdrawal/completion if collected under protocol version 3.0, or 30 days after study withdrawal/completion if collected under protocol version 4.0. If progressive disease is specified as the primary cause of death, the associated AE (recorded as ‘fatal’ in the AE page) will also be reported.

4.6.4 Clinical Laboratory Data

All clinical laboratory data for patients 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.

The normal ranges of all laboratory parameters are based on central laboratory ranges for patients' aged > 2 years and based on local laboratory ranges for patients aged 6 month to < 2 years at screening. The normal ranges of each of the laboratory parameters are based on gender and age of patients at the time of assessment.

Laboratory data will be listed for patients with laboratory abnormalities or values outside the normal ranges and will be flagged "H" for high and "L" for low.

The number and percentage of patients with abnormal results (in the direction of abnormality) will also be summarized for each laboratory parameter by previous treatment and overall at each time–point.

The actual values and change from baseline values for parameters of hematology, chemistry and coagulation will be summarized by previous treatment at each time-point.

In addition, shift tables to compare the status at baseline to each time-point, post–baseline (each scheduled assessment visit) abnormalities will be summarized by previous treatment and overall for all patients.

Patients with elevated post-baseline AST or ALT levels results at baseline and at post-baseline time-points (each scheduled assessment visit) will be summarized by previous treatment and overall for all patients.

Urinalysis laboratory test results at each time-point will be summarized by previous treatment and overall for all patients. A listing of abnormal urinalysis laboratory tests will be provided.

Data collected during safety follow-up under protocol version 3.0 will be summarized similarly.

4.6.5 Vital Signs

Vital signs measured throughout the study will include systolic and diastolic blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]), pulse rate (per minute), respiratory rate (per minute) and body temperature. The normal ranges for each vital sign parameter are based on the age of patient at the time of assessment. The vital signs data will be listed for patients with abnormal values or values outside the normal ranges by previous treatment and overall for all patients.

The number and percentage of patients with abnormal values (in the direction of abnormality) will also be summarized for each vital sign parameter at each time point by previous treatment and overall for all patients for the whole treatment period.

In addition, shift tables to compare the status at baseline to each time–point post-baseline (each scheduled assessment visit) will also be summarized by previous treatment and overall for all patients.

A listing of abnormal vital signs results will be provided.

Data collected during safety follow–up under protocol version 3.0 will be summarized similarly.

The normal ranges by age groups are given as follows (Table 2).

Table 2 Normal Ranges of Vital Signs Parameters by Age Group

	Age (months)		Age (years)			
	>6–≤12	**>12–≤24**	**>2–≤6**	**>6-≤8**	**>8–≤12**	**>12**
Vital signs parameters						
Diastolic Blood Pressure (mmHg)	55–65	55–70	60–80			40–90
Systolic Blood Pressure (mmHg)	80–100	90–105	90–125			90–140
Pulse Rate (beats/min)	80–120	70–110	70–130	60–110	55–100	50–100
Respiratory Rate (breaths/min)	25–40	20–30	18–30			12–20
Temperature (°C)	36.4–38		35.5–37.8			36.5–37.5

4.6.6 Electrocardiogram Data Analysis

The 12-lead ECG recordings are obtained in triplicate pre–dose at each scheduled assessment time-point. If the ECG assessment is performed at a scheduled assessment time-point and the results are not interpretable and recorded as 'NA', these results will not be included in the ECG analysis.

The ECG measured throughout this study includes the heart rate (HR) in beats per minute, the PR (or PQ) duration in ms, QRS duration in ms, QT duration in ms, QTcB (the QT duration corrected by Bazett's formula) in ms, QTcF (QT duration corrected by Fridericia's formula) in ms and the RR duration in ms.

4.6.6.1 ECG Data Analysis

The normal ranges for ECG parameters are based on the age of the patient at the time of assessment. The ECG data will be listed for patients with abnormalities/values outside the normal ranges or with a comment. The number and percentage of patients with abnormality results (in the direction of abnormality) will also be summarized for each ECG parameter by previous treatment and overall for all patients.

The overall ECG assessment interpretation results (Abnormal/Normal/Not done) at each time-point will be summarized separately for the investigator interpreted results and the reading center interpreted results. All overall ECG assessment interpretation results by the investigator and reading center with comments will also be listed.

Triplicate and average ECG results will be listed by previous treatment for all patients, where the average ECG result is defined as the average of any non-missing and non-zero triplicate measurements.

Shift tables for each of the ECGs parameters, PR duration, QT duration, QRS duration, RR duration, QTcB, QTcF, T wave, U wave and interpretation (ECG result) to compare the status at baseline to each time–point post baseline will be summarized by previous treatment and overall for all patients.

The actual numerical values and the change from baseline values for each of the ECG parameters will be summarized at each time point by previous treatment and overall for all patients.

Data collected during safety follow-up under protocol version 3.0 will be summarized similarly.

The following table (Table 3) shows the normal ranges on the actual values of each ECG variable by age groups.

Table 3 Normal Ranges of ECG Parameters by Age Group

	Age (Months)		**Age (years)**			
	>6–≤12	**>12–≤24**	**2–≤6**	**6–≤8**	**8–≤12**	**>12**
ECG Parameters						
Heart Rate (beats/min)	80–120	70–110	70–130	60–110	55–100	50–100
PR duration (ms)	80–120		80–160			120–200
QT Duration (ms)	230–420		260–390			200–500
QRS Duration (ms)	50–90		40–90			80–120

Table 3 Normal Ranges of ECG Parameters by Age Group (cont.)

RR Duration (ms)	500–750	450–860	460–860	450–1000	600–1090	600–1500
QTcF (ms)	370–450		380–450			300–450
QTcB (ms)	370–450		380–450			300–450

ECG = electrocardiogram.

The number and percentage of patients with ECG parameter values in the ranges given in Table 4 will be summarized.

Table 4 Ranges of ECG Parameters for Summary Tables

	Raw Value	Change from Baseline Value
ECG Parameters		
PR duration (ms) ≥ 6 months – ≤ 24 months old > 2 years – ≤ 12 years old > 12 years old	 ≤ 120 > 120 ≤ 160 > 160 ≤ 200 > 200	
QRS Duration (ms) ≤ 12 years old > 12 years old	 ≤ 90 > 90 ≤ 120 > 120	
QTcF (ms)	≤ 450 > 450 – ≤ 480 > 480 – ≤ 500 > 500	≤ 30 > 30 – ≤ 60 > 60
QTcB (ms)	≤ 450 > 450 – ≤ 480 > 480 – ≤ 500 > 500	≤ 30 > 30 – ≤ 60 > 60

ECG = electrocardiogram.

4.6.6.2 Time Matched QT Analysis

A time-matched QT profile assessment will be performed in patients aged 12 years or above at the 2-year reporting event. The main conclusion of the analysis will be stated in the ECG section of the clinical study report. The full analysis and results will be detailed in a separate report and attached as an appendix to the clinical study report. All available data for ECG and PK measurements will be included. Time points where both the ECG and PK assessment results are available will be taken into account for the analysis. The analysis period is the Open-label first 24 months risdiplam treatment period (0 to ≤ 24 months).

The QTcF values from the ECG assessments will be used for this analysis. Triplicate 12-lead ECGs were performed and the mean of the 3 values will be taken for the evaluation. For this time-matched analysis, the baselines will be taken as the mean QTcF values at Day_{-1} (i.e. prior to any risdiplam administration) at the approximate time-points matching the pre-dose, 1 hour (1h), 2 hours (2h), 4 hours (4h) and 6 hours (6h) time-points of assessment and there are at most 5 baseline values for each patient. The time-matched (hours of assessment) change from baseline values will be derived as the change from baseline in the mean QTcF values at each hour of assessment. The endpoint of this analysis is defined as the time-matched change from baseline in the mean QTcF values ($\Delta_{TM}QTcF$) across all hours.

All available time-matched change from baseline mean QTcF versus concentration values for each hour of assessment will be displayed in a scatter plot.

For the analysis of the change from baseline of QTcF ($\Delta_{TM}QTcF$), the following statistical model will be applied:

$$Y'_{itk} = (\alpha' + \alpha'_{it}) + (\beta' + \beta'_{it}) \cdot conc'_{itk} + \lambda'_t + \gamma' \cdot age'_i + (\lambda\beta')_t \cdot c'_{itk} + \beta'\gamma' \cdot age'_i \times conc'_{itk} + \delta'_l + \epsilon'_{ijk} \quad (2)$$

In this model,

- Y'_{itk} is the time-matched change from baseline in QTcF ($\Delta_{TM}QTcF$) for subject i at time t (time refers to the categorical hours of assessment as defined below) with repetition k.
- α' is an overall mean effect.
- α'_{it} are subject specific random intercepts (with mean zero and constant variance).
- β' is an overall slope.
- β'_{it} are subject specific random slopes (with mean zero and constant variance).
- $conc'_{itk}$ are the concentrations observed in subject i at time (hours of assessment) t with repetition k
- λ'_t is the effect of the categorical variable '$Time$' for the hours of assessment at Pre-dose, 1h, 2h, 4h or 6h.

- γ' is the coefficient for age.
- age'_i: Age at screening (in months).
- $(\lambda'\beta')_t$ is the coefficient for the interaction '$Time \times conc$'.
- $(\beta'\gamma')$ is the coefficient for the interaction '$age \times conc$'.
- δ'_l is the effect of the two-level categorical variable 'SEX'.
- ϵ'_{itk} are random error terms.

The above model allows the estimation of the time-matched change in QTcF value for a given concentration. The random error terms ϵ'_{itk} uses the same variance regardless of the time (hour of assessment): $\epsilon_{itk} \sim \mathcal{N}(0, \sigma^2)$. The random intercept α'_{it} will be assumed to be normally distributed with variance $\sigma^2_{\alpha'}$ and the random slopes β'_{it} with variance $\sigma^2_{\beta'}$.

The residuals (with respect to the fixed-effects estimates and to both the fixed and random-effects residuals) will be plotted against the predicted values

The fitted regression line and two-sided 90% confidence interval for the QTcF change from baseline by concentration will be plotted with different symbols for time.

If the upper limit of the two-sided 90%-CI of $\Delta_{TM}QTcF$ does not exceed 10ms, there will be no evidence for a prolongation in QTcF the time-matched analysis.

4.6.7 Suicidality Assessment

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) as well as any new instances of suicidality (C–SSRS since last visit). The interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality. A modified and reduced version (pediatric version) is used for children (aged 6–11 years). The C–SSRS assessments results are collected at baseline and at time-point specified as per the Schedule of Assessments in patients aged 6 years and older.

For patients aged 5 years or below at baseline, the C–SSRS assessment will only be performed at post-baseline time–point once they reach 6 years old. No baseline C–SSRS assessment results will be available for these patients. Missing data will not be imputed.

All C–SSRS data will be summarized by previous study participation and overall for patients.

The number and percentage of patients with the following results will be summarized for all patients with at least 1 post–baseline measurement regardless of whether they have a baseline measurement or not:

- Suicidal Ideation categorized by items 1 to 5
- Suicidal Behavior categorized by items 6 to 10
- Suicidal Ideation or Behavior categorized by items 1 to 10
- Self-Injurious Behavior without Suicidal Intent during treatment

Results will be summarized for the whole treatment period by previous treatment and overall.

The number and percentage of patients with at least one post-baseline assessment will also be presented in each summary table.

For those patients aged 5 years or below at baseline who reach 6 years of age at any time during the study, all available post-baseline C–SSRS assessment results will be listed by previous treatment.

Shift tables to demonstrate the change in C–SSRS endpoints (suicidal ideation and suicidal behavior, and self-injurious behaviors without suicidal intent) from baseline will be presented for all patients with a baseline measurement and at least one post-baseline measurement. Shift tables will be presented to compare the status at baseline to each time-point for all patients and previous treatment.

Results for those patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent will be listed at each time-point by previous treatment. For patients with suicidal ideation, the score of the intensity and the frequency will also be included in the listing. For patients with suicidal behavior, the number of attempts and information about lethality/medical damage for actual attempts will also be included in the listing.

Data from the follow–up period under protocol version 3.0 will be listed for any suicidal behavior, suicidal ideation or self-injurious behavior.

4.6.8 Ophthalmological Assessments

All ophthalmology assessment results will be classified into one of the three main categories, which include 1) ophthalmological examination, 2) imaging and 3) visual function.

Ophthalmological examination includes assessments of slit lamp examination, fundus examination, visual testing (including the Bruckner red reflex, corneal reflex, cover/uncover examination) and the intraocular pressure assessment.

Imaging includes assessments of the optical spectral domain optical coherence tomography (SD−OCT) assessment, the fundus photography assessment and the fundus auto fluorescence (FAF) assessment.

Visual Function includes assessments of the best corrected visual acuity (BCVA) test, the fix and follow test, visual acuity as appropriate for age (patients aged 2−10 years), the Sloan Low Contrast Test (adults and children aged 10 years and older), visual field threshold perimetry assessment (adults and children aged 10 years and older) and the simple visual field test (children aged 2 to 10 years).

Overview profile of the ophthalmology assessments results will be summarized (overview summary tables). Only results post-baseline (post original baseline) will be counted and summarized in the overview summary tables. Results will be summarized for each ophthalmology assessment and overall for all ophthalmology assessments. The number and percentage of patients with at least one abnormal or potential clinically significant result, and the total number of abnormal or potentially clinically significant results will be summarized. These results will be summarized by previous treatment and overall. In these overview summary tables, abnormal or potentially clinically significant results will be counted for each eye. For the same eye, if both abnormal and potentially clinically significant results are observed at the same assessment time-point, this will only be counted once.

Overview profile of the ophthalmology assessment results in last assessment visit will also be summarized (overview summary table in the last assessment visit). For each ophthalmology assessment and for each patient, the last assessment visit refers to the last visit/time-point up to the earliest of either 1) the end date of a period or 2) the clinical cutoff date or 3) date of study withdrawal with available assessment results. The results in the overview summary table in the last assessment visit will be summarized for each of the ophthalmology assessment and overall for all ophthalmology assessments. Abnormal or potentially clinically significant results will be counted for each eye. For the same eye, if both abnormal and potentially clinically significant results are observed at the last assessment visit, this will only be counted once. The number and percentage of patients with at least one abnormal or potential clinically significant result at the last assessment visit and the total number of abnormal or potentially clinically significant results at the last assessment will be summarized. Results will be summarized by previous treatment and overall.

The number and percentage of patients with at least one post-baseline visit will also be summarized in both the overview summary tables and the overview table in the last assessment visit for each ophthalmology assessment and overall for all ophthalmology assessments.

In addition, the ophthalmology assessment results will also be summarized by each time−point/visit (summary tables by visit). The number and percentage of patients with

at least one abnormal or potentially clinically significant result and the total number of abnormal or potentially clinically significant results will be summarized at each time–point for each ophthalmology assessment (except SD–OCT) and overall for all ophthalmology assessments. These results will be summarized by previous treatment and overall. The number of patients who completed the assessment at each visit will also be presented in the table.

A separate summary table by visit will also be presented for SD-OCT. Ophthalmological visits are performed every 13 weeks up to week 52, and then at week 78, week 104, and every 26 weeks after the Week 104 visit until the completion of the extension phase and at completion/early withdrawal visit and always comprised SD–OCT assessments. The number and percentage of patients with at least one abnormal or potentially significant SD–OCT results and the total number of abnormal or potentially clinically significant SD–OCT results will be summarized at each time-point by previous treatment and overall. The number of patients who reached a visit, the number and percentage of patients who completed the SD-OCT at each visit, and the number and percentage of patients who missed the SD–OCT assessment at each visit will also be summarized.

In addition, another summary table by visit will also be presented by only summarizing the numerical values obtained from each of the parameter under each of the ophthalmology assessments (numerical summary table by visit). The actual values and the change from baseline values will be summarized under each ophthalmology assessment for each parameter for each eye at each time–point by previous treatment and overall.

Data collected in any of the ophthalmological assessments during safety follow–up under protocol version 3.0 (Appendix 8) will be summarized similarly by previous treatment and overall.

Listings will be presented for all patients with an abnormal or potentially clinically significant result in any ophthalmological assessment. Listings of all ophthalmological assessments will be presented for all patients.

Details on the criteria for the potentially clinically significant results and abnormal results for each ophthalmology test are described in subsequent section.

4.6.8.1 Ophthalmological Examination

4.6.8.1.1 Ocular Examination (Slit-Lamp)

The slit-lamp examination will be performed for patients aged 2 years and older. An abnormal or potentially clinically significant result in slit lamp is defined as

- A clinically significant change (worse) from baseline (as assessed by the local ophthalmologist) result; or
- An abnormal result

For patients with a result meeting at least one of these criteria above, all results including the parameter, actual result for each parameter, any description and comments related to any of the above criteria will also be listed by previous treatment.

4.6.8.1.2 Fundus Examination

The fundus examination assessment will be performed for patients aged 2 years and older. An abnormal or potentially significant result in the fundus examination is defined as:

- A clinically significant change (worse) from baseline (as assessed by local ophthalmologist) result; or
- An abnormal result; or
- A retinal break; or
- A retinal detachment

For patients with a result meeting at least one these criteria above, all results including the parameter, actual result for each parameter, any description and comments related to any of the above criteria will be listed by previous treatment.

4.6.8.1.3 Ocular Examination (Visual Testing)

This assessment will be performed for patients aged 2–10 years and includes Bruckner test, corneal reflex, cover uncover test. Visual testing in patients aged 2–10 years includes the Bruckner red reflex, corneal reflex, cover/uncover examination, visual acuity as appropriate for age; the ophthalmological examination in infants aged 6 months to 2 years includes visual development, red reflex, external ocular examination, pupillary response, and ocular examination under magnification.

An abnormal or potentially clinically significant result in the visual testing assessment is defined as:

- A clinically significant change (worse) from baseline (as assessed by the local ophthalmologist) result; or,
- An abnormal result.

For patients with a result meeting at least one of these criteria above, all results including the parameter, actual result for each parameter, any description and comments related to any of the above criteria will be listed by previous treatment.

4.6.8.1.4 Intraocular Pressure Assessment

The intraocular pressure assessment will be performed in patients aged 2 years and older. The frequency of assessments was reduced to be performed at screening and at week 52, thereafter it will not be performed. For assessment methods other than “digital palpation”, the assessment results will be reported in continuous values in units of mmHg. For “digital palpation”, the assessment results will be either “normal”, “abnormal

high", and "abnormal low". The "abnormal high" and "abnormal low" results will be classified as "abnormal" results.

An abnormal or potentially clinically significant result in the intraocular pressure assessment is defined as:

- For method of "digital palpation", a clinical significant change (worse) from baseline (as assessed by the local ophthalmologist) result; or,
- For method of "digital palpation", an abnormal result; or,
- For methods other than "digital palpation", a post-baseline result with intraocular pressure of less than ($<$) 10 mmHg or greater than ($>$) 25 mmHg; or,
- For methods other than "digital palpation", the intraocular pressure with an increase of more than or equal to 5 mmHg compared to baseline or with a decrease of more than or equal to 5 mmHg compared to baseline (i.e., a change from (original) baseline value of $\geq +5$ or ≤ -5 mmHg).

For patients with a result meeting at least one of these criteria above, all results including the method used and any description and comments related to any of the above criteria will be listed by previous treatment; for the method of "digital palpation", the parameter, and actual result for each parameter will be listed by previous treatment, for methods other than "digital palpation", the actual numerical results and the baseline value and the change from baseline values will be listed by previous treatment.

4.6.8.2 Imaging

This will include the optical spectral domain-optical coherence tomography (SD−OCT) assessment, the fundus photography assessment and the fundus auto−fluorescence (FAF) assessment.

4.6.8.2.1 Spectral Domain−Optical Coherence Tomography (SD−OCT)

The SD−OCT will be performed for all patients. An abnormal or potentially clinically significant result in the SD-OCT assessment is defined as:

- A clinically significant change from baseline (as assessed by Annesley Eye Brain Center (AEBC) results; or,
- An abnormal macular OCT assessment; or,
- Any available result other than "Not Applicable" in the macular OCT diagnosis.

For patients with a result meeting at least one of these criteria above, all results including the parameter, actual result for each parameter, any description and comments related to any of the above criteria will be listed by previous treatment.

4.6.8.2.2 Fundus Photography

The fundus photography (FP), color fundus photography or the fundoscopy will be performed for all patients. Following protocol version 4, this assessment is no longer

performed after the week 52 visit. An abnormal or potentially clinically significant result in the fundus photography is defined as:

- A clinically significant change from baseline (as assessed by AEBC) result; or,
- An abnormal photo assessment result; or,
- Any available result other than “Not Applicable” in the photo diagnosis; or,
- A result with pigment observed (A “Yes” result in the “Pigment observed” question).

For patients with a result meeting at least one of these criteria above, all results including the parameter, actual result for each parameter, any description and comments related to any of the above criteria will be listed by previous treatment.

4.6.8.2.3 Fundus Auto Fluorescence

The fundus auto fluorescence (FAF) examination was removed in protocol version 2.0. All available results will be included in the analysis.

An abnormal or potentially clinically significant result in the fundus photography is defined as:

- A clinically significant change from baseline (as assessed by AEBC) result; or,
- An abnormal FAF macula assessment: or,
- A “Yes” result in the “Hypo-fluorescence present” question; or,
- A “Yes” result in the “Hyper-fluorescence present” question.

For patients with a result meeting at least one of these criteria above, all results including the parameter, actual result for each parameter, any description and comments related to any of the above criteria will be listed by previous treatment.

4.6.8.3 Visual Function

This will include the best corrected visual acuity (BCVA) test (patients aged >10 years), the fix and follow test (visual acuity test as appropriate for age (patients aged 6 months to 10 years), the Sloan low contrast test (adults and children 10 years and older), visual field threshold perimetry assessment (adults and children aged 10 years and older) and the simple visual field test (children aged 2 to 10 years).

4.6.8.3.1 Best Corrected Visual Acuity and Fix and Follow Tests

The BCVA test will be performed for patients aged >10 years. For those aged ≤ 10 years or unable to read letters or recognize shapes, the ‘fix and follow’ test may be performed instead of the BCVA. For the BCVA, an abnormal or potentially clinically significant result is defined as:

- For methods of “Early Treatment Diabetic Retinopathy Study (ETDRS)” or “Patti Pics”, a decrease of more than or equal to 9 optotypes (i.e., letters or symbols) that could be read compared baseline. (i.e., change from baseline in the number of optotypes that could be read of ≤ -9); or

- For methods of “ETDRS” or “Patti Pics”, an increase of more than or equal to 0.18 in the EDTRS log score (i.e., a change from baseline in the EDTRS log score of ≥ 0.18)
- For off-chart visual acuity: a clinically significant change from baseline result

For the fix and follow test, an abnormal or potentially clinically significant result is defined as:

- a clinically significant change (worse) form baseline (as assessed by the local ophthalmologist); or,
- an abnormal result.

For patients with a result meeting at least one of these criteria above, all results including the method used (EDTRS, Patti Pics, Off chart), the parameter, the actual result of each parameter; for EDTRS and Patti Pics the total number optotypes correctly read, the change from baseline in the number of optotypes that are correctly read, the actual log score and the change from baseline in the log score; any off chart visual acuity result (count fingers, hand motion, light perception, no light perception), any description or comments related to any of the above criteria will be listed by previous treatment.

4.6.8.3.2 Sloan Low Contrast Test

The Sloan low contrast test was removed in protocol version 2.0. All available Sloan low contrast test results will be included in the analysis.

An abnormal or potentially clinically significant result for the Sloan low contrast test is defined as:

- A decrease of more than or equal to 7 in the total number of letters that could be read correctly compared to baseline (i.e., a change from baseline of ≤ -7 in the total number of letters that could be correctly read)
- An increase of more than or equal to 0.14 in the log CS compared to baseline (i.e., a change from baseline in the log CS of ≥ 0.14)

For patients with a result meeting at least one of these criteria above, all results including the parameter, the actual result of each parameter, the total number of letters correctly read, the change from baseline in the number of letters that are correctly read, the log CS score and the change from baseline log CS score, any description or comments related to any of the above criteria will be listed by previous treatment.

4.6.8.3.3 Visual Field Threshold Perimetry

The visual field threshold perimetry assessment will be performed in all adults, adolescents and cooperative children ≥ 10 years. An abnormal or potentially significant result for the visual field threshold perimetry test is defined as:

- A clinically significant change from baseline (as assessed by AEBC) result; or,

- A result other than “Normal”, “Unreliable”, “Not Applicable”, or “Not performed” in the visual field pattern assessment; or,
- A result of “worse” or “worse compared to unscheduled baseline” for the visual field comparison.

For patients with a result meeting at least one of these criteria above, all results including the parameter, actual result for each parameter, any description and comments related to any of the above criteria will be listed by previous treatment.

4.6.8.3.4 Simple Visual Field Test

This assessment will be performed for all patients aged 2−10 years, or in other patients who cannot perform visual field threshold perimetry assessment. An abnormal or potentially clinically significant result for the simple visual field test is defined as:

- A clinically significant change (worse) from baseline (as assessed by the local ophthalmologist); or,
- An abnormal result.

For patients with a result meeting at least one of these criteria above, all results including the parameter, actual result for each parameter, any description and comments related to any of the above criteria will be listed by previous treatment.

4.6.9 Tanner Staging (patient aged 9 to 17 years)

Tanner staging will be determined at baseline, Month 12 and subsequent yearly visits in all patients aged 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. The Tanner staging results at baseline will be summarized separately by gender. The number and percentage of patients, median ages and the age ranges of patients within each Tanner stage at baseline will be presented by previous treatment and overall for all applicable patients.

In addition, results of delayed puberty will also be summarized by previous study participation. Delayed puberty is defined as follows:

- Girls: age at assessment ≥ 13 years old with a Tanner stage of < 2
- Boys: age at assessment ≥ 14 years old with a Tanner stage of < 2

The number and percentage of patients with delayed puberty will be presented at each time−point by previous treatment and overall for all patients.

A shift table to compare the puberty status (normal, delayed, and missing) at baseline to Month 12 and Month 24 will also be summarized by previous treatment and for overall all patients.

A listing of Tanner staging assessments will be provided.

4.6.10 Anthropometric Examination

For all patients, actual value and change from baseline values for body weight, height, ulna length (if available), and BMI will be summarized at each post-baseline time-point by previous treatment and overall for all patients. For patients aged up to 5 years old (at screening), the actual value and the change from baseline of head and chest circumference values at each time-point will also be summarized by previous treatment and overall for all patients.

The following formulas are used to derive the height of the patient with their ulna length measured:

a) In patients aged 2–18 years, formulas of Gauld et al. (2004)
   - Males: Height (cm) = 4.605 × ulna length (cm) + 1.308 × age (years) + 28.003
   - Females: Height (cm) = 4.459 × ulna length (cm) + 1.315 × age (years) + 31.485

b) In patients aged 19–25 year old, MUST formulas (Madden et al. 2012; Elia 2003)
   - Males: Height (cm) = 79.2 + [3.60 × ulna length (cm)]
   - Females: Height (cm) = 95.6 + [2.77 × ulna length (cm)]

In addition, shift tables for BMI category (<18.5, 18.5-24.9, 25.0-29.9 and ≥30) to compare the status at baseline to each time–point post–baseline will be summarized by previous treatment for patients aged 20 years or above.

Percentile of Anthropometric Examination

The WHO child growth standards (2010) will be used to summarize the percentile and the change from baseline percentile for patients aged 2 up to 5 years old inclusively for the following parameters.

- weight–for–age,
- length/height–for–age,
- weight–for length/height,
- head circumference–for–age
- BMI–for–age

In addition, the WHO growth reference data (2017) will also be used to summarize the percentile and the change from baseline percentile for:

- the length/height–for–age and BMI–for-age for patients aged above 5 to 19 years old
- the weight–for–age in patients aged above 5 up to 10 years old.

Given the above mentioned age limitations for growth reference charts, the following will be presented:

- the percentile for weight–for–age will only be presented up to 10 years old
- the percentile for length/height–for–age and BMI–for–age will only be presented up to 19 years old
- The percentile for weight–for length/height and head circumference–for–age, will also be summarized for patients aged 5 or below.

The percentile and the change from baseline percentile will be summarized at each time–point by previous treatment and overall for all patients.

The number and percentage of patients for weight-for-age, and length/height-for-age, head circumference-for-age and BMI-for-age will be summarized within each category of percentile ($<$3rd, $\geq$3rd to $<$5th, $\geq$5th to $<$10th, $\geq$10th to $<$25th, $\geq$25th to $<$50th, and $\geq$50th) by previous treatment and overall for all patients.

Shift tables for each parameter (weight–for-age, length/height–for–age, head circumference–for–age and BMI–for–age) to compare the percentile at baseline ($<$3rd, $\geq$3rd to $<$5th, $\geq$5th to $<$10th, $\geq$10th to $<$25th, $\geq$25th to $<$50th, and $\geq$50th) to each time-point post-baseline will be summarized by previous treatment and overall for all patients.

The WHO growth reference data (2017) only extends up to the 19th birthday. For those aged between 19 and 20 years, an age of exactly 19 years will be assumed in order to compute a BMI-for-age and length/height-for-age percentile. Full or imputed dates of birth are used to calculate the patient's age in days at the assessment.

Age at assessment (days) = Date of assessment – Full or imputed Date of Birth

Patients with ages at assessment of 6941-7305 days use the WHO derivation for an age of 6940 days. In the case where a patient's calculated age at baseline assessment is greater than 7305 days (based on an imputed date of birth), but where the recorded age is 19 years, the WHO derivation for an age of 6940 days is used.

4.6.11 Neurological Examination

Examination will be performed by asking questions to the patient and 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 include the following: examination of social interaction (school, friends, activities, job as appropriate), memory (e.g., with short word recall), reasoning and language, drawing, etc.

Number and percentage of patients with neurological examination will be summarized by each time-point and previous treatment and overall for all patients.

Individual patient listings will be provided which contain all results for patients who have 'Neurological conditions besides those expected with SMA' by previous treatment.

4.7 MISSING DATA

No imputation will be applied for missing data for any of the safety variables. For partial dates imputation will be done for safety data and documented in the programming rules.

Missing birthday will be imputed as follows:

- If the year is available the day and month will be imputed as 15th June.
- If the months and the year are available the day will be imputed with the 15th

The handling of missing data for the efficacy variables (MFM32, RULM, HFSME, 6MWT, SMAIS, HINE-2, BSID-III and pulmonary testing) is described in corresponding sections within this SAP.

4.8 INTERIM ANALYSIS

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

An interim analysis of all available safety and potentially efficacy data will be performed to support the initial filing and registration of risdiplam. The interim analysis will be performed by the Sponsor.

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

4.9 ANALYSIS RELATED TO COVID-19 PANDEMIC

On 11 March 2020, the World Health Organization (WHO) characterized the outbreak of Coronavirus Disease 2019 (COVID-19), caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a pandemic. The COVID-19 pandemic has had an impact on the conduct of clinical studies of medical products, on study patients, and on the collection and analysis of clinical study data. It is difficult to determine the start of the COVID-19 outbreak and the Sponsor decided to use 1 December 2019 based on early cases reported in Mainland China. Therefore, the window for all analyses of COVID-19 associated events for each reporting event would start from 1 December 2019 until the clinical cutoff date for each of the corresponding reporting events.

JEWELFISH had the first patient enrolled in March 2017 and the last patient enrolled in January 2020. When the pandemic disruption occurred, the study was 83.9% enrolled. The following COVID-19 related analyses will be performed for reporting events.

4.9.1 Disposition

The number and percentage of patients who discontinued early due to COVID-19 will be summarized in the same disposition tables as stated in Section 4.2.3 for the open-label

treatment period, extension phase and follow-up. The reasons for early discontinuation due to COVID-19 during each of the periods will also be summarized and listed in the same outputs as stated in Section 4.2.3.

4.9.2 Protocol Deviations

The number and percentage of patients with at least one COVID-19 related protocol deviation and the number of COVID-19 related protocol deviations will be summarized for all patients. The reason for major protocol deviations related to the COVID-19 pandemic will also be summarized for all patients. The COVID-19-related major protocol deviations with descriptions and reasons for each corresponding protocol deviation will also be listed.

4.9.3 Safety Analysis

New safety analysis concepts were created to identify COVID-19 related AEs:

- Confirmed or suspected COVID-19: The narrow MedDRA COVID-19 SMQ to identify events related to the SARS-CoV-2 virus.
- COVID-19 Associated Events: This search strategy includes all of the confirmed/suspected AEs from the narrow MedDRA COVID-19 SMQ above. In addition, in patients with confirmed COVID-19 AEs by narrow MedDRA SMQ, any additional AEs that occurred within ≤7 days before and ≤30 days after the start date of the confirmed COVID-19 infection or positive PCR test (using “Roche Standard AEGT – COVID-19 Preferred Terms for Confirmed Cases”) are included.
- Potential Long COVID-19 Symptoms: all AEs with a duration >30 days occurring after a confirmed COVID-19 infection or positive PCR test, including AEs reported ≤7 days before the onset of a confirmed COVID-19 infection or positive PCR and AEs reported until the end of study participation. Unresolved AEs are assumed to have a duration >30 days.

All analyses will use the most current version of any SMQ.

A summary table of adverse events associated with COVID-19 will be presented. The table will include confirmed/suspected COVID-19 AEs as reported in the narrow COVID-19 SMQ plus COVID associated AEs which meet the criteria for the Roche Standard AEGT COVID-19 preferred terms for confirmed cases.

Patients with confirmed or suspected COVID-19-infection AEs based on narrow search strategy will be listed. In addition, the COVID-19-associated AEs based on broad search strategy, which includes all the confirmed and suspected COVID-19 cases and all additional AEs occurring from 7 days prior to and up to 30 days after the onset data for the confirmed COVID-19 cases will also be listed.

A listing of adverse events of duration >30 days occurring after an initial diagnosis of a confirmed COVID-19 infection will be presented. The listing will include all AEs with a

duration of >30 days occurring after a confirmed COVID-19 infection or positive PCR test. The listing will include AEs reported ≤7 days before the onset of a confirmed COVID-19 infection or positive PCR test and AEs reported until the end of study participation, if the AEs last >30 days.

A listing of adverse events associated with COVID-19 leading to study discontinuation will also be presented. The listing will include confirmed/suspected COVID-19 infections reported in the narrow COVID-19 SMQ in addition to COVID associated AEs which meet the criteria for Roche Standard AEGT COVID-19 preferred terms for confirmed cases if the AE leads to study discontinuation.

4.9.4 Demographic and Baseline Characteristics

A summary and listing of demographic and baseline characteristics of patients with confirmed/suspected COVID-19 will be presented.

4.9.5 Medical History

A summary of previous and concurrent medical history in patients with confirmed/suspected COVID-19 will be presented.

4.9.6 Additional Observations

All COVID-19-related observations are/will be recorded as free text in the additional observation eCRF page. All COVID-19-related additional observation results will be listed.

4.10 CHANGES TO THE ANALYSIS PLANNED IN THE PROTOCOL

The protocol specified that a database lock would occur for an interim analysis to support the initial filing and registration of risdiplam. Additional interim analyses may occur to support other activities.

The protocol specified that safety data will be summarized for the first 12-month period. Summaries of liver laboratory results and C-SSRS results will instead be presented for the whole treatment period because time trends are not a focus for this data, and there have been no previous findings. Similarly, and for the same rationale, the overview tables for all ophthalmological assessments and ophthalmological assessments in the last visit will be presented for the whole treatment period.

The protocol specified ‘ability to swallow’ as an exploratory outcome measure, and the proportion of patients with the ability to swallow at Month 12 and Month 24 was specified as an exploratory analysis. Additionally, the protocol specified time to loss of swallowing as an exploratory objective. Due to the small number of patients for whom this data is collected, and considering this is not clinically assessed but based on interview of the patient or caregiver, time to loss of swallowing has been removed as an exploratory objective in the SAP. The proportion of patients with the ability to swallow will not be

calculated. Instead, individual patient narratives will provide swallowing data on a patient-level.

The protocol specified that patient adherence to smartphone-based monitoring (patients aged 6-60 years) and the potential correlations between collected sensor data and patients' MFM scores (patients aged 6-60 years) would be evaluated as exploratory objectives. Both objectives have been removed from this SAP as this data will be analysed separately.

Additional COVID-19 related analyses have been added.

5. REFERENCES

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Appendix 1
Protocol Synopsis

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
PROTOCOLNUMBER:	BP39054
VERSION NUMBER:	4
EUDRACT NUMBER:	2016-004184-39
IND NUMBER:	128972
NCT NUMBER:	NCT03032172
TEST PRODUCT:	Risdiplam (RO7034067)
PHASE:	II
INDICATION:	Spinal Muscular Atrophy
SPONSOR:	F. Hoffmann-La Roche Ltd.

OBJECTIVES

Primary Objectives

The primary objectives of this study are as follows:

- To evaluate the safety and tolerability of risdiplam.
- To investigate the pharmacokinetics (PK) of risdiplam and metabolites as appropriate.

Secondary Objective

The secondary objective for this study is as follows:

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

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 measured by 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)

STUDY DESIGN

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 24-month period. After completion of the 24-month treatment period, the patient will be given the opportunity to enter the extension 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 extension, the patient may continue in the study until the end of study (EOS), provided that risdiplam is not commercially available in the patient's country. The treatment with study medication in the extension phase will continue as per the main study in regards to dosing.

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

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.

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 104 weeks
- Thereafter, patients will be given the opportunity to enter the extension phase of the study
- If a patient completes or withdraws early from study treatment, the patient will be requested to attend a study completion/early withdrawal visit and then followed with a phone call from the site 30 days after the study completion/early withdrawal visit.

NUMBER OF PATIENTS

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

TARGET POPULATION

The study population consists of adult and pediatric patients with SMA aged 6 months to 60 years who have been previously enrolled in Study BP29420 (Moonfish) or previously treated with nusinersen, AVXS-101, or olesoxime.

INCLUSION/EXCLUSION CRITERIA

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 nas-ogastric, 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).

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 Columbia-Suicide Severity Rating Scale (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-thecounter 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.
- 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.

END OF STUDY

Because this study includes an extension phase for all enrolled patients, it will continue until risdiplam is commercially available, the study is terminated per local regulation, or the Sponsor decides to terminate the study.

The end of this study is defined as the date when the last patient last visit (LPLV) occurs. LPLV is expected to occur approximately 5 years after the last patient is enrolled (completion of 24 months treatment phase and 3 years extension phase).

LENGTH OF STUDY

The length of the study is expected to be at least 5 years after the last patient is enrolled in the study. The length of the study will not exceed 5 years after the last patient is enrolled in the study. After a patient has completed 3 years in the extension, the patient may continue in the study until EOS, provided that risdiplam is not commercially available in the patient's country.

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) scale, 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.
- 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

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

PHARMACOKINETIC OUTCOME MEASURES

The PK outcome measures 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.

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 Schedules of Assessments and detailed tables, 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.

EXPLORATORY OUTCOME MEASURES

The exploratory outcomes measures for this study are:

- Disease-related adverse events
- Motor function measure (MFM) (32 item version)
- Hammersmith Functional Motor Scale Expanded (HFMSE)
- Revised Upper Limb Module (RULM)
- Gross Motor Scale of the Bayley Scales of Infant and Toddler development–Third Edition (BSID-III)
- Hammersmith Infant Neurological Examination Module 2 (HINE-2).
- Six-minute walk test (6MWT) (for ambulant patients only)
- Sniff nasal inspiratory pressure (SNIP)
- Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and peak cough flow (PCF)
- SMA Independence Scale (SMAIS) (Sensor data collected using smartphone-based monitoring as part of the digital biomarker approach)
- Ventilation-free survival (i.e., without need for permanent ventilation, defined as ≥16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following, the resolution of an acute reversible event or tracheostomy)
- Ability to swallow

ROCHE RESEARCH BIOSAMPLE REPOSITORY (RBR)

The Roche Research Biosample Repository (RBR) is a centrally administered group of facilities for the long-term storage of human biological 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 to participate in this optional Research Biosample Repository. Only patients aged 12–60 years will be invited to participate. Collected specimens will be used to study the association of biomarkers with efficacy, adverse events, or disease progression, to study drug response, including drug effects and the processes of drug absorption and disposition, and to increase the knowledge and understanding of the disease biology. These samples will also aid in the development of biomarker or diagnostic assays and establish the performance characteristics of these assays. The following samples will be collected for identification of dynamic (noninherited) biomarkers:

- Blood samples for 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 samples 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.

INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

Test product

Two-bottle formulation – Powder and solvent for oral solution, 20 mg and 120 mg Risdiplam "two-bottle" clinical formulation is a powder and solvent for constitution to an oral solution. Risdiplam drug product is composed of two bottles; one containing 20 mg or 120 mg of risdiplam substance (no excipients) and another with excipients blend (powder for solvent for reconstitution). The excipient blend bottle is constituted with water for injection and entirely transferred to the drug substance bottle to yield an oral solution containing 0.25 mg/mL or 1.5 mg/mL of risdiplam.

One-bottle formulation – Powder for oral solution, 60 mg

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.

Throughout the study, the study medication (risdiplam) 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.

All IMPs will be supplied and packaged by the Sponsor.

PROCEDURES

Informed consent will be obtained prior to any study-specific procedures. Following eligibility at screening and the confirmation at baseline, patients will be enrolled into the study. The study assessments and examinations will be conducted as described in the Schedules of Assessments.

STATISTICAL METHODS

PRIMARY ANALYSIS

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.

SAFETY ANALYSES

The safety analysis population will include all patients who received at least one dose of risdiplam, whether prematurely withdrawn from the study or not.

All safety analyses will be based on the safety analysis population.

As appropriate, listings and summary tables will be provided for safety and tolerability assessments, including:

- 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.
- Incidence of clinically significant findings on neurological examination.
- Anthropometric examination including weight, height, head and chest circumference.

Safety data will be summarized using descriptive statistics for the safety analysis population for the 12-month period at the time of the 12-month analysis reporting event and for all available safety data collected at the time of the analysis.

PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

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

All PK and PD 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 will be tabulated and plotted.

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 Month 12 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.

The Intent-To-Treat (ITT) population is defined as all enrolled patients, regardless of whether they received risdiplam or not. All exploratory efficacy analyses 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.

Analysis of digital biomarker sensor data will include evaluation of patient adherence and correlations with clinical outcomes. The report will be handled separately from the clinical study reports of BP39054.

EXPLORATORY ECG ANALYSIS OF QTc

Categorical summaries will be presented for absolute and time-matched change from baseline for QT, QTcB and QTcF. For the analysis of the time-matched change from baseline in QTcF, all subjects in the safety population with at least one non-missing value will be included. A mixed-effects ANOVA model will be used for the analysis of time-matched change from baseline in QTcF. In addition, time-matched QTcF values and PK data from this study will be pooled with time-matched QTcF and corresponding PK values from studies in healthy volunteers (Entry-in-Humans and PK ethnicity studies) and in patients treated with risdiplam to explore the relationship between risdiplam plasma concentrations and QTc interval.

SAMPLE SIZE JUSTIFICATION

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-naive patients and patients who previously received nusinersen or AVXS-101.

Interim Analyses

An interim analysis of all available safety and efficacy data will be performed to support the initial filing and registration of risdiplam. 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.

LIST OF PROHIBITED MEDICATIONS

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 including nusinersen (SPINRAZA™) 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 or potential retinal toxicity liabilities: e.g., oral retinoids including over-the-counter formulations, amiodarone, phenothiazines, and chronic use of minocycline.

Patients should not have received the following drugs previously (these are also prohibited during the study): Quinolines (chloroquine and hydroxychloroquine), thioridazine, retigabin, and vigabatrin.

Use of the following therapies is prohibited for patients during the study and for at least 1 year prior to enrollment, and mothers of patients if breastfeeding the patient during the study and within 90 days of enrollment:

- Desferoxamine, topiramate, latanoprost, niacin (not applicable if used as a nutritional supplement), rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon, or any other drugs known to cause retinal toxicity in humans.

Appendix 2 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
Hormone panel [i,e]		x					x					

Appendix 2
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)	
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]	x						x	x		x	x	
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]		x							x			x
Digital biomarker– remote [p, r]			x									
Blood sample for RBR (optional) [e,s]			x									
Clinical genotyping				x [t]								

Appendix 2
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)	
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 3.

Appendix 3 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]		Extension Phase [a]			*Comp/EW* [a]		Follow-Up *Phone call*
Day	D 456	D 546	D 547	D 637	D 728	D 729	Every 13 weeks	Every 26 weeks D 1	Every 26 weeks D 2	D 1	D 2	*Comp/EW + 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]		x			x			x		x		
Tanner staging [m]					x					x		
In vivo mRNA [f]						x					x	

Appendix 3
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]		Extension Phase [a]			*Comp/EW* [a]		Follow-Up *Phone call*
Day	D 456	D 546	D 547	D 637	D 728	D 729	Every 13 weeks	Every 26 weeks D 1	Every 26 weeks D 2	D 1	D 2	*Comp/EW + 30 days*
(Visit window, *days*)	(± 7)	(± 7)		(± 7)	(± 7)		(± 14)	(± 14)				(± 7)
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]			x			x			x		x	
Digital biomarker–remote [p, r]	x											
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											
Daily diary	Daily									x		
Adverse events	x											*x*
Previous and concomitant treatments	x											

Appendix 3
Schedule of Assessments for Patients Aged 2–60 Years: Year 2 through End of Study (cont.)

6MWT = Six-Minute Walk Test; C-SSRS = Columbia-Suicide Severity Rating Scale; D = Day; Comp/EW = Completion/Early Withdrawal; 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.

[a] See Section 4.6.2.2, Table 2 and Table 3 of the protocol 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 extension phase, only body weight will be measured. At all other visits (including every 26 weeks during the extension 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 3.

[g] Timing and number of samples as outlined in Appendix 3.

[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.

[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.

Appendix 3
Schedule of Assessments for Patients Aged 2–60 Years: Year 2 through End of Study (cont.)

[l] See Appendix 8 for details on required ophthalmology assessments according to the visit and the group.

[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.

[q] Only patients of ≥6 years of age.

[r] Digital biomarker assessments will only be conducted by participants older than 6. The smartphone must be returned to the clinical site in case of study withdrawal, end of the study, or upon request.

[s] 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.

[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.

Appendix 4 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				

Appendix 4
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]
Week 13	Day 91 [c]	Predose	x	x	x	x		
		+1 hr	x	x				
		+2 hr	x	x				
		+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

Appendix 4
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]
Extension Phase			x [d]					
Completion/Early Withdrawal	Day 1		x					
	Day 2			x	x	x	x	x

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 of the protocol.

[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 extension phase.

Appendix 5 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]	x					x	x	x	x
In vivo mRNA [f]			x		x (4 hr) [d]		x		x
SMN protein [f]			x		x (4 hr) [d]		x		x

Appendix 5
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 6 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	Extension Phase		*Comp/EW*	Follow-up *phone call*
Day	Day 456	Day 546	Day 637	Day 728	Every 13 weeks	Every 26 weeks		*Comp/EW + 30 days*
(Visit window, *days*)	(± 7)	(± 7)	(± 7)	(± 7)	(± 14)	(± 14)		(± 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]		x		x		x	x	
In vivo mRNA [f]				x			x	
SMN protein [f]				x			x	
BSID-III-gross motor score		x		x		x	x	
HINE2		x		x		x	x	
Level of respiratory support	x	x	x	x		x	x	

Appendix 6
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	Extension Phase		*Comp/EW*	Follow-up *phone call*
Day	Day 456	Day 546	Day 637	Day 728	Every 13 weeks	Every 26 weeks		*Comp/EW + 30 days*
(Visit window, *days*)	(± 7)	(± 7)	(± 7)	(± 7)	(± 14)	(± 14)		(± 7)
Nutritional check [k]	x	x	x	x		x	x	
Clinical genotyping								
Study medication dispensation/return	x [m]						x [p]	
Daily administration of study medication	Daily							
Daily diary	Daily							
Adverse events	x							*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; PK = pharmacokinetic; 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 the parent(s)/guardian(s) agrees, follow-up phone calls should occur every 2 weeks after the early withdrawal visit until *the* Follow-*Up phone call* 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 7.

[g] Timing and number of samples as outlined in Appendix 7.

[h] Predose.

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

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

[j] See Appendix 8 for details on required ophthalmology assessments according to the visit and the group.

[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 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.

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

[o] Collection of body weight only.

[p] No dispensation of study drug.

Appendix 7 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			

Appendix 7
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
Week 91	Day 637	Predose	x	x		
		+ 2 hr	x			
		+ 4 hr	x			
		+ 6 hr	x			
Week 104	Day 728	Predose	x	x	x	x
Extension Phase		Predose	x [a]	x		
Completion/Early Withdrawal			x	x	x	x

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 extension phase.

Appendix 8 Ophthalmological Assessments

Week	Screening	13	26	39	52	78	104	EXT	Completion/ Early Withdrawal
Adults and children ≥ 10 years									
Best corrected visual acuity	x	x	x	x	x	x	x	x [c]	x
Threshold perimetry [e]	x		x		x	x	x	x [c]	x
Slit lamp and fundus examination	x	x	x	x	x	x	x	x [c]	x
Intraocular pressure [a]	x				x				x [f]
Color fundus photography	x		x		x				x [f]
SD-OCT	x	x	x	x	x	x	x	x [c]	x
Children aged 2–10 years									
Visual testing [b]	x	x	x	x	x	x	x	x [c]	x
Intraocular pressure [a]	x				x				x [f]
Slit Lamp and fundus examination	x	x	x	x	x	x	x	x [c]	x
Color fundus photography	x		x		x				x [f]
SD-OCT	x	x	x	x	x	x	x	x [c]	x
Infants aged 6 months to 2 years									
Examination [d]	x	x	x	x	x	x	x	x [c]	x
Color fundus photography	x		x		x				x [f]
SD-OCT	*x*	*x*	*x*	*x*	*x*	*x*	*x*	x [c]	*x*

EXT = extension study; SD-OCT = spectral domain-optical coherence tomography.

[a] Tonometry or digital palpation of the globes as appropriate for age.

[b] Bruckner test, fix and follow test, cover-uncover test, simple visual field test, visual acuity as appropriate for age.

[c] Every 26 weeks after the Week 104 visit until the completion of the extension phase.

[d] The ophthalmology examination in infants includes visual development, red reflex, external ocular examination, pupillary response, fix and follow test and ocular examination under magnification.

[e] After a first unsuccessful attempt, threshold perimetry may be replaced by simple visual field testing.

[f] *Not required if early withdrawal occurs after Week 52.*

[g] *Assessments only required in the event of Early Withdrawal and the visits occur before last patient last visit in the study.*