Official Title: A Two-Part Seamless, Multi-Center Randomized, Placebo-Controlled, Double Blind Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of RO7034067 in Type 2 and 3 Spinal Muscular Atrophy Patients (SUNFISH)

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STATISTICAL ANALYSIS PLAN (SUNFISH Part 1)

TITLE: **A TWO-PART SEAMLESS, MULTI-CENTER RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE BLIND STUDY TO INVESTIGATE THE SAFETY,TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND EFFICACY OF RO7034067 IN TYPE 2 AND 3 SPINAL MUSCULAR ATROPHY PATIENTS (SUNFISH)**

PROTOCOL NUMBER: BP39055

STUDY DRUG: Risdiplam (RO7034067)

VERSION NUMBER: 2

IND NUMBER: 128972

EUDRACT NUMBER: 2016-000750-35

SPONSOR: F. Hoffmann-La Roche Ltd.

PLAN PREPARED BY: ███████████████ , Ph.D.

DATE FINAL: Version 1: 13 February 2019

DATE(S) AMENDED: Version 2: See electronic date stamp below

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Date and Time(UTC)	Reason for Signing	Name
04-Mar-2020 12:53:57	Company Signatory	████████

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

The main purpose of this amendment is to include analyses for both safety and efficacy that will be performed for data collected beyond 12 months on risdiplam treatment. This Statistical Analysis Plan (SAP) Version 2 for Study BP39055 (Part 1) has been amended to incorporate the following changes:

- A new section has been added for the analyses on the comparison of Part 1 data with external comparator data.

- Instead of using the term 'Part 2 dose level' in Version 1 of the SAP, the term 'pivotal dose' will be used instead throughout this Version 2 of the SAP.

- The time window for the efficacy analyses will be based on the study visit with the scheduled efficacy assessment and the time window for the safety analyses will be based on the visit window, even if the assessment is not scheduled to be performed at that visit.

- According to the MFM scoring manual, all missing items at a visit will be imputed as 0 prior to the calculation of the total score. There are some patients who performed the MFM20 at baseline and had performed the MFM32 scale at all timepoints from Week 52 onwards. Therefore, the missing 12 items for these patients at baseline could only show an improvement post-baseline and would therefore lead to bias in the analysis of the change from baseline total score at Months 12, 18 and 24 for the ITT population. In order to remove such bias, any MFM32 analyses will be based on the MFM analysis population (the ITT population excluding patients who performed the MFM20 scale at any timepoint) instead of the intent-to-treat (ITT) population as stated in Version 1. A sensitivity analysis will be performed based on the ITT population.

- For responder analyses for MFM, Hammersmith functional motor scale expanded (HFMSE), and revised upper limb module (RULM), the proportion of responders will be derived based on the number of patients with an available total score at the respective timepoint.

- Additional plots (waterfall plots) of the individual change from adjusted baseline total score for HFMSE and RULM are added.

- Additional analysis to summarize the proportion of patients with change from adjusted baseline in MFM32 total score of ≥ 4 at each timepoint is added.

- Disease-related adverse events (AEs) will be reported based on more than one sets of basket to the AE datasets

- Clarifications have been added such that the efficacy analyses on the all exposure to (active) risdiplam pivotal dose treatment period that were performed for the 12-month reporting event will not be performed for the 24-month reporting event.

- Additional forest plots for subgroup analyses of the mean change from adjusted baseline total score by age group, SMA Type with ambulatory status, SMN2 copy number and investigational sites will be presented for MFM32, HFMSE, and RULM.

- For all safety data, if multiple valid results for a variable are recorded in the same time window (including assessments performed at an unscheduled visit or an early treatment discontinuation visit), the current version is updated such that 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. This is to ensure consistency with other studies with risdiplam.

- Additional analyses to summarize the AE results by patient years for every 12 months (0 to ≤12 months, >12 to ≤24 months), every 18 months (0 to ≤18 months) and for every 24 months (0 to ≤24 months) for the all exposure to risdiplam treatment period have been added.

- Additional analyses to summarize the AE by greatest intensity adjusted per 100 patients years and AE by causality (AE related to study drug) adjusted per 100 patients years for the all exposure to risdiplam treatment period have been added.

- Additional analyses, the overview of AE summary table and the AE summary table by system organ class (SOC) and preferred term (PT) summary table will be presented for the first 24 months on risdiplam treatment period.

- For the AE outcome summary tables, the results will be presented both by patient counts and by event counts.

- Additional analyses to summarize the most common AEs reported in ≥15% of patients who receive any treatment have been added.

- Listing of urinalysis test results will be provided.

- Normal range of the vital sign parameter diastolic blood pressure (DBP) for patients above 12 years old is corrected to 40–90 mmHg instead of 40–120 mmHg in the previous version.

- Additional analyses are added to summarize the numerical values and the change from baseline numerical values for each of the ECG parameters at each timepoint for the whole treatment period.

- Updates have been made to the analyses for the ophthalmological and the anthropometric examination results to improve clarity.

- Protocol deviations will only be summarized for the whole treatment period.

- All previous and concomitant medications results are now coded by WHODrug Global B3 Format Dictionary. Updates have been made to summarize all medications results.

- In Version 1 of the SAP, the '<' signs were missing in the definition for the delayed puberty and have now been updated in this version.

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

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1. BACKGROUND

This Statistical Analysis Plan (SAP) documents the data-handling rules, derivation rules, and statistical methods of summarizing and analyzing safety and efficacy data collected from patients with Type 2 or Type 3 (ambulant and non-ambulant) Spinal Muscular Atrophy (SMA) for Part 1, the exploratory dose-finding part of Study BP39055 (SUNFISH). This SAP will only cover Part 1 of the study. The rules for handling safety and efficacy data for patients in Part 2 of Study BP39055 will be documented in a separate SAP and will not be covered here. This SAP will also include analyses to compare the Part 1 results with external comparator data.

Within this SAP, the terms 'placebo group' or 'placebo patients' refer to patients who were initially randomized to and received placebo treatment. The term 'active' treatment means 'risdiplam' treatment. The phrase 'patients initially on active treatment' refers to patients who were initially randomized to and received risdiplam (RO7034067)/active treatment. The term 'by treatment' or 'by treatment group' means 'by the treatment patients were initially randomized to and received'.

2. STUDY DESIGN

This is a seamless, multi-center, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of risdiplam in adult and pediatric Type 2 and Type 3 (ambulant and non-ambulant) SMA patients.

The study consists of two parts:

- An exploratory dose-finding part (Part 1).
- A confirmatory part (Part 2), starting once the dose has been selected in Part 1.

The two parts of the study are independent, have their own objectives and eligibility criteria, and will be analyzed separately. Part 1 patients did not roll over into Part 2. Part 2 is the confirmatory part of the study to investigate the efficacy and safety of risdiplam in patients with Type 2 and Type 3 (non-ambulatory only) SMA aged 2 to 25 years. Please refer to the protocol for details on the study design for Part 2 of the study.

Part 1 is a double-blinded, placebo-controlled (for a minimum of 12 weeks), randomized (risdiplam: placebo [2:1]), exploratory dose-finding study in patients with Type 2 and Type 3 (ambulant and non-ambulant) SMA. This is followed by an open-label extension phase. The primary objective is to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam and to select the dose for Part 2 of the study.

The study design of Part 1 of the study is shown as follows in Figure 1.

Figure 1 Study Design for SUNFISH Part 1
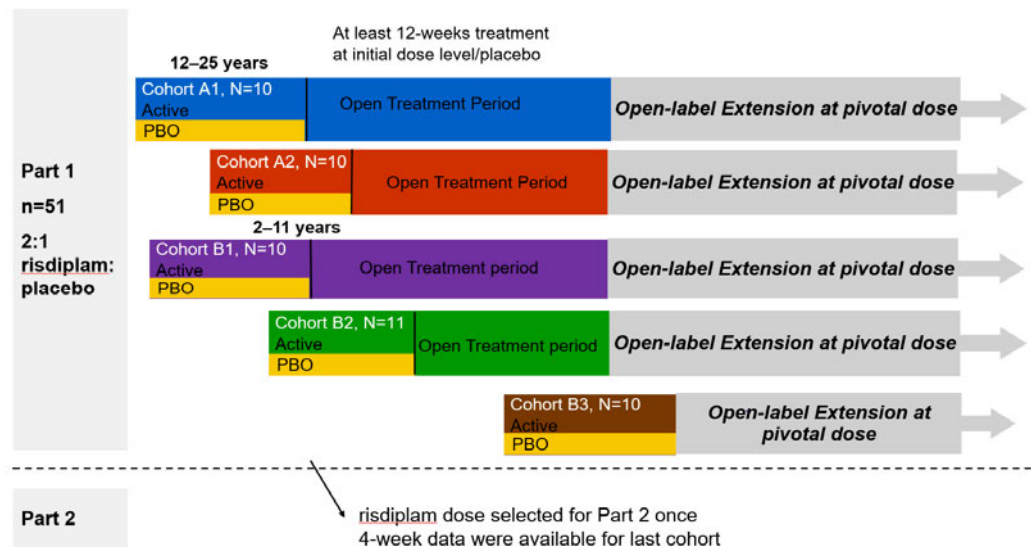
*Please note that placebo patients within each cohort did not switch to risdiplam on the same date, and patients within each cohort did not switch to risdiplam pivotal dose on the same date. Please refer to the analysis periods section (Section 2.4.2) for details on the start and end day for each period.

For Part 1 of the study, a total of 51 patients were enrolled in five cohorts. Patients were enrolled in two age groups: (1) Group B: Age 2–11 years and (2) Group A: Age 12–25 years, with 3 cohorts for Group B and 2 cohorts for Group A. Patients were randomized in a 2:1 ratio to active risdiplam treatment or placebo within each cohort.

Throughout Part 1 of the study, all decisions including enrollment, dose escalation, and switching of placebo patients to active treatment were made by an Internal Monitoring Committee (IMC) and proceeded as follows:

- Enrolment into the study was initially opened to adult and adolescent patients (Cohort A1) receiving blinded RO7034067 3 mg once daily (first dose level as defined in the protocol, targeting an $AUC_{0-24h,ss}$ of 700 ng.h/mL); 10 patients aged 12–16 years were included in Cohort A1. Once RO7034067 at this dose level was shown to be safe and well-tolerated for at least 4 weeks in 9 patients enrolled in Cohort A1 (minimum as per protocol was 3 patients aged 12–17 years on active treatment, which was ensured with a minimum of 6 patients and a randomization of 2:1), enrolment was then opened to a cohort of younger patients (Cohort B1). The dose recommended by the IMC for this age group according to the target $AUC_{0-24h,ss}$ of 700 ng.h/mL was 0.02 mg/kg; 10 patients aged 3–11 years were included in Cohort B1.

- At the same time point (i.e., once safety and tolerability were confirmed based on the review of at least 4 weeks of treatment at 3 mg once daily in 9 patients in

Cohort A1), enrolment was opened to a higher dose level cohort of 9 adult and adolescent patients (Cohort A2) receiving RO7034067 5 mg once daily. As per protocol, the higher dose level was determined as such to achieve maximum SMN protein increase, without exceeding the exposure cap (C_{max} 400 ng/mL; mean $AUC_{0-24h,ss}$ 2000 ng.h/mL); 10 patients aged $13-24$ years were included in Cohort A2.

- Based on the review of a minimum of 4 weeks of treatment at 0.02 mg/kg in 9 patients enrolled in Cohort B1, the following recommendations were made by the IMC: i) to increase the dose in patients who were receiving active risdiplam treatment in cohort B1 at that time to 0.05 mg/kg without exceeding a cap dose of 3 mg, and ii) to enroll a minimum of 9 additional patients aged $2-11$ years at a dose of 0.05 mg/kg without exceeding a cap dose of 3 mg (Cohort B2), targeting at least 5 patients aged $2-6$ years; 11 patients aged $2-6$ years were included in this additional cohort (Cohort B2).

- Once RO7034067 was shown to be safe and well-tolerated for at least 4 weeks in 9 patients enrolled in Cohort B2 at the dose of 0.05 mg/kg, the recommendation was made by the IMC to increase the dose in all patients that were on active risdiplam treatment at that time in Cohorts B1 and B2 to 0.15 mg/kg without exceeding a cap dose of 3 mg. At the same time point, enrollment was opened to another cohort of 9 patients at the dose of 0.25 mg/kg without exceeding a cap dose of 5 mg (Cohort B3), determined such as to achieve maximum Survival of Motor Neuron (SMN) protein increase, without exceeding the exposure cap (C_{max} 400 ng/mL; mean $AUC0_{-24h,ss}$ 2000 ng.h/mL); 10 patients aged $2-11$ years were included in Cohort B3.

- Upon completion of at least 12 weeks of placebo-controlled treatment by a minimum of 9 patients of each cohort, the IMC reviewed all available data from the cohort to make the decision to switch placebo patients to active treatment at the dose tested in their respective cohort.

- For the last cohort in Part 1 (Cohort B3), all available safety, tolerability, PK and PD data following completion of a minimum of 4 weeks treatment by the 9th patient (including all available data for the 10th patient of the last cohort who was enrolled approximately 1 week after the 9th patient, and all available data from all previous cohorts) reviewed by the IMC in order to select the dose to be administered in Part 2 of the study. This dose selection was confirmed by the external iDMC following review of the same data package.

- Following review of all available Part 1 data by the iDMC and confirmation of the IMC dose selection, Part 2 has commenced and all patients from Part 1 (placebo and those on lower doses of RO7034067) switched to the dose selected for Part 2, as part of the open label extension (OLE) phase of this study. Patients from the last cohort of Part 1 had to complete treatment out to the end of the 12-week treatment period of their cohort before entering the OLE. Patients will continue to be followed up for safety, tolerability and efficacy as part of the OLE phase of the study. All placebo patients performed the Week 17 scheduled assessment prior to switching to risdiplam treatment. As per protocol, they had repeated all assessments from Day 1 onwards as planned in the Schedule of Assessment (SoA) after switching to

risdiplam treatment to ensure they had the same safety monitoring as those initially randomized to and who received risdiplam treatment.

As described above, the duration of the study for each patient enrolled in Part 1 (not including the OLE phase) was divided as follows:

- Screening: Up to 30 days prior to first dose
- Baseline: Day -1
- Treatment period: Double-blind treatment (Placebo-Controlled period) for a minimum of 12 weeks, followed by open-label active treatment (as decided by IMC)

The OLE phase, which includes regular monitoring of safety, tolerability and efficacy, is planned to run until risdiplam is commercially available to patients who participate in their countries or until the Sponsor ceases producing or studying risdiplam. If a patient withdraws or is withdrawn from the clinical study or study treatment at any time, they will be asked to participate in the follow-up period of the study as described in the SoA.

All patients were randomized on Day -1, one day before the first administration of study medication (either placebo or active risdiplam) on Day 1.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the SoA tables for Part 1 of the study in Appendix 2, Appendix 3, and Appendix 4.

2.2 OUTCOME MEASURES

Please refer to the Protocol Synopsis in Appendix 1 for safety, pharmacokinetics, pharmacodynamics, and efficacy measures.

2.3 DETERMINATION OF SAMPLE SIZE

The target sample size for Part 1 was based not on statistical calculation but on practical consideration in order to select the dose level for Part 2 of the study. The target sample size for Part 1 was 36 patients with the plan to enroll in total 4 cohorts of 9 patients (randomized 6 active vs 3 placebo) to each cohort, with 2 cohorts in each of the two age groups of $2-11$ and $12-25$ years. Up to 36 additional patients could be enrolled to test higher dose level cohorts for a maximum total of 72 patients enrolled in Part 1. With 6 patients on active treatment in each dose level cohort, there was a 74% chance to detect an AE in at least 1 patient, given that the true underlying adverse event rate was 20%. With 12 patients receiving active drug per dose/exposure level, this chance increased to 93%.

In total, 51 patients were enrolled into five cohorts in Part 1 of the study.

2.4 ANALYSIS TIMING

2.4.1 Data Cut Definition for Analysis

The clinical data cutoff date for the 12 months on risdiplam treatment reporting event (called 12 months reporting event throughout this SAP) is defined as the date when the last patient enrolled in Part 1 completed his/her 18-month assessment which is also the date of the second day of his/her Week 78 visit. This is a fixed date data cut, which means the same clinical data cutoff date will be applied for all patients for this reporting event. From this clinical data cutoff date, all patients from Part 1 have also been treated with risdiplam at the pivotal dose for at least 12 months.

Another clinical data cut will be taken when all Part 1 patients have completed his/her 24 months of treatment on risdiplam at any dose level and also completed 24 months of risdiplam treatment at pivotal dose (called 24 months reporting event throughout this SAP). A fixed date data cut, i.e., the same clinical data cutoff date for all patients, will be applied for all Part 1 patients for this 24 months reporting event.

All available safety and efficacy data up to the clinical cutoff date will be analyzed and reported.

2.4.2 Analysis Periods

All available data will be analyzed separately in one of the following study periods of Part 1:

- **Day 1 to Week 12 (Day 84) period:** This is the minimum placebo-controlled period for all patients. As per the study design of Part 1, placebo patients had to complete at least 12 weeks of placebo treatment prior to switching to risdiplam treatment, and all placebo patients from Part 1 were actually on placebo treatment for at least 12 weeks. For all patients, the start time of this period is when the first dose of study medication, either placebo or risdiplam, is administered to each individual. The end time of this period is midnight of Day 85 for each individual. Data from this period will be summarized by treatment and/or age groups, and total for all patients (all risdiplam patients age 2−11 years, all risdiplam patients age 12−25 years, all placebo patients age 2−11 years, all placebo patients age 12−25 years, all patients on risdiplam treatment, all patients on placebo treatment, all patients age 2−11 years old, all patients age 12−25 years old and all patients age 2−25 years old). Results of selective safety parameters will also be grouped by cohort (based on initial risdiplam dose level) and placebo treatment (risdiplam 0.02 mg/kg, risdiplam 0.05 mg/kg, risdiplam 0.25 mg/kg, risdiplam 3 mg, risdiplam 5 mg and all placebo patients). Further details will be described in corresponding sections.

- **Placebo-controlled period/ Double-blinded treatment period:** This is the treatment period before placebo patients were switched to risdiplam treatment. All placebo patients could only switch to risdiplam treatment after receiving confirmation from the IMC. Depending on each individual visit schedule, each placebo patient from Part 1 was switched to risdiplam treatment on a different study/visit day, having a range of approximately 4 months to 7 months on the placebo treatment. For all

patients, the start time of the period is when the first dose of study medication, either placebo or risdiplam, is administered to each individual. For all patients, the completion date (end day) of this period is provided by the investigators in the electronic case report form (eCRF) and is different depending on individual visit schedule. Note since all placebo patients have to repeat their assessment from Day 1 after switching to risdiplam treatment, the visits labelled with 'RO' are those visits after placebo patients switched to risdiplam treatment. (e.g., 'Day 1 RO'/'Week 17 RO' visits refer to the Day 1 or Week 17 visits after placebo patients received the risdiplam treatment). The 'RO' label will only be used up to Week 52 on risdiplam treatment. All visits on or after Week 52 on risdiplam treatment for these placebo patients will be labelled without the 'RO' label. Data from this period will be summarized by treatment and/or age groups, and total for all patients. (All risdiplam patients age $2-11$ years, all risdiplam patients age $12-25$ years, all placebo patients age $2-11$ years, all placebo patients age $12-25$ years, all patients on risdiplam treatment, all patients on placebo treatment, all patients age $2-11$ years, all patients age $12-25$ years, and all patients age $2-25$ years). Results of selective safety parameters will also be grouped by cohort and placebo treatment (risdiplam 0.02 mg/kg, risdiplam 0.05 mg/kg, risdiplam 0.25 mg/kg, risdiplam 3 mg, risdiplam 5 mg and all placebo patients). Results of selective efficacy parameters will also be grouped by cohort and placebo treatment with age groups (risdiplam 0.02 mg/kg, risdiplam 0.05 mg/kg, risdiplam 0.25 mg/kg, risdiplam 3 mg, risdiplam 5 mg, placebo age 2-11 years, placebo age 12-25 years). Further details will be described in corresponding sections.

- **Open label treatment period:** This is the treatment period after all placebo patients enrolled have switched to risdiplam treatment at any dose level, and before the IMC decided on the pivotal dose and patients switched to risdiplam treatment at the pivotal dose.

  The start day of this period will be the same as the end day of the placebo-controlled period for each individual patient. After the sites were informed about the dose level of Part 2, the end day of this period is the date of the next site visit when the pivotal dose is administered to each individual in Cohort A1, B1, A2 and B2.

  For all patients in cohort A1, B1, B2, the end day of this period is also the date of the visit when the first dose of pivotal dose is administered for each individual.

  Since the IMC decided the pivotal dose prior to all patients completing 12 weeks of treatment in the last Cohort B3 (which is before all placebo patients in this same Cohort are allowed to switch to risdiplam treatment), all placebo patients in Cohort B3 remained on placebo for at least 12 weeks and hence were switched directly to the iDMC confirmed pivotal dose of risdiplam treatment.

  Therefore, all patients in Cohort B3 do not have an open label treatment period and entered directly from the placebo-controlled period to the Open Label Extension Phase. Data from this period will be summarized by age groups of $2-11$ and $12-25$ years, and total for all patients.

- **Open label extension phase (OLE):** This is the treatment period after the iDMC confirmed the pivotal dose and all patients within the same cohort have switched to and received the pivotal dose of the risdiplam treatment. After the sites were informed about the dose level of Part 2, the start day of this period is the date of the next site visit when the pivotal dose is administered to each individual. Data from this period will be summarized by age groups of $2-11$ and $12-25$ years, and total for all patients.

- **Follow-up period:** This applies to all patients who discontinue treatment and /or withdraw from the study early at any time during Part 1 of the study. 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 from the follow-up period will be listed.

- **All exposure to (active) risdiplam treatment period:** This is the treatment period after each individual receives active risdiplam treatment at any dose level. This will include all active risdiplam treatment periods in 1) placebo-controlled period for patients initially randomized to and received active risdiplam treatment 2) open label treatment period for all patients, and 3) OLE phase for all patients during Part 1 of the study. For all patients, the start day is the date of first dose of active risdiplam treatment at any dose level and the end day is the clinical cutoff date. Data will be summarized by age groups of $2-11$ and $12-25$ years, and total for all patients.

- **All exposure to (active) risdiplam at pivotal dose treatment period:** This is the treatment period after each individual receives the active risdiplam treatment at the pivotal dose. This will include all active risdiplam treatment at the pivotal dose in the 1) placebo-controlled period for patients from Cohort A2 and B3 who received the risdiplam treatment at pivotal dose from the beginning, 2) open label treatment period for all patients from Cohort A2, and 3) OLE phase for all patients during Part 1 of the study. For all patients, the start day is the date of the first dose of risdiplam treatment at the pivotal dose and the end day is the clinical cutoff date. Data from this period will be summarized by age groups of $2-11$ and $12-25$ years, and total for all patients**.**

- **Whole treatment period:** For all patients, the start time of the period is when the first dose of study medication, either placebo or risdiplam, is administered to each individual. The end day of the period is the date of the clinical cutoff date, which is also the date of the second day of the Week 78 visit of the last enrolled patient in Part 1 of the study. Data from this period will be summarized by treatment and/or age groups, and total for all patients (all risdiplam patients age $2-11$ years, all risdiplam patients age $12-25$ years, all placebo patients age $2-11$ years, all placebo patients age $12-25$ years, all patients on risdiplam treatment, all patients on placebo treatment, all patients age $2-11$ years, all patients age $12-25$ years, and all patients age $2-25$ years).

The following Table 1 will provide an overview on which analysis period will be used for each data type.

Table 1   Overview of Analysis Treatment Period

Data Type	Day 1 to Week 12 (Day 84) period	Placebo-Controlled period	Open Label Treatment period	Open label Extension phase	All Exposure to risdiplam treatment period	All Exposure to risdiplam at pivotal dose treatment period	Whole treatment period
Disposition		✓(c)	✓(c)	✓			
Analysis populations and Enrollment		✓					
Protocol Deviation		✓(c)	✓(c)				✓
Previous & Concomitant SMA related surgeries and procedure							✓
Previous and Concomitant Medical History							✓
Previous and Concomitant Medications							✓
Nutrition check-up **for each timepoint**							✓
Exposure of Study Medication		✓(c)			✓		
Adverse Events[a]	✓(c)	✓(c)			✓	✓(c)	
Laboratory parameters- abnormal values summary tables **for each timepoint**							✓

Table 1   Overview of Analysis Treatment Period (cont.)

Data Type	Day 1 to Week 12 (Day 84) period	Placebo-Controlled period	Open Label Treatment period	Open label Extension phase	All Exposure to risdiplam treatment period	All Exposure to risdiplam at pivotal dose treatment period	Whole treatment period
Laboratory parameters- shift tables **for each timepoint**							✓
Vital signs- abnormal values summary tables for each timepoint							✓
Vital Signs – shift tables for each timepoint							✓
Electrocardiogram (ECG)- abnormal values summary tables for each timepoint							✓
ECG-shift table for each timepoint							✓
Suicidality Assessment (C-SSRS)- summary tables on number of events							✓
Suicidality Assessment (C-SSRS)- shift tables for each timepoint							✓
Ophthalmology – Overview summary tables (Number of clinically significant		✓(b),(c)			✓(b)		

Table 1   Overview of Analysis Treatment Period (cont.)

Data Type	Day 1 to Week 12 (Day 84) period	Placebo-Controlled period	Open Label Treatment period	Open label Extension phase	All Exposure to risdiplam treatment period	All Exposure to risdiplam at pivotal dose treatment period	Whole treatment period
values and abnormal values)							
Ophthalmology – Overview summary tables in the last assessment visit (number of clinically significant values and abnormal values)		✓(b), (c)			✓(b)		
Ophthalmology – Summary table **at each timepoint** (Number of clinically significant values and abnormal values at each timepoint)							✓
Ophthalmology – Numerical values summary tables at each timepoint (Actual numerical values and change from original baseline values)							✓
Anthropometric Exam for each timepoint							✓
Motor Function Measure (MFM) for		✓(c)			✓	✓(d)	

Table 1   Overview of Analysis Treatment Period (cont.)

Data Type	Day 1 to Week 12 (Day 84) period	Placebo-Controlled period	Open Label Treatment period	Open label Extension phase	All Exposure to risdiplam treatment period	All Exposure to risdiplam at pivotal dose treatment period	Whole treatment period
each timepoint							
Hammersmith Functional Motor Scale Expanded (HFMSE) for each timepoint					✓	✓(d)	
Revised Upper Limb Module (RULM) for each timepoint					✓	✓(d)	
Respiratory Data: sniff nasal inspiratory pressure (SNIP), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and peak cough flow (PCF) for each timepoint					✓	✓(d)(only on FVC)	
Patient reported & Parent/Caregiver reported PedsQL 3.0& 4.0 for each timepoint					✓(c)		

(a) The analysis treatment periods for each of the different types of Adverse Events will be described in Section 4.8.2

(b) Overview results for each period.

(c) Only for the 12 months reporting event. Analyses will not be performed for the 24 months reporting event.

(d) Will only perform as sensitivity analyses for the 12 months reporting event. Analyses will not be performed for the 24 months reporting event.

3. STUDY CONDUCT

3.1 RANDOMIZATION PROCEDURES

Randomization is performed using an Interactive (voice/web) Response System (IxRS).

In Part 1 of the study, patients who meet all eligibility criteria after screening were randomly assigned to either risdiplam or placebo. Patients are randomized within each cohort to risdiplam or placebo in a 2:1 ratio.

Sites should call the IxRS to enter the patient into screening and to register a screen failure. The randomization call to the IxRS should occur on Day – 1 after the patient's eligibility (i.e., inclusion/exclusion criteria) has been confirmed. The patient number is allocated by IxRS and is used in the clinical database to record data in the eCRF.

3.2 INDEPENDENT REVIEW FACILITY

3.2.1 Ophthalmological Examinations

Images obtained from optical coherence tomography (OCT) assessments, fundus photography assessments, fundus auto-fluorescence (FAF) (if performed) examinations, and visual field perimetry threshold (if performed) assessments are sent to the central readers in the Annesley Eye Brain Center (AEBC; formerly the Optic Nerve Research Center) for review. This includes an assessment of clinically significant changes from baseline in each of these examinations at each time-point (each scheduled assessment). The role and the process of the review of the AEBC are documented in a separate charter.

3.3 DATA MONITORING

The internal monitoring committee (IMC) consists of selected Roche representatives: Clinical Pharmacologist, Translational Medicine Leader, Safety Science Leader, Statistician, and Statistical Programmer. The IMC was responsible for monitoring the safety of patients, for selecting the dose for Part 2 and for making the following decisions during Part 1:

- Decision to open enrolment to Group B (patients aged 2 – 11 years) and decision on the dose (Dose Level 1) administered in the first cohort of Group B.

- Data package reviewed for this decision: all available PK, PD (SMN mRNA, SMN protein), safety and tolerability data (including AEs, ECGs, vital signs, clinical laboratory tests, ophthalmology tests) in a minimum of 3 adolescent patients (age 12 – 17 years) having received at least 4-week treatment with risdiplam (active treatment) at Dose Level 1 (patients from first Group A cohort).

- Dose-escalation decisions (to a higher dose-level) in Group A and in Group B, and associated dose-selection decisions.

- Data package reviewed for this decision: all available PK, PD (SMN mRNA, SMN protein), safety and tolerability data (including AEs, ECGs, vital signs, clinical laboratory test results, ophthalmology monitoring) in a minimum of 9 patients from

the previous cohort(s) treated for at least 4-weeks (some patients will have longer treatment duration) at the previous dose-level(s).

- Decision to switch placebo patients to active risdiplam following completion of at least 12 weeks of placebo-controlled treatment in each Part 1 cohort.

- Data package reviewed for this decision: all available PK, PD (*SMN* mRNA, SMN protein), safety and tolerability data (including AEs, ECGs, vital signs, clinical laboratory test results, ophthalmology monitoring) in a minimum of 9 patients from the respective cohort treated for 12 weeks (some patients had longer treatment duration), and all available data from the previous cohort(s).

- For stopping rules, see stopping criteria defined in protocol Section 5.2.4.

- Selected dose to be administered in Part 2 of the study

- Data reviewed: all available PK, PD, safety and tolerability data at the point where the last patient of the last cohort in Part 1 reached 4 weeks of treatment (a number of patients had much longer treatment duration).

Upon review of all available Part 1 data by the iDMC and confirmation of the IMC dose-selection decision, Part 2 started and all patients from Part 1 were switched to the dose selected for Part 2 as part of the OLE phase of this study.

In addition to reviewing data at these pre-defined time-points, the IMC has met and reviewed the data on an ad-hoc basis throughout Part 1 of the study, as detailed in the Charter.

The roles, responsibilities, membership, scope of activities, time of meetings and communication plan for the IMC were documented in the Charter prior to the initiation of the study.

4. STATISTICAL METHODS

4.1 ANALYSIS POPULATIONS

The number and percentage of patients included in each of the analysis populations (as described subsequently) will be summarized by age group $2-11$ and $12-25$ years old, and total for all patients.

4.1.1 Safety Analysis Population
4.1.1.1 Safety Population

All patients in Part 1, who received at least one dose of the study medication, risdiplam or placebo, whether prematurely withdrawn or not, will be included in the safety population.

Patients included in the safety population will be summarized as follows:

- Patients who received any active risdiplam treatment during the Day 1 to Week 12 period and the placebo-controlled period will be reported under the active risdiplam treatment group.

- Patients who receive only placebo during the Day 1 to Week 12 period and the placebo-controlled period will be reported under the placebo group.

- For patients who receive an initial risdiplam dose level of a cohort different from the initial risdiplam dose of a cohort they were randomized to, will be reported under the cohort with the initial risdiplam dose level received.

4.1.1.2   All Exposure Population

All patients who received at least one dose of risdiplam will be included in the risdiplam all exposure population.

For patients randomized to placebo prior to switching to any dose level of risdiplam, their data will only be included from the date of the first active dose of risdiplam received. This population will be the analysis population for the all exposure to risdiplam (at any dose level) treatment period.

4.1.2   Pharmacokinetic Analysis Population

All patients with at least one timepoint with a measureable concentration are included in the PK analysis data set. Patients were only excluded from the PK analysis population if they significantly violated the inclusion or exclusion criteria, deviated significantly from the protocol, or if data were unavailable or incomplete, which could influence the PK analysis. Excluded cases will be documented together with the reason for exclusion.

4.1.3   Pharmacodynamics Analysis Population

All patients with at least one timepoint with results in SMN protein and SMN2 mRNA are included in the PD analysis data set. Patients were only excluded from the PD analysis population if they significantly violated the inclusion or exclusion criteria, deviated significantly from the protocol, or if data were unavailable or incomplete, which could influence the PD analysis. Excluded cases will be documented together with the reason of exclusion.

4.1.4   Efficacy Analysis Population

The intent-to-treat (ITT) population defined as all randomized patients in Part 1 will be the primary analysis population for all efficacy analyses except for any MFM32 analyses. Patients who were not randomized but received study medication will be excluded from the ITT population.

4.1.4.1   MFM Analysis Population

The Motor Function Measure (MFM) is a 32-item scale that evaluates the physical function of the patients. The full MFM32 will be administered to all patients. The MFM

analysis population is defined as the ITT population excluding patients who performed the MFM20 scale at any timepoint as confirmed by a protocol deviation. This will be the primary analysis population for all MFM32 analyses.

4.2 ANALYSIS OF STUDY CONDUCT

4.2.1 Study Enrollment

The number and percentage of patients in each of the ITT, MFM analysis, safety populations and all exposure to risdiplam population will be summarized by age group (2 – 11 years and 12 – 25 years) and total for all patients. The number and percentage of patients excluded from each of the populations will be summarized by reason for exclusion. The patients excluded from the analysis populations will also be listed. The number and percentage of patients enrolled at each country and site will also be summarized by age groups of 2 – 11 and 12 – 25 years, and total for all patients.

4.2.2 Patient Disposition

The number and percentage of patients randomized/entered, completed and discontinued early will be summarized for the placebo-controlled period, open label treatment period and the OLE phase, and results will be listed for the follow-up period. Results from the placebo controlled period will be summarized 1) by cohort and placebo treatment with age groups, and 2) age groups and total for all patients (risdiplam 0.02 mg/kg, risdiplam 0.05 mg/kg, risdiplam 0.25 mg/kg, risdiplam 3 mg, risdiplam 5 mg, placebo age 2 – 11 years, placebo age 12 – 25 years, all age 2 – 11 years, all aged 12 – 25 years and total for all patients). Results from the open treatment period, OLE phase will be summarized by age groups and total for all patients (all patients age 2 – 11 years old, all patients age 12 – 25 years old and all patients age 2 – 25 years old). The reasons for early discontinuation during each of the periods will also be summarized and listed.

4.2.3 Protocol Deviations

The major protocol violations will be identified according to the Management of Violations to Protocol Specifications document before database lock for the primary analysis. The number and percentage of patients with major protocol violations categorized by protocol violation criterion will be summarized by 1) cohort and placebo treatment with age groups and 2) by age groups and total for all patients (risdiplam 0.02 mg/kg, risdiplam 0.05 mg/kg, risdiplam 0.25 mg/kg, risdiplam 3 mg, risdiplam 5 mg, placebo age 2 – 11 years, placebo age 12 – 25 years, all age 2 – 11 years, all aged 12 – 25 years and total for all patients for the whole treatment period. Results from the follow-up period will be listed. Major protocol deviations will also be listed and evaluated for their potential effects on the interpretation of study results.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

4.3.1 <u>Demographics and Baseline Characteristics</u>

Demographic and baseline characteristics will be summarized for the ITT population using descriptive statistics, means, standard deviations, medians, interquartile range and ranges for continuous variables and number and percentages for categorical variables, as appropriate. The (original) baseline is defined as the last measurement prior to first dose day of study medication (placebo or active risdiplam). Data will be grouped by 1) cohort and placebo treatment with age groups and 2) by age groups and total for all patients (risdiplam 0.02 mg/kg, risdiplam 0.05 mg/kg, risdiplam 0.25 mg/kg, risdiplam 3 mg, risdiplam 5 mg, placebo age 2 – 11 years, placebo age 12 – 25 years, all age 2 – 11 years, all aged 12 – 25 years and total for all patients).

This will include the following parameters:

- Age at randomization (years)
- Age at screening (years)
- Gender
- Height (in centimeters [cm])
- Height-for-age percentile (for ≤19 years old)
- Weight (in kilograms [kg])
- Weight-for-age percentile (for ≤10 years old)
- Body mass index (BMI)
- BMI-for-age percentile (for ≤19 years old)
- Head circumference (in cm) (those aged 5 years or younger at screening)
- Head circumference-for-age percentile (for ≤ 5 years old)
- Self/caregiver-reported race
- Self/caregiver reported ethnicity

4.3.2 <u>SMA Disease Characteristics</u>

The following SMA disease characteristics at original baseline will be summarized for the ITT population by 1) cohort and placebo treatment with age groups and 2) by age groups and total for all patients (risdiplam 0.02 mg/kg, risdiplam 0.05 mg/kg, risdiplam 0.25 mg/kg, risdiplam 3 mg, risdiplam 5 mg, placebo age 2 – 11 years, placebo age 12 – 25 years, all age 2 – 11 years, all aged 12 – 25 years and total for all patients) for the following:

- SMN2 copy number (from genotype analysis)
- SMA type (2 or 3)
- Ambulatory status (Ambulant or non-ambulant)
- Initial SMA Symptoms, best response

- Age of onset for initial SMA symptoms in months.
- Duration of disease prior to first dose of study medication (placebo or risdiplam) which is also the time from onset of initial SMA symptom to the first dose of study medication (placebo or risdiplam) in months, defined as

$$\frac{Date\ of\ first\ dose\ of\ study\ medication - Date\ of\ initial\ SMA\ symptom\ onset}{365}\ x\ 12$$

- Duration of disease prior to first dose of risdiplam which is also the time from onset of initial SMA symptom to the first dose of risdiplam in months, defined as

$$\frac{Date\ of\ first\ dose\ of\ risdiplam - Date\ of\ initial\ SMA\ symptom\ onset}{365}\ x\ 12$$

- Tracheostomy (yes/no)
- Patient's current level of motor function
- Highest motor function achieved
- Motor function achieved and maintained, and the corresponding age achieved and/or age lost in months
- Respiratory device(s) used within 2 weeks prior (no pulmonary care, Cough Assist-used daily for therapy, not illness related, Cough Assist-used with an illness, BiPAP Support for less than 16 hours per day, BiPAP Support for more than 16 hours per day, airway clearance through cough assistance)
- 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 before screening (yes/no)
- Hip subluxation or dislocation (yes/no)
- Hip surgery (yes/no)
- Number and percentage of patients who could and could not sit (sitter and non-sitters).
- Sitting is defined as with a score of ≥ 1 in item 9 of the MFM scale and 'Could not sit' is defined as with a score of <1 in item 9 of the MFM
- Number and percentage of patients who could or could not stand
- Standing is defined as with a score of ≥ 1 in item 25 of MFM and 'Could not stand' is defined as with a score of <1 in item 25 of MFM
- Number and percentage of patients who could or could not walk (walkers and non-walkers)
- Walking is defined as with a score of ≥ 2 in item 20 of HFMSE (able to take >4 steps unaided) and 'Could not walk' is defined as with a score of <2 in item 20 of HFMSE (able to take ≤ 4 steps unaided)

4.3.3 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 [PT]') and System Organ Class (SOC) based on the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA). All analyses will be performed using these PT and body systems.

All SMA related surgeries and procedures data will be summarized for the ITT population. Surgeries or procedures performed prior to the first dose date of the study medication (placebo or risdiplam) will be summarized separately. For the coded terms and those surgeries or procedures performed prior to the first dose date (previous surgeries), the number and percentage of patients who underwent at least one SMA-related surgery and procedure , and the number of surgeries and procedures reported will be summarized by age groups of 2- 11 and 12 – 25 years and total for all patients. Similarly for the coded terms on or after the first dose of study medication, the number and percentage of patients who underwent at least one SMA-related surgery and procedure , and the number of surgeries and procedures reported will be summarized by age groups of 2- 11 and 12 – 25 years and total for all patients for the whole treatment period. 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.

In addition, 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 by age groups of 2-11 and 12 -25 years and total for all patients.

For those with tendon release or spinal surgery, data categorized by the following will also be summarized by age groups of 2 – 11 and 12 – 25 years, and total for all treatment groups:

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

Tendon release and spinal surgeries performed prior to the first dose date and for those performed on or after the first dose date up to study withdrawal or completion will be summarized separately.

For the safety follow-up period, surgeries or procedures performed on or after Day 1 and up to Week 52 after study withdrawal/completion will be listed.

All SMA related surgeries and procedures results will also be listed which will include the investigator reported terms and the corresponding terms by SOC, PT and the lowest level term.

4.3.4   <u>Previous and Concomitant Medical History</u>

For all conditions, the term entered by the investigator describing the condition (the 'verbatim term') will be assigned to a standardized term (the 'PT') and SOC based on the most up-to-date version of MedDRA. All analyses will be performed using these PT and body systems.

All medical conditions from 30 days prior to the screening visit will be reported for the ITT population. Previous conditions and concomitant conditions at baseline will be summarized separately. The number and percentage of patients with previous conditions at baseline (including conditions with an onset date within 30 days prior to screening visit or conditions with an onset date within the 30 days of the screening visit; and the end date is prior to first dose) and concurrent conditions at baseline (starts prior to the first dose and with no end date or with an end date after the first dose) will be summarized by age groups of $2-11$ and $12-25$ years, and total for all patients for the whole treatment period. 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 conditions and concurrent conditions at baseline will be summarized separately.

4.3.5   <u>Previous and Concomitant Medications</u>

For all medications, the term (Generic term) entered by the investigator describing the medications will be coded based on the latest version of the WHODrug Global B3 Format Dictionary. The generic term will be coded for 4 Anatomical Therapeutic Chemical (ATC) classes. Each generic term will have one or more ATC classes. The results will be presented in 2 summary tables by 1) the medication classes and preferred name only for the ATC class 2 and 2) preferred name.

All medications taken by the patients from 30 days prior to the screening visit will be reported for the ITT population. Previous medication (with a start date prior to the screening visit or with a start date within 30 days of the screening visit; and with an end date prior to the first dose date) and concomitant medications (with a start date on or

after the first dose of medication up to the date of study withdrawal/completion or no end date) will be summarized separately.

The number and percentage of patients taking at least one medication and the total number of medications taken previously will be presented by age groups of $2-11$ and $12-25$ years, and total for all patients. Similarly, the number and percentage of patients taking at least one medication and the total number of concomitant medication taken will be summarized by age groups of 2-11, $12-25$ years and total for all patients for the whole treatment period. Multiple uses of a specific medication for a patient were counted once in the frequency for the medication. For summary Table 1, the results will be summarized overall, for each medication class and for each preferred term. In this summary table, medications may appear under multiple medication classes. Multiple uses within a specific medication class for a patient will be counted once in the frequency for the medication class. All medication results will be listed.

Medications with a start date from 1 day up to 52 weeks after study withdrawal/completion will also be listed.

Treatments given for an adverse event (AE) will be summarized. If applicable, treatment given for prophylaxis may also be summarized.

4.3.6 Physiotherapy, Occupational Therapy, and Other Forms of Exercise Therapy

All therapies used by patients from 30 days prior to the screening visit are recorded and will be reported at timepoint specified in the SoA. For multiple records with the same start day and same therapies on the same patient, the record collected as the last scheduled time point prior to the clinical cutoff date marked as ongoing or with no end/stop date will be taken for the analysis.

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 age groups of $2-11$ and $12-25$ years, and total for all patients.

4.3.7 Taste Assessment

The taste of the study medication was accessed in patients aged 6 or above after dose administration on Day 7 of the study.

In adults and adolescents (age $12-25$ years), taste was assessed by a taste questionnaire that each patient should complete; entries were reviewed for completeness by the site staff and the patient was asked to complete any blank items. In children aged $6-11$ years, taste was assessed using a five−point facial visual hedonic scale; children were encouraged to select the visual face that best reflects how much they liked the taste of the ingested study drug solution.

The number and percentage of patients within each category on the taste assessment result will be summarized separately for age group of $6-11$ (children) and $12-25$ (adolescents) years.

4.3.8 Nutrition Check-Up

Nutritional assessment was performed for all patients at the time points indicated in the SoA. The 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 number and percentage of patients for each meal type (Solid Food, Modified Oral Food Intake, Nasogastric Food Intake, 100% Gastronomy Tube Fed, Oral Fluid (Milk) Food Intake or Mixed (Fluid/Puréed Food) Oral Food Intake) will be summarized at each timepoint by age group $2-11$, $12-25$ years, and total for all patients for the whole treatment period.

4.4 EFFICACY ANALYSIS

All efficacy endpoints in SUNFISH Part 1 are considered as exploratory. The ITT population will be the primary analysis population for all exploratory efficacy endpoints except for the MFM32 analyses. All MFM32 analyses except for any MFM sensitivity analyses will be based on the MFM analysis population as defined in Section 4.1.4.1. The efficacy analyses will only include data from patients randomized into Part 1 of the study. For patients who withdraw or are withdrawn early from the study and have received prohibited medication(s) intended for treatment of SMA prior to study withdrawal, the efficacy analyses will be based on available data up to the time of receiving these prohibited medication(s). The prohibited medications intended for treatment of SMA are defined in the protocol Section 4.5.2.

The baseline/original baseline for Part 1 of the study is defined as the last measurement prior to first dose of the study medication, either placebo or risdiplam. The adjusted baseline is defined as the last measurement prior to the first dose of active risdiplam treatment at any dose level. The pivotal dose adjusted baseline is defined as the last measurement prior to the first risdiplam treatment at the pivotal dose.

Efficacy analyses (except the disease related adverse events endpoints) will be mainly based on the all exposure to risdiplam treatment period using an adjusted baseline (re-baseline for placebo patients). The efficacy data after each individual received the risdiplam treatment will be presented and summarized descriptively using summary statistics at each timepoint by age groups of $2-11$ and $12-25$ years, and total for all patients.

During the placebo-controlled period, there is only one post-baseline (original baseline) efficacy assessment at Week 17. Additional analysis will also be performed on selective efficacy endpoints for the placebo-controlled period (up to Week 17).

Efficacy Data from Part 1 of the study will also be compared to external comparator data. Details for these analyses will be discussed in Section 5.

Efficacy Data Visit Time Window

A time window is defined for each visit, starting midway between the scheduled visit day and the previous study visit day, and ending midway between that visit and the next study visit (if applicable). Results for assessments that are conducted at unscheduled or withdrawal visits will be assigned to the appropriate study visit with the scheduled efficacy assessment 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.

For those initially randomized to and who received placebo, the data after switching to risdiplam treatment will be time-windowed based on the study visit with the scheduled efficacy assessment as for those initially randomized to and who received risdiplam treatment.

The exploratory efficacy endpoints of Part 1 of the study will include

Motor Function

- Total score and the change from adjusted baseline total score on the Motor Function Measure (MFM).
- Total score and the change from adjusted baseline total scores on the Hammersmith Functional Motor Scale Expanded (HFMSE).
- Total score and the change from adjusted baseline total scores on the revised upper limb module (RULM).
- Proportion of patients with change from adjusted baseline $\geq \times$ (value of x will be defined in subsequent sections) points in the total MFM32 score, total HFMSE score and total RULM score.

Respiratory

- The best values, the best value expressed as a percentage of the predicted value (best percentage predicted values), the change from adjusted baseline in the best values and the change from adjusted baseline best percentage predicted values for the Sniff Nasal Inspiratory Pressure (SNIP)

For patients aged 6 years or above at screening

- The best values, the best percentage predicted values, the change from adjusted baseline best values and the change from adjusted baseline best percentage predicted values for the Forced expiratory volume in 1 second (FEV1).

- The best values, the best percentage predicted values, the change from adjusted baseline best values and the change from adjusted baseline best percentage predicted values for the Forced vital capacity (FVC).

- The best values, the best percentage predicted values, the change from adjusted baseline best values and the change from adjusted baseline best percentage predicted values for the Peak cough flow (PCF).

Patient- and Parent/Caregiver-Reported Outcomes

- Total scores and the change from adjusted baseline in the total scores for the parent/caregiver reported Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scale.

- Total scores and the change from adjusted baseline in the total scores for the parent/caregiver reported PedsQL 3.0 Neuromuscular module.

- For patients age 8 – 25 years

- Total score and the change from adjusted baseline in the total scores for the patient-reported PedsQL 4.0 Generic Core Scale.

- For patients age 8–18 years

- Total score and the change from adjusted baseline in the total scores for the patient-reported PedsQL 3.0 Neuromuscular module.

Disease-Related Adverse Events

- Number of disease related adverse Events

- Disease related adverse events adjusted for patient years

4.4.1 Motor Function

4.4.1.1 Motor Function Measure (MFM)

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

- 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 $0-100$ 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.

The full MFM32 should be administered to all patients across all age groups.

The MFM20 item scale is a reduced MFM scale with 20 items (De-Lattre et al 2013). The items of the MFM20 are also classified in the same 3 domains as for the MFM32 item scale. The MFM20 includes items 1, 3, 4, 5, 6, 7, 9, 10, 11, 12, 14, 18, 21, 22, 23, 24, 25, 27, 30, and 32. The MFM20 total score is also expressed as a percentage of the maximum score possible for the MFM20 scale, which is the sum of 20 items scores divided by 60 and multiplied by 100.

4.4.1.2   Hammersmith Functional Motor Scale Expanded

The HFMSE was developed to assess the motor function ability of individuals aged two years or older, with Type 2 and 3 SMA (O'Hagen et al. 2007). The scale contains 33 items which score on a 3-point Likert scale ($0-2$) and are summed to derive the total score ranging from 0 to 66, with lower scores indicating greater impairment. Please refer to the manual and score sheet for details on classifications of scores $0-2$ for each of the 33 items.

The HFMSE was designed to assess important functional abilities, including standing, transfer, ambulation, and proximal and axial function.

4.4.1.3   Revised Upper Limb Module

The RULM is a scale that assesses specifically the motor performance of the upper limbs in SMA patients. It consists of twenty items that test proximal and distal motor functions of the arm in patients with SMA. The first entry item, used to determine study eligibility 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) with lower scores indicating greater impairment.

4.4.1.4 Analysis of the Motor Function Outcome

The analyses for the MFM scale will be based on the MFM analysis population and analyses for HFMSE and RULM will be based on the ITT population.

For the MFM, HFMSE, and RULM scale, for items that are recorded as 'Not Done' in the eCRF are considered as missing with missing item scores. If the assessment has been administered at a visit with some missing items, the missing item scores will be set to 0 (unable to perform the task) prior to the calculation of the total score. Missing total scores will not be imputed.

The MFM32 total scores and the change from the adjusted baseline in the total MFM32 scores will be summarized descriptively for the MFM analysis population at each timepoint (at adjusted baseline and at each scheduled assessment visit) by age groups of $2-11$ and $12-25$ years, and total for all patients. The 95% confidence interval (CI) of the mean total scores and the mean change from adjusted baseline scores will also be presented at each timepoint.

The total scores and the change from adjusted baseline total scores in the MFM32 domain scores of D1, D2 and D3, and the combined score of $D1+D2$ and $D2+D3$ will also be summarized for the MFM analysis population at each timepoint by age groups of $2-11$ years, $12-25$ years, and total for all patients. The 95% CI of the mean total scores and the mean change from adjusted baseline total scores will also be presented at each timepoint.

In addition, responder analyses to summarize the number and percentage of the responders will also be performed on the MFM32 total score. The proportion of patients who achieve the following responses (responders) on the MFM32 total score will be summarized for the MFM analysis population at each timepoint by age groups $2-11$ and $12-25$ years, and total for all patients

1) Stabilization and improvement (i.e., change from adjusted baseline in the total MFM32 score ≥ 0);

2) Improvement with a change from adjusted baseline in the total MFM32 score ≥ 1;

3) Improvement with a change from adjusted baseline in the total MFM32 score ≥ 2;

4) Improvement with a change from adjusted baseline in the total MFM32 score ≥ 3;

5) Improvement with a change from adjusted baseline in the total MFM32 score ≥ 4;

The proportion will be calculated based on the number of patients with available results at each timepoint. Missing results at each timepoint or the number of available results

will also be presented at each timepoint. Using normal approximation where appropriate, the 95% CI of each of the above proportions will also be presented at each timepoint.

The total score and the change from adjusted baseline total score of HFMSE and RULM will be summarized descriptively at each timepoint for the ITT population by age groups of $2-11$ and $12-25$ years, and total for all patients. The 95% CI of the mean total scores and the mean change from adjusted baseline total scores in HFMSE and RULM will also be presented.

Similar responder analyses will also be performed to summarize the number and percentage of the responders on the total HFMSE and RULM score. The proportion of patients with a change from adjusted baseline in the total HFMSE and RULM score of greater or equal to 0 (achieving stabilization or improvement), greater or equal to 1, greater or equal to 2 and greater of equal to 3 will also be summarized at each timepoint by age groups of $2-11$ and $12-25$ years, and total for all patients. The proportion will also be calculated based on the number of patients with available results at each timepoint. Missing results or/and the number of available results at each timepoint will also be presented.

The individual change from adjusted baseline in the MFM32 total score for the MFM analysis population, in the HFMSE total score, and in the RULM total score for the ITT population at Month 12 (12 months on risdiplam treatment) and at Month 24 (24 months on risdiplam treatment) will be plotted in waterfall plots with x-axis by ascending values of 1) age, 2) total MFM32 score at adjusted baseline and 3) duration of disease prior to first risdiplam treatment in months.

The total MFM32 score and the change from original baseline in the total MFM32 score will be also be summarized descriptively for the MFM analysis population at each timepoint by cohort and placebo treatment with age groups (risdiplam 0.02 mg/kg, risdiplam 0.05 mg/kg, risdiplam 0.25 mg/kg, risdiplam 3 mg, risdiplam 5 mg and placebo age $2-11$ years, placebo age $12-25$ years) up to Week 17 for the placebo-controlled period. The 95% confidence interval (CI) of the mean total scores and the mean change from original baseline scores will also be presented at each timepoint.

4.4.2 Respiratory Measures and Analysis of Respiratory Measures

The respiratory tests for Part 1 of the study include the sniff nasal inspiratory pressure (SNIP) and the spirometry tests. The SNIP test will be performed for all patients and the spirometry test will only be performed for patients aged $6-25$ years at screening.

The respiratory measurements obtained will include the SNIP, forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and peak cough flow (PCF) of which FVC, FEV1, and PCF are results obtained from the spirometry tests.

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

The best values (in litres) and the best value expressed as a percentage of the predicted value (best percentage predicted values) for each of the respiratory measurements will be used for the analyses.

For all patients, the best value and the change from adjusted baseline best values, the best percentage predicted values and the change from adjusted baseline best percentage predicted values of SNIP will be summarized at each timepoint by age groups $2-11$ and $12-25$ years, and total for all patients.

For patients aged 6 or above at screening, the best values and the change from adjusted baseline best values, the best percentage predicted values and the change from adjusted baseline best percentage predicted values of FVC, FEV1 and PCF will be summarized at each timepoint for the ITT population by age groups $6-11$ and $12-25$ years, and total for all patients.

The 95% CI of the mean best values, mean best percentage predicted values, mean change from adjusted baseline best values and the mean change from adjusted baseline best percentage predicted values of SNIP, FVC, FEV1 and PCF will also be presented at each timepoint.

4.4.3   <u>Patient- and Parent/Caregiver-Reported Outcomes</u>

The Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scale was developed to assess health-related quality of life (HRQoL) in both healthy and disease populations (Varni et al 1999). The PedsQL 4.0 Generic Core Scale contains 23 items across four domains: Physical (8 items), Social (5 items), Emotional (5 items) and School (5 items) functioning. The PedsQL 3.0 Neuromuscular module was developed specifically for use in neuromuscular diseases including SMA. The measure contains 25 items across three domains: About my neuromuscular disease (17 items), Communication (3 items), and about my family resources (5 items), and the measurement properties have been assessed in SMA patients with supportive evidence identified.

For Part 1 of the study, the PedsQL 4.0 Generic Core Scale will be completed by patients aged 8 years or older and the PedsQL 3.0 Neuromuscular module will be completed by patients aged $8-18$ years.

A parent-reported/caregiver-reported (a parent or caregiver, if no parent is available) version of the PedsQL 4.0 Generic Core scale for all patients age 2 or above and the PedsQL 3.0 Neuromuscular module will also be completed for all patients aged $2-18$ years. The PedsQL 4.0 Generic Core scale and PedsQL 3.0 Neuromuscular module questionnaires assesses the same content across the four domains or three

domains as the patient-reported version as described above. For patients age $2-4$ years, the parent/caregiver-reported PedsQL 4.0 Generic Core scale also assesses the same content across the four domains as for the parent/caregiver reported PedsQL 4.0 Generic Core scale for patients aged 5 years or above, but with a total of 21 items in the scale having only 3 items in the domain for School functioning.

Both the patient and parent/caregiver-reported PedsQL 4.0 Generic Core Scale and PedsQL 3.0 Neuromuscular module data are only collected up to Week 52 visit (up to Week 52 on risdiplam treatment) for all Part 1 patients. For both scales, each item raw score is reversed and converted to a $0-100$ scale, such that for $0=100$, $1=75$, $2=50$, $3=25$, $4=0$, where higher scores indicate better HRQoL. The total score will be calculated as the sum of all the converted item scores over the number of items answered on the scale. If 50% of the items in the scale are missing, the scale score and hence the total score will not be computed.

The patient and parent/caregiver−reported results for the ITT population will be summarized separately.

For patients aged 8 years or above in the patient-reported PedsQL 4.0 Generic Core total score and change from adjusted baseline total score will be summarized as total for all patients (8 years or above) at each timepoint until 12 months on risdiplam treatment. Similarly, for patients aged 8 to 18 years in the PedsQL 3.0 Neuromuscular module, the total scores and the change from adjusted baseline total scores will be summarized by as total for all patients at each timepoint up to 12 months on risdiplam treatment.

For the parent/caregiver reported PedsQL 4.0 Generic Core Scale and the PedsQL 3.0 Neuromuscular module, the total score and the change from adjusted baseline total score will be summarized by age groups of $2-4$, $5-25$ (PedsQL 4.0)/ 5-18 (PedsQL 3.0) years, and total for all patients at each timepoint up to 12 months on risdiplam.

In addition, the number and percentage of patients or parents/caregivers who have scale scores and total scores computed will also be presented at each timepoint.

4.4.4 Disease-Related Adverse Events

The disease related AE and the disease related AE rate per 100 patient-years will be presented.

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

- Narrow prospectively defined baskets of MedDRA lowest level terms. This basket was defined based on a group of CDC terms selected from an age and gender matched case control study comparing CDC code rate observed in patients with and without SMA using commercially available insurance claim data (CLAIMS and

Market scan data). The lowest level terms included in each basket, coded using the latest version of MedDRA.

- Broad prospectively defined basket with events selected at preferred term level from all AEs reported in ongoing clinical trials. For both wide and narrow baskets, terms have been defined for each of the following medical concepts: disease-related AE overall basket, gastro-intestinal disorders, lower respiratory tract infections, respiratory impairment, neuro-musculo-skeletal and connective tissues, nutrition and growth, cardiac not elsewhere classified (NEC) and other NEC.

Note: the same lowest level term/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 based on the narrow term basket will be summarized descriptively and by treatment and/or age groups, and total for all patients for the Day 1 to Week 12 period, and by age groups and total for all patients for the all exposure to risdiplam treatment period and the all exposure to risdiplam pivotal dose treatment period for the 12 months reporting event. For the 24 months reporting event, 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 for the narrow and broad terms baskets for the all exposure to risdiplam treatment period by age groups and total for all patients. Percentages will be based on the number in the safety population.

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 $\div$ total patient-years at risk) $\times 100$.

where the total patient-years at risk is defined as

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

The 95% CI 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.

The disease related AE rate (average number of events) per 100 patient years will be summarized for the placebo-controlled period by treatment and/or age groups, and total for all patients; and summarized by age groups of $2-11$ and $12-25$ years, and total for

all patients for the all exposure to risdiplam treatment period and the all exposure to risdiplam pivotal dose treatment period. For both the all exposure to risdiplam treatment period and the all exposure to risdiplam pivotal dose treatment period, the disease-related AE rate per 100 patient-years will be presented by time unit for every 6 months of 0 to ≤ 6 months, > 6 to ≤ 12 months, > 12 to ≤ 18 months, > 18 to ≤ 24 months, > 24 to ≤ 30 months etc., 0 to ≤ 12, 0 to ≤ 18 months, 0 to ≤ 24 months and for the whole corresponding treatment periods up to clinical cutoff date.

4.4.5 Sensitivity Analysis

As a supportive analysis to assess the robustness of the results, sensitivity analyses will be performed on the Motor Function Measure (MFM), HFMSE and RULM.

For All Exposure to Active Risdiplam Treatment Period at Any Dose Level

The following analyses will be performed for the all exposure to active risdiplam treatment period based on the adjusted baseline.

The total score and change from adjusted baseline total score for each of the analyses below will be summarized descriptively at each timepoint and with 95% CIs on the mean total score and the mean change from adjusted baseline total score presented:

- MFM analyses on the full 32 item scale (MFM32 total scores) , summarized by age group of 2 – 11 and 12 – 25 years, and total for all patients for the entire ITT population. For those who performed the MFM20 at any timepoint will also be included in this analysis by imputing 0 to any missing item scores prior to the calculation of the MFM32 total score.

- MFM analysis on the 20 item scale (MFM20 total scores) only for those patients who have performed the MFM20- item scale confirmed by a protocol deviation, at any time point. These results will be summarized.

- MFM32 analysis based on the MFM analysis population, HFMSE and RULM analyses based on the ITT population, summarized by age group of 2 – 11 and 12 – 25 years, and total for all patients, by excluding the following:

    – Patients with baseline HFMSE total score less than 10 or greater than 54, OR

    – Patients with severe scoliosis at screening. Severe scoliosis is defined as scoliosis with a degree of curve > 40 degree at screening, OR

    – Patients with both of the above.

For All Exposure to Risdiplam at Pivotal Dose Treatment Period

Additional sensitivity analyses will also be performed for the all exposure to active risdiplam pivotal dose treatment period based on the pivotal dose adjusted baseline only for the 12 months reporting event but not for the 24 months reporting event. The following

- MFM32 analysis

- HFMSE analysis
- RULM analysis

FVC analysis (for patients aged 6 or above at screening) will be performed for the ITT population. The total scores/best values and best percentage predicted values, and the change from the pivotal dose adjusted baseline total scores/ best value and best percentage predicted values will be summarized by age group of 2−11 (for MFM, HFMSE and RULM)/6−11(for FVC) and 12−25 years, and total for all patients at each timepoint. The 95% CI of the mean total score, mean best values, mean best percentage predicted values, the mean change from pivotal dose adjusted baseline in the total score, best values and best percentage predicted values will also be presented at each timepoint.

In addition, MFM32 analysis will also be performed on the all exposure to risdiplam at pivotal dose treatment period by excluding those patients who performed the MFM20 scale at any timepoint as confirmed by a protocol deviation. This analysis was only performed for the 12 months reporting event but will not be performed for the 24 months reporting event. The MFM32 total score, change from the pivotal dose adjusted baseline total score and the corresponding 95% CI for the mean total score and change from the pivotal dose adjusted baseline will be also be summarized by age group of 2−11, 12−25 years old, and total for all patients.

4.4.6   Subgroup Analysis

The consistency of the efficacy endpoints for MFM32, HFMSE and RULM will be explored for the following subgroups.

- Age group (2−5, 6−11, 12−17, 18−25 years at randomization)
- SMA Type with ambulatory status (SMA Type 2, SMA Type 3 ambulant, SMA Type 3 non-ambulant)
- SMN2 Copy number (2, 3, 4 or unknown)

The subgroup analyses will be based on the MFM analysis population for the MFM32 and ITT population for the HFMSE and RULM on the all exposure to risdiplam treatment period. The total score and the change from adjusted baseline total score in MFM32, HFMSE and RULM will be summarized at each timepoint. The corresponding 95% CI of the mean total score and mean change from adjusted baseline total score will also be presented at each timepoint. The change from adjusted baseline in the MFM32 total score, HFMSE total score, and RULM total score was and will also be presented in a forest plot for the overall population and by the above 3 subgroups at Month 12 and Month 24, respectively with the corresponding 95% CI of the mean change of adjusted baseline total score.

In addition, the change from adjusted baseline in the MFM32 total score at Month 12 and Month 24 was and will be explored for the following subgroup.

- Investigational sites (for sites with less than 5 patients enrolled will be pooled for analysis)

The above subgroup analyses will also be based on the MFM analysis population for the all exposure to risdiplam treatment period. The change from adjusted baseline in the MFM32 total score was and will also be presented in a forest plot at Month 12 and Month 24 for the overall population and by investigational sites with the corresponding 95% CI confidence interval of the mean change of adjusted baseline in the MFM32 total score.

4.5 PHARMACOKINETIC ANALYSES

Patient exposure to risdiplam and the following parameters will be assessed (if possible, based on the available data):

- 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.

The PK samples are collected as per the SoA in the protocol for all Part 1 patient (Appendix 2).

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

Individual and mean plasma concentration of risdiplam and metabolite(s) versus time data will be tabulated and plotted.

Nonlinear mixed effects modeling (software NONMEM) will be used to analyze the sparse samples of concentration-time data of risdiplam (and its metabolites if deemed necessary). Population and individual PK parameters will be estimated and the influence of various covariates (such as age, gender, body weight, etc.) 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) will be derived from the model for each individual included in the PK analysis and will be presented descriptively.

The details of the modeling and exploratory analyses will be reported in a document separate from the Clinical Study Report (CSR).

4.6 PHARMACODYNAMIC ANALYSES

The PD parameters collected from Part 1 of the study include the in vivo SMN mRNA and SMN protein in blood. The PD samples are collected as per the SoA in the protocol for all Part 1 patients (Appendix 2).

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 of the modeling and exploratory analyses will be reported in a document separate from the CSR.

4.7 PHARMACOECONOMIC ANALYSIS

Analysis of pharmacoeconomic (PE) data (EQ-5D-5L, Work Productivity and Activity Impairment: Caregiver-SMA (WPAI-CG-SMA) and the production of a final PE report will be handled separately from the clinical reports of this study.

Information obtained in this study may be combined with other data such as cost data or other clinical parameters in the production of a final PE report. Details of the PE analyses will be reported in a document separate from the CSR.

4.8 SAFETY ANALYSES

The safety endpoints of SUNFISH Part 1 include, but may not be limited to, the following:

- Incidence of AEs (overall, by severity and by relationship to study medication)
- Incidence of serious AEs (SAEs)
- Incidence of treatment discontinuations due to AEs
- Incidence of deaths
- 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

All patients who receive at least one dose of risdiplam or placebo will be included in the safety population. For Part 1 of the study, all available safety data up to the clinical cutoff date will be reported. Safety data will be summarized for at least one of the following periods:

- Day 1 to Week 12 (Day 84).

- Placebo-controlled period.
- All exposure to risdiplam treatment period
- All exposure to risdiplam pivotal dose treatment period (only for 12 months reporting event)
- Whole treatment period

For the Day 1 to Week 12 period and the placebo-controlled period, safety data will be summarized by treatment and/or age groups, and total for all patients (all risdiplam patients age 2−11 years, all risdiplam patients age 12−25 years, all placebo patients age 2−11 years, all placebo patients age 12−25 years, all patients on risdiplam treatment, all patients on placebo treatment, all patients age 2−11 years old, all patients age 12−25 years old and all patients age 2−25 years old). Selective safety parameters will also be summarized by cohort and placebo treatment for these 2 periods.

For the all exposure to risdiplam treatment period, and the all exposure to risdiplam pivotal dose treatment period (only for 12 months reporting event) , the data will be summarized by age groups of 2−11 and 12−25 years; and total for all patients.

Safety Data Visit Time Window

A time window is defined for each visit, starting midway between the scheduled visit day and the previous study visit day, and ending midway between that visit and the next study visit (if applicable). Results for assessments that are conducted at unscheduled or withdrawal visits will be assigned to the appropriate study visit according to the visit window, even if the assessment is not scheduled to be performed at that visit.

For those initially randomized to and who received placebo, the data after switching to risdiplam treatment will be time-windowed based on the scheduled visits as for those initially randomized to and who received risdiplam treatment. 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 data, except for laboratory data, where the worst record will be selected for summary of the data.

4.8.1 Exposure of Study Medication

The extent of exposure of study medication data will be summarized for the placebo-controlled period, first 24 months all exposure to risdiplam treatment period and the all exposure to risdiplam treatment period separately using descriptive statistics. The extent of exposure to study medication will be summarized by treatment and/or age groups, and total for all patients for the placebo-controlled period, and by age group of 2−11 and 12−25 years, and the all exposure to risdiplam treatment period.

The following extent of exposure of study medication will be included in each of the summary tables:

- Duration of study medication
  - For the placebo-controlled period, this is the duration on any study medication, either placebo or risdiplam, which will be calculated from the first day of the study medication to the last day of study medication during the placebo-controlled period, and is calculated by

Duration of study medication=Date of the last dose $-$ Date of first dose $+1$ (day).

  - The all exposure to risdiplam treatment period, refers to the duration on risdiplam treatment at any dose level, will be calculated similarly as

Duration of risdiplam treatment=Date of the last dose of risdiplam treatment $-$ Date of first dose of risdiplam treatment at any dose level $+1$ (day).

  - For those initially randomized to and who received placebo treatment, the first date of risdiplam treatment (at any dose level) is the date of their individual "Day 1 RO" visit.

    In addition, the duration on the pivotal dose of risdiplam treatment will also be summarized and presented in the summary table for the all exposure to risdiplam treatment period, which is calculated by

Duration of risdiplam treatment at pivotal dose =Date of the last dose of risdiplam treatment at pivotal dose $-$ Date of first dose of risdiplam treatment at pivotal dose $+1$ (day).

- Number and percentage of patients with duration of study medication/risdiplam treatment/risdiplam treatment at pivotal dose grouped by time unit for every 6 months (0 to $\leq$ 6 months, $>$ 6 to $\leq$ 12 months, $>$ 12 to $\leq$ 18 months, $>$ 18 to $\leq$ 24 months, $>$ 24 to $\leq$ 30 months, etc.)
- Number of dose(s) taken
- Number of missed dose(s)
- Number of over-dose(s)
- Number of partial dose(s) taken
- Dose intensity in percentage, which is calculated by

Dose intensity $\% =$ (number of non-missing doses $\div$ number of doses expected for the duration the patient is already on the study) $\times 100$

- The number and percentage of patients with dose intensity $<$ 80% and $\geq$ 80%

Note: 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 and reported.

4.8.2   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 'PT') 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 PT. 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, AEs and SAEs by SOC and PT, AEs by greatest intensity/severity according to the 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 overview summary of AEs and the AEs/SAEs by SOC and PT results will be summarized in 2 ways 1) by cohort and placebo treatment (risdiplam 0.02 mg/kg, risdiplam 0.05 mg/kg, risdiplam 0.25 mg/kg, risdiplam 3 mg, risdiplam 5 mg and all placebo patients) and 2) by treatment and/or age groups, and total for all patients (all risdiplam patients age $2-11$ years, all risdiplam patients age $12-25$ years, all placebo patients age $2-11$ years, all placebo patients age $12-25$ years, all patients on risdiplam treatment, all patients on placebo treatment, all patients age $2-11$ years old, all patients age $12-25$ years old and all patients age $2-25$ years old), for the Day 1 to Week 12 period and the placebo-controlled period.

The most common AEs reported in $\geq 5\%$ and $\geq 15\%$ of patients who receive any treatment 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 results, the number of patients and the number of events will be reported separately in two summary tables.

The AE and SAE rate by PT adjusted for patient years for all occurrences will also be summarized overall for all SOCs, for each SOC and for each PT. The AE and 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 ÷ total patient-years at risk) × 100.

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

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% CI 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/SAE rate. The AE/SAE rate results for the All exposure to risdiplam treatment period or for the all exposure to risdiplam pivotal dose treatment period will be presented by time unit for every 6 months of 0 to ≤6 months, >6 to ≤12 months, >12 to ≤18 months, >18 to ≤24 months, >24 to ≤30 months, etc., 0 to ≤12 months, 0 to ≤18 months, 0 to ≤24 months and for the whole corresponding treatment periods up to clinical cutoff date.

The AE by greatest intensity/severity rate adjusted per 100 patient years and the AE related to study drug rate adjusted per 100 patient years will also be presented for the all exposure to risdiplam treatment period by time unit for every 6 months of 0 to ≤6 months, >6 to ≤12 months, >12 to ≤18 months, >18 to ≤24 months, >24 to ≤30 months, etc., 0 to ≤12 months, 0 to ≤18 months, 0 to ≤24 months and for the whole corresponding treatment periods up to clinical cutoff date.

AEs of Special Interest will also be listed. The AEs of special interest are defined in the protocol.

Table 2 provides an overview of the treatment periods that will be used to summarize AEs as described above.

Table 2   Overview of Analysis Treatment Periods for Adverse Events

	Day 1 to Week 12 period	Placebo-controlled period	All exposure to risdiplam treatment period	All exposure to risdiplam at pivotal dose treatment period [c]
Overview summary of AEs/SAEs	✓[e]	✓	✓	✓
AEs/SAEs by PT	✓[e]	✓	✓	✓
AEs by intensity (grade)		✓	✓	✓
AEs related to study medication		✓	✓	✓
AEs leading to study medication adjustment			✓	✓
AEs leading to withdrawal of study treatment			✓	✓
AE outcomes			✓	✓
Most common AEs reported in ≥ 5 % and ≥15% of patients who receive any treatment			✓	✓
AE/SAEs rate per 100 patient years		✓	✓	✓
AEs by intensity rate per 100 patient years			✓	
AE s related to study drug rate per 100 patient years			✓	

AE = adverse event; PT = Preferred Term; SAEs = serious adverse event.

[e] will be grouped by 1) cohort and placebo treatment and 2) grouped by treatment and/or age groups, and total for all patients

[c] Only for the 12 months reporting event. Analyses will not be performed for the 24 months reporting event

Note: All available data at the time of the clinical cutoff date will be reported. All AE records with a start date on or before the clinical cutoff date will be included in the data cut.

- **Day 1 to Week 12 period**. For all patients, this will include the AEs with onset during the first 84 days on study medication, placebo or risdiplam; or existing AEs which worsen in intensity during the first 84 days on study medication, specifically:

    – with onset date on or after the first day of administration of the study medication (placebo or active Risdiplam) (Day 1); OR

    – with onset date prior to the first dose day (Day 1), is unresolved, and the most extreme intensity is worse than the initial intensity;

and up to the earliest date of study withdrawal during the Day 1 to Week 12 period or before dose administration on Day 85 for each individual.

- **Placebo-controlled period**. For all patients, this will include the AEs with onset during the placebo-controlled period or existing AEs which worsen in intensity during the placebo-controlled period, specifically:

    – with onset date on or after the first day of administration of the study medication (placebo or active risdiplam) (Day 1); OR

    – with onset date prior to the first dose day (Day 1), is unresolved, and the most extreme intensity is worse than the initial intensity;

and up to the earliest date of study withdrawal during the placebo-controlled period or before dose administration of risdiplam treatment on the completion date of the placebo-controlled period as provided in the eCRF for each individual patients.

- **All exposure to risdiplam treatment period**. For all patients, this includes the AEs with onset during their active risdiplam treatment period at any dose level or existing AEs which worsen in intensity during their active risdiplam treatment period, specifically:

    – with onset date on or after the first active risdiplam treatment at any dose level; OR

    – with onset before the first risdiplam treatment at any dose level, is unresolved, and the most extreme intensity is greater than the initial intensity;

and up to the earliest date of study withdrawal during their all exposure to risdiplam treatment period.

- **All exposure to risdiplam pivotal dose treatment period (only for the 12 months reporting event).** For all patients, this will include the AEs with onset during their active risdiplam pivotal dose treatment period or existing AEs which worsen in intensity during their active risdiplam pivotal dose treatment period, specifically:

    – with onset date on or after the first active risdiplam treatment at the pivotal dose; OR

    – with onset date before the first risdiplam treatment at the pivotal dose, is unresolved and the most extreme intensity is greater than the initial intensity.

- **Follow-up period:** This only applies to any patient who discontinues treatment and /or withdraws from the study early at any time during Part 1 of the study. This includes the AEs for which
  - the onset date is from 1 day (Day 1 follow up) and up to 52 weeks after study withdrawal/completion; OR
  - the onset date is before Day 1 follow up, is unresolved and the most extreme intensity is greater than the initial intensity during their follow-up 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, AE related to study medication, AE by intensity and AEs resulting in death. Listings will also be presented for AEs of special interest and AEs of special interest rate during the all exposure to risdiplam treatment period.

All AEs results during the follow-up period will be listed.

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.

4.8.3   Deaths

Individual patient listings will be presented with all the details for patients who died at any time during Part 1 of the study and up to 52 weeks after study withdrawal/completion. 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.

4.8.4   Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Data will be presented using the International System of Units (SI units;

Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing. The normal ranges of all laboratory parameters are based on central laboratory ranges. 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 range and will be labeled "H" for high or "L" for low. The number and percentage of patients with abnormality results (in the direction of abnormality) will also be summarized by treatment and/or age groups, and total for all patients for each laboratory parameter at each time point for the whole treatment period. The change from baseline values for parameters of hematology, creatinine phosphokinase, creatinine, blood urea nitrogen, and transaminase will also be summarized at each timepoint by treatment and/or age groups, and total for all patients (all risdiplam patients age $2-11$ years, all risdiplam patients age $12-25$ years, all placebo patients age $2-11$ years, all placebo patients age $12-25$ years, all patients on risdiplam treatment, all patients on placebo treatment, all patients age $2-11$ years, all patients age $12-25$ years, and all patients age $2-25$ years) for the whole treatment period.

Shift tables to compare the status at original baseline to each timepoint (each scheduled assessment visit) post-baseline will also be summarized by treatment and/or age groups, and total for all patients for the whole treatment period.

Patients with Elevated Post-Baseline AST or ALT Levels results at baseline and at post-baseline timepoints will be summarized by treatment and/age groups, and total for all patients for the whole treatment period. All urinalysis test results will also be listed.

Data collected during safety follow-up will be listed.

4.8.5   Vital Signs

Vital signs measured throughout the study will include systolic and diastolic blood pressure (SBP and DBP) in millimeter of mercury (mmHg), pulse rate (beats per minute), respiratory rate (breaths per minute) and body temperature in degree Celsius (°C). The normal ranges for each vital sign parameter are based on the age of the patient at the time of assessment. The vital signs data will be listed for patients with abnormal values or values outside the normal ranges. The number and percentage of patients with abnormal values (in the direction of abnormality) will also be summarized by treatment and/or age groups, and total for all patients (all risdiplam patients age $2-11$ years, all risdiplam patients age $12-25$ years, all placebo patients age $2-11$ years, all placebo patients age $12-25$ years, all patients on risdiplam treatment, all patients on placebo treatment, all patients age $2-11$ years, all patients age $12-25$ years, and all patients age $2-25$ years) for each vital-sign parameter at each timepoint for the whole treatment period.

Shift tables to compare the status at original baseline to each timepoint (each scheduled assessment visit) post-baseline will be summarized similarly by treatment and/or age groups, and total for all patients for the whole treatment period.

Data from the follow-up period will be listed.

Table 3 shows the normal ranges of each vital sign parameters by age.

Table 3   Normal Ranges of Vital Signs Parameters by Age

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

4.8.6   Electrocardiogram Data Analysis

The 12-lead ECG recordings are obtained in triplicate pre-dose at each scheduled assessment timepoint for Part 1 of the study.

If the ECG assessment is performed at a scheduled assessment timepoint and the results are not interpretable and recorded as 'NA', these results will not be included in the ECG analysis.

Time matched ECG assessments are performed in patients ≥ 12 years of age on Day 28 (Week 4), 56 (Week 8) and 609 (Week 87 on risdiplam treatment) at pre-dose, 1, 2, 4 and 6 hours post-dose. In patients below 12 years of age, only a pre-dose ECG is to be obtained; no post-dose ECGs are required unless the Investigator deems them necessary for safety. Triplicate ECG assessment results are obtained at each scheduled timepoint and hours as specified in the SoA in the protocol.

The baseline value of each ECG parameter will be defined as the average of all available records at the last timepoint prior to the first dose of study medication (Note: all patients should have performed the pre-dose ECG assessment on Day 1. The baseline value will be the average of all available records at pre-dose on Day 1 for each ECG parameter).

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

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 or values outside the normal ranges. The number and percentage of patients with abnormality results (in the direction of abnormality) will also be summarized for each ECG parameter at each timepoint (and at each hour if time matched ECG assessment results are available) by treatment and/or age groups, and total for all patients (all risdiplam patients age 2−11 years, all risdiplam patients age 12−25 years, all placebo patients age 2−11 years, all placebo patients age 12−25 years, all patients on risdiplam treatment, all patients on placebo treatment, all patients age 2−11 years, all patients age 12−25 years, and all patients age 2−25 years) for the whole treatment period.

Triplicate and average ECG results of any abnormalities will also be listed, where the average ECG result is defined as the average of any non-missing and non-zero triplicate measurements.

The numerical ECG results and the change from baseline values for each of the ECG parameters will also be summarized by treatment and/or age group and total for all patients for the whole treatment period. Shift tables for each of the ECG parameters, PR duration, QT duration, QRS duration, RR duration, QTcB, QTcF, T-wave, U-wave and interpretation (ECG result) to compare the status at original baseline to each timepoint post-baseline will also be summarized by treatment and/or age groups, and total for all patients for the whole treatment period.

Table 4 shows the normal ranges of each ECG variable by age.

Table 4   Normal Ranges of ECG Parameters by Age

	Age (years)			
	2 to ≤6	**6 to ≤8**	**8 to ≤12**	**>12**
ECG Parameters				
Heart Rate (beats/min)	70−130	60−110	55−100	50−100
PR duration (ms)	80−160			120−200
QT Duration (ms)	260−390			200−500
QRS Duration (ms)	40−90			80−120
RR Duration (ms)	460−860	450−1000	600−1090	600−1500
QTcF (ms)	380−450			300−450
QTcB (ms)	380−450			300−450

The number and percentage of patients with ECG parameter values within each of the ranges given in Table 5 will be summarized by treatment and/or age groups, and total for all patients at each timepoint and hours (for available time-matched ECG assessment results) (all risdiplam patients age 2 – 11 years, all risdiplam patients age 12 – 25 years, all placebo patients age 2 – 11 years, all placebo patients age 12 – 25 years, all patients on risdiplam treatment and all patients on placebo treatment) for the whole treatment period.

Data collected from the follow-up period will be listed.

Table 5   Ranges of ECG Parameters for Summary Tables

	Raw Value	**Change from Baseline Value**
ECG Parameters		
PR duration (ms) ≤12 years old >12 years old	≤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

4.8.7   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 is used for children (aged 6 – 11 years). The C-SSRS assessments results are collected at baseline and at timepoints specified as per the SoA 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 timepoint once they reach 6 years of age. No baseline C-SSRS assessment results will be available for these patients. Missing data will not be imputed.

The number and percentage of patients with

- 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

will be summarized for all patients with at least 1 post-baseline measurement regardless of whether they have a baseline measurement or not. Results will be summarized by age groups of $6-11$, $12-25$ years, and total for all patients for the whole treatment period. The number and percentage of patients with at least one post-baseline assessment will also be presented in the summary.

For those patients aged 5 years or below at baseline and reach 6 years at any time during the study, all available post-baseline C-SSRS assessment results will be listed.

Shift tables to demonstrate the change in C-SSRS endpoints (suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent) from original baseline will be presented for all patients with a (original) baseline measurement and at least one post-baseline measurement. Shift table will be presented by treatment and/or age groups, and total for all patients (all risdiplam patients age $6-11$ years, all risdiplam patients age $12-25$ years, all placebo patients age $6-11$ years, all placebo patients age $12-25$ years, all patients on risdiplam treatment, all patients on placebo treatment, all patients age $6-11$ years, all patients age $12-25$ years, and all patients age $6-25$ years) at each timepoint for the whole treatment period.

Results for those patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent will be listed. 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 will be listed.

4.8.8 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, the Sloan Low Contrast Test, visual field threshold perimetry assessment and the simple visual field tests.

Overview profile of the ophthalmology assessment results will be summarized (overview summary table). 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 treatment and/or age groups, and total for all patients for the placebo-controlled period and by age groups of 2–11 and 12–25 years, and total for all patients for the all exposure to risdiplam treatment period. 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 timepoint, this will only be counted once.

Overview profile of the ophthalmology assessment results in the 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/timepoint 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 or 4) end of study 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 potentially clinically significant results at the last assessment visit and the total number of abnormal or potentially clinically significant results at the last assessment visit will be summarized. Results will be summarized by treatment and/or age groups, and total for all patients for the placebo-controlled period and by age groups of 2 – 11 and 12 – 25 years, and total for all patients for the all exposure to risdiplam treatment period.

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 timepoint/visit (summary table by visit). The number and percentage of patients with at least one abnormal or potentially clinically significant results and the total number of abnormal or potentially clinically significant results will be summarized at each timepoint for each ophthalmology assessment (except SD-OCT) and overall for all ophthalmology assessments. These results will be summarized by treatment and/or age groups, and total for all patients for the whole treatment period. The number of patients who completed the assessment at each visit will also be presented in each table.

A separate summary table by visit will also be presented for SD-OCT. Ophthalmological visits are performed every 2 months throughout the study and always comprised SD-OCT assessments. The number and percentage of patients with at least one abnormal or potentially clinically significant SD-OCT results and the total number of abnormal or potentially clinically significant SD-OCT results will be summarized at each timepoint (presented at least for every 2 months) by treatment and/or age groups for the whole treatment period. The number of patients who reached a visit, the number and percentage of patients who completed the SD-OCT assessment 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 (original baseline) values will be summarized under each ophthalmology assessment for each parameter for each eye at each timepoint by treatment and/or age groups for the whole treatment period.

Data collected in any of the ophthalmological assessments (see Section 4.8.8.1.1 to Section 4.8.8.3.4) during safety follow-up will be listed.

Listings will also be presented for all patients with an abnormal or potentially clinically significant results in any of the ophthalmology tests.

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

4.8.8.1 Ophthalmological Examination

This will include the slit-lamp examination, fundus examination, visual testing (including the Bruckner red reflex, corneal reflex, cover/uncover examination) and the intraocular pressure assessment.

4.8.8.1.1 Ocular Examination (Slit-Lamp)

The slit-lamp examination will be performed in all patients across all age groups.

An abnormal or potentially clinically significant results 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 results 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.

4.8.8.1.2 Fundus Examination

The fundus examination assessment will be performed in all patients across all age groups. An abnormal or potentially clinically significant result in fundus examination is defined as:

- A clinically significant change (worse) from baseline (as assessed by local ophthalmologist) results; or

- An abnormal result; or

- A retinal break; or

- A retinal detachment

- For patients with a results 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.

4.8.8.1.3 Ocular Examination (Visual Testing)

This assessment will be performed in patients aged 10 years or younger. 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 local ophthalmologist) results; 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, and description and comments related to any of the above criteria will be listed.

4.8.8.1.4 Intraocular Pressure Assessment

The intraocular pressure assessment will be performed in all patients across all age groups. For assessment method other than 'digital palpation', the assessment results will be reported in continuous value in unit 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 visual testing 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 $\leq$ -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; for method of "digital palpation", the parameter, and actual result for each parameter will be listed, for methods other than "digital palpation", the actual numerical results and the baseline value and the change from baseline values will be listed.

4.8.8.2 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.

4.8.8.2.1 Optical Spectral Domain-Optical Coherence Tomography (SD-OCT)

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

- A clinically significant change from baseline 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.

4.8.8.2.2 Fundus Photography

The fundus photography or the funduscopy will be performed in all patients across all age groups. An abnormal or potentially clinically significant results in the fundus photography is defined as:

- A clinically significant change from baseline 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' results 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.

4.8.8.2.3 Fundus Auto-Fluorescence

The fundus auto-fluorescence examination was introduced when Part 1 of the study was initiated and performed in all patients across all age groups. Since Protocol Version 3 (rest of the world), the FAF examination has been removed and is not required to be performed in patients in the rest of the world population (Patients enrolled in countries other than in the United States). 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 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.

4.8.8.3 Visual Function

This will include the best corrected visual acuity (BCVA) test, the fix and follow test, the Sloan low contrast test, visual field threshold perimetry assessment and the simple visual field test.

4.8.8.3.1 Best Corrected Visual Acuity and Fix and Follow Tests

The BCVA test will be performed in all patients across all age groups. For those aged 10 years or under and 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 "ETDRS" or "Patti Pics", a decrease of more than or equal to 9 optotypes (i.e. letters or symbols) that could be read compared to baseline. (i.e., change from baseline in the number of optotypes that could be read of ≤ -9); or

- For method 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) from baseline result; or

- An abnormal result.

For patients with a result meeting at least one of these criteria above, all results including the method used (ETDRS, Patti Pics, Off Chart), the parameter, the actual result of each parameter; for ETDRS and Patti Pics, the total number of 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.

4.8.8.3.2   Sloan Low Contrast Test

The Sloan low contrast test was introduced when Part 1 of the study was initiated and performed in all patients across all age groups. Since Protocol Version 3 (rest of the world), the Sloan low contrast test has been removed and is not required to be performed in patients in the rest of the world population (patients enrolled in countries other than in the United States).All available Sloan low contrast test assessment results will be reported.

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 $\leq$ -7 in the total number of letters that could be read correctly)

- 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.

4.8.8.3.3   Visual Field Threshold Perimetry

The visual field threshold perimetry assessment will be performed in all adults, adolescents and cooperative children > 10.

An abnormal or potentially clinically significant result for the Visual Field Threshold Perimetry test is defined as

- A clinically significant change from baseline 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.

4.8.8.3.4   Simple Visual Field Test

This assessment will be performed in all patients aged 10 years or younger, or in other patients who cannot perform the visual field threshold perimetry assessment.

An abnormal or potentially clinically significant result from the Simple Visual Field test is defined as:

- A clinically significant change (worse) from baseline 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.

4.8.9   <u>Anthropometric Examination</u>

The actual value and change from baseline values for body weight, height, ulna length (if available), and BMI will be summarized at each post-baseline timepoint by treatment and/or age groups, and total for all patients for the whole treatment period. For patients aged up to 5 years , the actual value and the change from baseline of head circumference values at each timepoint will also be summarized as total for all applicable patients.

The following formulae were used to derive the height of the patient with their ulna length measured:

- In patients aged 2 − 18 years, formulae 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

- In patients aged 19–25 year old, MUST formulae (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)]

The WHO child growth standards (2006) will be used to summarize the percentile and the change from baseline percentile for the weight-for-age, length/height-for-age, head circumference-for-age and BMI-for-age for patients aged 2 up to 5 years inclusively. In addition, the World Health Organization (WHO) growth reference data (2007) will be also be used to summarize the percentile and the change from baseline percentile for the length/height-for-age, BMI-for-age for patients aged above 5 to 19 years old, and for the weight-for-age in patients aged above 5 to 10 years old.

Since the WHO growth reference data for weight-for-age is not available for patients above 10 years of age and also not available for patients above 19 years old for length/height-for-age, BMI-for-age, the percentile for length/height-for-age and BMI-for-age will only be presented up to 19 years old, and the percentile for head circumference-for-age will only be presented up to 5 years old.

The percentile and the change from baseline percentile for the weight-for-age, length/height-for-age and BMI for age will be summarized at each timepoint by treatment and/or age groups, and total for all patients for the whole treatment period. For the head circumference-for-age, the percentile and the change from baseline percentile will summarized at each timepoint for the whole treatment period.

For the weight-for-age length/height-for-age, head circumference–for-age, and BMI-for-age, the number and percentage of patients within each of the category of percentiles (<3rd, ≥3rd to <5th, ≥5th to <10th, ≥10th to <25th, ≥25th to <50th, and ≥50th) will be summarized by treatment and/or age groups, and total for all patients for the whole treatment period.

Shift tables for weight-for-age, length/height-for-age, head circumference-for-age, and BMI-for-age to compare the percentile at baseline (<3rd, ≥3rd to <5th, ≥5th to <10th, ≥10th to <25th, ≥25th to <50th, and ≥50th) to each timepoint post-baseline will be summarized by treatment and/or age groups and total for all patients for whole treatment period.

4.8.10 Neurological Examination

Examination will be performed by asking questions to the patient and his/her 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, friend, activities, job

as appropriate), memory (e.g., with short word recall), reasoning and language, drawing, etc.

Individual patient listings will be provided which contain all results for patients who have 'Neurological condition not expected with SMA'.

4.8.11 Tanner Staging

Tanner staging will be determined at the baseline and at Week 104 in all patients age $9 - 17$ years old.

The tanner staging results at baseline will be summarized separately by gender. The number and percentage of patients who performed the tanner staging assessment and the number and percentage of patients with tanner staging results within each stage (categorized by Stage I to Stage V) at baseline and at post-baseline timepoint(s) will be presented for all applicable patients. Similar results may also be summarized at baseline and at post-baseline timepoint(s) for patients aged 12 years or above at enrollment.

The median ages and the age ranges of patients within each stage of the staging assessment results at baseline and post-baseline timepoint(s) may be also be presented by treatment and/or age group and total for all applicable patients.

In addition, results of delayed puberty will also be summarized for the whole treatment period. Delayed puberty is defined as follows:

- For girls ≥ 13 years old with a tanner stage of < 2
- For boys ≥ 14 years old with a tanner stage of < 2

The number and percentage of patients with Delayed puberty will be presented at each timepoint by treatment and/or age group and total for all applicable patients for the whole treatment period.

Lisiting will be provided which contains all results of the tanner staging and delayed puberty.

A shift table to compare the pubertal status (Normal, Delayed and Missing) at original baseline to each timepoint post-baseline may also be summarized by treatment and/or age group and total for all applicable patients for the whole treatment period.

4.9 MISSING DATA

No imputation will be applied for missing data for any of the safety variables. The handling of missing data for the efficacy variables is described in corresponding sections within this SAP.

5. ANALYSES TO COMPARE SUNFISH PART 1 DATA WITH EXTERNAL COMPARATORS

Analyses will be undertaken to compare the mean change from baseline in MFM total score at Month 24 on risdiplam treatment at any dose level in SUNFISH Part 1 to changes observed in an external comparator group of patients. This SAP will only document the analyses on the comparisons at Month 24 and the analyses results will be documented separately from the CSR.

5.1 DATA SOURCES FOR EXTERNAL COMPARATOR

The external comparator population will be selected from:

Natural History Study (BP29540)

The NatHis-SMA study is a European, prospective, multicenter, longitudinal natural history study of Type 2 and Type 3 SMA patients conducted at 9 reference centers for neuromuscular diseases in France, Belgium and Germany between May 2015 and May 2018. The study is an investigator-sponsored, Roche-supported study run by the French Institute of Myology (BP29540; NCT02391831). The primary objective of this study is to characterize the disease course in SMA Type 2 and Type 3 patients using standardized evaluations, including the MFM. The study included 81 patients aged between 2 and 29 years. The maximum duration for participation for each patient was 24 months and all patients were evaluated every 6 months.

Olesoxime Study (WN29836)

Study WN29836 was a Phase II, placebo-controlled, randomized, adaptive, parallel group, double-blind, multicenter study, designed to assess the efficacy and safety of olexosime 10 mg/kg q.d. over a period of 2 years (104 weeks), in 3- to 25-year-old patients with Type 2 or non-ambulant Type 3 SMA. Only the placebo arm of this study will be utilized in this analysis.

The study enrolled 165 patients (57 randomized to placebo) aged between 3 and 25 years from sites in Belgium, France, Germany, Italy, the Netherlands, Poland, and the United Kingdom.

5.2 STATISTICAL METHODS

The external comparator population will be selected to match the SUNFISH Part 1 ITT population (defined as all randomized patients regardless of whether they received treatment or not) based on key inclusion/exclusion criteria. All patients with Type 2 or Type 3 (ambulant or non-ambulant) with an MFM assessment at baseline and also with at least one post-baseline assessment at Month 12 or Month 24 will be included in the external comparator population and will be included in the analysis.

Although all patients in SUNFISH Part 1 were to be assessed using MFM32 regardless of age, patients under the age of 6 in NatHis-SMA study and the placebo group of Study WN29836 were assessed using MFM20 and patients aged 6 and over were to perform MFM32. In order to use the MFM data from all patients and to enable MFM scores to be compared to external controls across all ages, data from patients who completed the MFM32 and those who completed the MFM20 need to be placed onto the same scale. The MFM32 and MFM20 will be transformed onto a 0–100 scale and the resulting score is defined as the 'MFM Total Score'. The change from baseline in the MFM total score will be derived based on MFM32 for all patients aged 6 years or above and MFM20 for all patients aged less than 6 years old; for visits where the MFM32 was used in patients aged less than 6 years, the 12 additional items will not count towards the scoring algorithm.

5.2.1 Inverse Probability of Treatment Weighting

Inverse probability of treatment weighting (IPTW) will be used to create a pseudo-population with similar covariate distributions in the treated and untreated groups. A propensity score will be estimated for each patient using logistic regression incorporating potential predictors of treatment assignment (risdiplam vs no risdiplam) as independent variables. The potential predictors to be included in the model will be age at enrollment (years), SMA type (Type 2 and Type 3), ambulatory status (non-ambulant or ambulant), baseline MFM total score, presence of scoliosis at baseline (Y/N), SMN2 copy number (2,3,4) and the MFM scale used in this analysis (MFM32 for aged $\geq$ 6 years, MFM20 for aged <6 years). Patients with missing data for at least one prognostic factor are excluded from the analysis. In addition, patients with missing total MFM score at baseline and Month 12 or Month 24 will be excluded.

Trimming will be applied to include only patients with an overlapping distribution of propensity scores. IPTW will be applied to the propensity scores to derive weights only in the external control group based on the average effect for treated patients (ATT) approach. To control for too much influence of patients with very low propensity scores, weights will be truncated at the 99th percentile.

Data for any patients in SUNFISH who are excluded from the analysis following trimming will be presented separately in a listing.

5.2.2 Variable Balance Assessment

The variance balance between the treated and untreated groups will be assessed pre and post-weighting. Pre- and post-weighted propensity scores will be presented graphically and standardized mean differences (SMDs) will be computed for all covariates and will be summarised and presented graphically. Adequate balance will be assumed if all SMDs are less than 0.25 (Stuart 2010) but the impact of variables with SMDs >0.1 will be assessed.

If adequate balance is not achieved (at least 1 SMD >0.25), an alternative approach such as matching SUNFISH to the external comparator group using coarsened exact matching may be applied to explore whether better balance can be obtained.

5.2.3   <u>Statistical Analysis</u>

The baseline characteristics will be presented for the weighted and unweighted groups.

Descriptive statistics will be presented for the change from baseline in MFM total score at Month 24 for the weighted and unweighted groups. In addition, the change from baseline in the MFM total score at Month 24 will be analyzed using the Mixed Model Repeated Measure (MMRM) model. For this MMRM analysis, patients with baseline and at least one post-baseline timepoint at Month 12 or Month 24 MFM total score will be included in the analysis. This mixed-effect model will contain components for fixed effects, random effects and the random error term. The dependent variable of this model is the absolute change from baseline in the total MFM score. The independent variables will include treatment, baseline MFM total score, time (time of assessment, i.e., the study visits in weeks [Weeks 52, 78, and 104 –categorical], treatment –by-time interaction, baseline-by-time interaction, age at enrollment, SMA Type, ambulatory status, SMN2 copy number, MFM scale used and presence of scoliosis at baseline. The random effect will include the subject/patient effect. Time will be a repeated variable within a patient (random effects). Patient, treatment, time, SMA Type, ambulatory status, SMN2 copy number, MFM scale used and presence of scoliosis at baseline will be treated as factors variables, and baseline MFM total score and age at enrollment as covariates.

If the model does not converge by including all the independent variables as described above, only selective independent variables will be included in the MMRM model. These selective independent variables will include treatment, baseline MFM total score, time, MFM scale used, presence of scoliosis, treatment–by–time and baseline score-by time interaction; of which baseline MFM total score, treatment, MFM scale use and presence of scoliosis, are covariates that were statistically significant (with p-value ≤ 0.05) previously at the 12 months reporting event based on an ANCOVA analysis.

An unstructured variance-covariance matrix will be applied to model the within-patient variability in the MMRM model. The components of variance and covariance matrix will be estimated by the restricted maximum likelihood method. Denominator degrees of freedom will be estimated using the Kenward–Roger approximation (2009). If the model which includes selective covariates does not converge, a heterogeneous autoregressive variance-covariance matrix will then be applied to model the within-patient variability in the MMRM model. The Statistical Analysis System (SAS) code for this MMRM analysis is included in Appendix 5.

The least square mean (LS mean) change from baseline in MFM total score, treatment difference and 95% CI at all timepoints up to Month 24 will be also be presented for the

weighted and unweighted groups. The LS means and the corresponding 95% CI on the change from baseline in MFM total score at each timepoint up to Week 104 will also be plotted by treatment group for the weighted and unweighted groups.

Descriptive statistics for the proportion of patients who achieved an improvement which is also a change from baseline of ≥ 0, ≥ 1, ≥ 2, ≥ 3, ≥ 4 in the total MFM score at Month 12 and at Month 24 will be presented for the weighted and unweighted groups. The proportion of patients who achieve an improvement of change from baseline of ≥ 0 and ≥ 3 in the total MFM score at Month 24 will be analyzed using a logistic regression model. This model will include treatment, MFM total baseline score and age at enrollment as covariates, and SMA type, ambulatory status, SMN2 copy number, MFM scale and presence of scoliosis as factors. The odds ratio and 95% CI will be reported. The proportion of the responders for summary table and the logistic regression analysis above will be based on all patients with available MFM total score at both baseline and Month 24.

A scatter plot of the individual changes from baseline will be presented for the MFM total score at Month 24 for the unweighted group. In addition, scatter plots of the MFM total score (MFM20 or MFM32 total score) will also be presented separately for patients with the MFM20 total score which are those patients aged <6 years old at enrollment and for patients with the MFM32 total scores which are those patients aged ≥ 6 years old at enrollment.

5.2.4 <u>Subgroup Analyses</u>

Subgroup analysis will also be performed for the change from baseline in the MFM total score at Month 24 for the following age groups:

- ≥ 2 years to <6 years
- ≥ 6 years to <16 years
- ≥ 16 years

The results from the subgroup analysis will be presented in forest plots for the weighted group with the overall treatment difference and 95% CI.

The main analysis will be based on a comparison of SUNFISH Part 1 with the pooled external control data.

5.2.5 <u>Sensitivity Analyses</u>

Sensitivity analysis will also be performed by comparing the SUNFISH Part 1 results with each of the external control groups separately, that is, for

- SUNFISH Part 1 versus NatHis-SMA study
- SUNFISH Part 1 versus placebo arm of Study WN29836 (based on non-ambulant patients only)

Responder analyses will also be performed by considering patients with missing MFM total score at Month 24 as non-responders. The proportion and percentage of patients who achieved an improvement of a change from baseline of ≥0, ≥1, ≥2, ≥3, ≥4 in the total MFM score at Month 24 will be summarized for the weighted and unweighted groups. The proportion of patients who achieve an improvement of a change from baseline of ≥0 and ≥3 in the total MFM score at Month 24 will also be analyzed using the same logistic regression model as defined in Section 5.2.3 The odds ratio and 95% CI will be reported. These two analyses will be performed by comparing the SUNFISH Part 1 results with the entire external comparator population, and also by comparing the SUNFISH Part 1 results separately with NatHis-SMA study (Study BP29540) or with placebo arm of Study WN29836 (non-ambulant patient) study for the weighted and unweighted groups.

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Appendix 1
Protocol Synopsis

TITLE: A TWO PART SEAMLESS MULTI-CENTER RANDOMIZED PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND EFFICACY OF RO7034067 IN TYPE 2 AND 3 SPINAL MUSCULAR ATROPHY PATIENTS

PROTOCOL NUMBER: BP39055

VERSION: 4

Eudract Number: 2016-000750-35

IND NUMBER: 128972

TEST PRODUCT: RO7034067

PHASE: II

INDICATION: Type 2 and 3 spinal muscular atrophy

SPONSOR: F. Hoffmann-La Roche Ltd

OBJECTIVES

Primary Objective:

The primary objectives for the study are as follows:

Part 1

To evaluate the safety, tolerability, PK and PD of RO7034067 in patients with Type 2 and Type 3 (ambulant or non-ambulant) spinal muscular atrophy (SMA), and to select the dose for Part 2 of the study.

Part 2

To evaluate efficacy of RO7034067 compared to placebo in terms of motor function in Type 2 and non-ambulant Type 3 SMA patients, as assessed by the change from baseline in the total score of the motor function measure (MFM) at 12 months.

Secondary Objectives

There are no secondary objectives for Part 1 of this study.

Secondary objectives for Part 2 are as follows:

To investigate the PK/PD relationship of RO7034067 by PK/PD modeling (PD to include *SMN2* mRNA and survival of motor neuron [SMN] protein).

To investigate the efficacy of 12-month treatment with RO7034067 in terms of motor function as assessed by the Hammersmith functional motor scale expanded (HFMSE) *and* the revised

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upper limb module (RULM)

- *To investigate the efficacy of 12-month treatment with RO7034067 in terms of responder analyses of the MFM, HFMSE, and RULM*

To investigate the efficacy of 12-month treatment with RO7034067 in terms of respiratory function as assessed by sniff nasal inspiratory pressure (SNIP) and, in patients aged 6 years and older, by maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and peak cough flow (PCF).

To investigate the proportion of patients who experience a pre-specified disease-related adverse event by Month 12.

To investigate the efficacy of 12-month treatment with RO7034067 in terms of global health status as assessed by the Clinical Global Impression of Change (CGI-C).

To investigate the efficacy of 12-month treatment with RO7034067 in terms of patient-reported and caregiver-reported independence, as measured by the SMA Independence Scale (SMAIS).

To investigate the safety and tolerability of RO7034067 treatment.

Exploratory Objectives

The exploratory objectives for this study are as follows:

Part 1

To investigate the PK/PD relationship of RO7034067 by PK/PD modeling (PD to include *SMN2* mRNA and SMN protein).

To explore the effect of RO7034067 on motor function, respiratory function, and pre-specified adverse events (in terms of proportion of patients experiencing them) and patient-reported QOL measures, in line with the secondary objectives of Part 2.

Part 2

To investigate efficacy of RO7034067 treatment beyond 12 months in terms of motor function as assessed by the MFM, the HFMSE and the RULM.

To investigate efficacy of RO7034067 treatment beyond 12 months in terms of respiratory function as assessed by SNIP, MIP, MEP, FVC, FEV1 and PCF.

To investigate the proportion of patients who experience pre-specified disease-related adverse events beyond Month 12 of treatment.

To investigate the efficacy of RO7034067 beyond 12 months in terms of patient-reported and caregiver-reported independence, as measured by the SMA Independence Scale (SMAIS).

Other exploratory objectives of the study include:

To assess the impact of RO7034067 treatment and conduct economic modeling on caregiver resource use and health-related quality of life using the Work Productivity and Activity Impairment: Caregiver (WPAI:CG) and the EQ-5D-5L, respectively.

To explore the correlation of motor function, and pulmonary function measures (as appropriate) with in vivo *SMN2* mRNA and SMN protein in blood.

To assess the taste of the RO7034067 oral solution.

STUDY DESIGN

Description of Study

The study consists of two parts:

Part 1 is a double-blinded, placebo-controlled, dose-finding part. Patients will be randomized to RO7034067 active treatment or placebo (2:1 ratio), administered once daily.

Enrollment will start with the first cohort of Group A (i.e., adult and adolescent patients [age 12–25 years]).

Once RO7034067 at the first dose level has been shown to be safe and well-tolerated for at

least 4 weeks in a minimum of 3 adolescent patients (age 12-17 years) on active treatment, enrollment will be opened to the first cohort of younger patients (Group B, age 2-11 years). The first dose administered to both age groups will target an AUC0-24h,ss of 700 ng • h/milk

Safety and tolerability at this first dose level will be confirmed for the respective age groups based on at least 4-week treatment duration in all patients of the cohort (i.e., patients enrolled first will have longer treatment duration). Once safety and tolerability of the first dose level is confirmed, enrollment will be opened to another cohort of 9 patients each in the respective age groups, at a higher dose level. This higher dose level will be determined such as to achieve maximum SMN protein increase, with the corresponding target exposure not exceeding the exposure cap (Cmax 400 ng/mL; AUC0-24h,ss 2000 ng• h/mL).

Once the last patient of the last cohort in Part 1 (higher dose level in either of the two age groups, depending on recruitment) has completed 4 weeks of treatment, all available safety, tolerability, PK and PD data will be reviewed by an Internal Monitoring Committee (IMC) which will recommend the dose for Part 2 of the study.

Once Part 1 patients have completed the 12-week double-blinded treatment period and the Part 2 dose has been selected, all Part 1 patients will then be switched to the Part 2 dose and followed up for safety, tolerability and efficacy as part of the open-label extension (OLE) phase of the study.

 Part 2, the confirmatory part, will start once the dose has been selected in Part 1 by the IMC and has been confirmed by the iDMC.

Part 2 of Study BP39055 will investigate the efficacy and safety of R07034067 over a 24-month treatment period, in Type 2/3 (non-ambulant only) SMA patients of 2 to 25 years of age.

A total of 168 patients will be randomized (2:1) to receive either RO7034067 at the dose of 5 mg once daily (o.d.) for patients with a body weight (BW) $\geq$ 20kg and 0.25 mg/kg for patients with a BW $<$ 20 kg, or placebo. Randomization will be stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years at randomization). No more than 30 patients will be randomized into the 18 to 25 years of age group. A minimum of 45 patients will be randomized into each of the other 3 age groups. Patients from Part 1 will not be included in Part 2.

The primary analysis will be conducted and the Sponsor unblinded once the last patient completes 12 months of treatment (i.e., before all patients have completed 24 months of treatment).

Patients receiving placebo will be switched to RO7034067 in a blinded manner after 12 months of treatment and treatment will then continue until Month 24, after which patients will be offered the opportunity to enter the OLE phase where they will be monitored regularly for safety, tolerability and efficacy.

NUMBER OF PATIENTS

In Part 1, at least 36 patients will be randomized in a 2:1 ratio to RO7034067 or placebo. If required, to enable the dose selection for Part 2, up to an additional 36 patients may be enrolled, for a total number of a maximum of 72 patients.

In Part 2 of the study 168 patients will be randomized 2:1 to RO7034067 or placebo (i.e., 112 patients on RO7034067 and 56 patients on placebo).

TARGET POPULATION

Part 1 will enroll patients with Type 2 and 3 SMA (ambulant and non-ambulant) aged 2-25 years.

Part 2 of the study will include Type 2 and non-ambulant Type 3 SMA patients aged 2−25 years.

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:

Patients must meet the following criteria for study entry:
1. Males and females 2 to 25 years of age inclusive (at screening).

2. For Part 1: Type 2 or 3 SMA ambulant or non-ambulant.

For Part 2: Type 2 or 3 SMA non-ambulant. Non-ambulant is defined as not having the ability to walk unassisted (i.e., without braces, assisted devices such as canes, crutches or calipers, or person/hand-held assistance) for 10 m or more.

3. Confirmed diagnosis of 5q-autosomal recessive SMA, including:

   o Genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the SMN1 gene.

Clinical symptoms attributable to Type 2 or Type 3 SMA.

4. For non-ambulant patients in Part 2 (at screening):

   o RULM entry item A (Brooke score) $\geq$ 2 (i.e., "Can raise 1 or 2 hands to the mouth, but cannot raise a 200 g weight in it to the mouth").

   o Ability to sit independently (i.e., scores a $\geq$ 1 on item 9 of the MFM 32 "with support of one or both upper limbs maintains the seated position for 5 seconds").

5. Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonisation (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the patient according to ICH and local regulations and assent must be given whenever possible.

6. Negative blood pregnancy test at screening (all women of childbearing potential, including those who have had a tubal ligation), and agreement to comply with measures to prevent pregnancy and restrictions on egg and sperm donation, as below:

   a) For women who are not prematurely menopausal ($\geq$ 12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent (refrain from heterosexual intercourse) or to 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 last dose of study drug. Women must refrain from donating eggs during this same period. The reliability of sexual abstinence needs to 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. Barrier methods must always be supplemented with the use of a spermicide.

   b) 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. 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.

   c) For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

   d) With female partners 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 last 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 spermatogenic cycle duration and drug elimination process.

   e) With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study drug. The reliability of sexual abstinence needs to 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.

Exclusion criteria:

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

1. Inability to meet study requirements.

2. Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening, or 5 half-lives of the drug, whichever is longer.

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

4. Any history of cell therapy.

5. Hospitalization for a pulmonary event within the last 2 months or planned at time of screening.

6. Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 months.

7. Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases as considered to be clinically significant by the Investigator.

8. Pregnant or lactating women.

9. Suspicion of regular consumption of drug of abuse.

10. Positive urine test for drugs of abuse or alcohol at screening or baseline visit (adolescents and adults only).

11. Cardiovascular, blood pressure, and heart rate:

    a. 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.

    b. Adolescents (12−17 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 50 bpm or > 100 bpm.

    c. Children (6−11 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 60 bpm or > 120 bpm.

    d. Children (2−5 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate < 70 bpm or > 140 bpm.

12. Presence of clinically significant ECG abnormalities before study drug administration (e.g., second or third degree AV block, confirmed QTcF > 460 ms for patients age > 10 years or QTcB > 460 ms for children up to age 10 years as Bazett's correction is more appropriate in young children) from average of triplicate measurement 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 patients as determined by the Investigator.

13. History of malignancy if not considered cured.

14. Significant risk for suicidal behavior, in the opinion of the Investigator as assessed by the C-SSRS (> 6 years of age).

15. Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration.

16. 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).

17. Use of the following medications within 90 days prior to randomization: riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease muscle strength, agents with known or presumed histone deacetylase (HDAC) inhibitory effect, and medications with known phototoxicity liabilities (e.g., oral retinoids including over the counter formulations, amiodarone, phenothiazines and chronic use of minocycline). (Patients who are on inhaled corticosteroids, administered either through a nebulizer or an inhaler, will be

allowed in the study)

18. Recently initiated treatment (within < 6 months prior to randomization) 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 months before randomization 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.

19. 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 (12 months) prior to randomization is not allowed.

20. 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 creatine kinase and LDH. Out of range creatine kinase levels should be reviewed in light of the underlying SMA pathology of the patient; elevated levels per se do not disqualify the patient from the study. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility.

21. Donation or loss of blood ≥ 10% of blood volume within three months prior to screening.

22. Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to RO7034067 or to the constituents of its formulation (see RO7034067 Investigator's Brochure).

23. 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.

24. Recent history (less than one 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) must be discussed with the Investigator, ophthalmologist, and with the Sponsor, who will jointly make the decision if the patient may be enrolled in the study. Patients in whom OCT measurement of sufficient quality cannot be obtained at screening will not be enrolled.

25. Patients requiring invasive ventilation or tracheostomy.

26. *Any inhibitor or inducer of FMO1 or FMO3 taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing.*

END OF STUDY

Treatment with RO7034067 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 OLE phase of the study, which will include regular monitoring of safety, tolerability and efficacy. Unless the development of the drug is stopped, the patient's treatment in the OLE may continue for an additional 3 years (patients will be treated for a total duration of at least 5 years). Thereafter, treatment will continue until the drug is available commercially 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 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.

LENGTH OF STUDY

For each subject the study will consist of:

- A screening visit, up to 30 days prior to the first dose of study drug.
- A minimum of 12-week double-blind treatment period for patients enrolled in Part 1.
- 12-month double-blind treatment period followed by 12-month active treatment period for patients enrolled in Part 2.

- Thereafter patients will be given the opportunity to enter the open-label extension (OLE) phase of the study (for both Parts 1 and 2).

If a patient is withdrawn from *study treatment*, the patient will be requested to attend follow-up visits, as described in the Schedule of Assessments (SoA).

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events.
- Incidence and severity of serious adverse events.
- Incidence of treatment discontinuations due to adverse events.
- Incidence of abnormal laboratory values.
- Incidence of abnormal ECG values.
- Incidence of abnormal vital signs (body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate).
- Physical examination including examination of the skin, mouth, pharynx and larynx
- Neurological examination
- Height, weight and head circumference.
- Incidence of emergence or worsening of items of the Columbia-Suicide Severity Rating Scale (C-SSRS: adult version for adults and adolescents, pediatric version for patients aged 6–11 years).
- Ophthalmological examination:

  For adults, adolescents and cooperative children ($\geq$ 10 year old): Ophthalmological examination including best corrected visual acuity (ETDRS) and Sloan low contrast *(Part 1 only excluding open-label extension)*, intra-ocular pressure (IOP), slit lamp examination of the anterior and posterior segment including the cornea, anterior chamber, funduscopy (with indirect ophthalmoscopy and eye dilation as needed), visual field-threshold perimetry testing *(or simple visual field test such as easier perimetry protocols or as last resort confrontation visual field testing if perimetry is not possible), spectral domain* optical coherence tomography (SD-OCT), FAF *(Part 1 only excluding open-label extension)* and fundus photography (7-field) or *image captured during funduscopy*, dark adaptation measurement (at selected sites; *Part 1 only excluding open-label extension*) according to SoA.

  For children < 10 years old: Bruckner test, fix and follow test, cover-uncover test, visual acuity, simple visual field test, slit lamp examination, *IOP,* fundus photography *or image captured during funduscopy* and SD-OCT.
- For patients aged 9–17 years old at screening, physical examination at baseline and Month 24 will include formal Tanner staging for pubertal status.

PHARMACOKINETIC OUTCOME MEASURES

Patient exposure to RO7034067 will be assessed and the following parameters calculated (if possible, based on the available data):

- Concentration per timepoint listed.
- C_{max} (maximum plasma concentration)
- AUC (area under the concentration-time curve)
- Concentration at the end of a dosing interval (C_{trough}) to assess steady-state.
- Other PK parameters as appropriate.

PHARMACODYNAMIC OUTCOME MEASURES

The pharmacodynamics outcome measures for this study are as follows:

- *SMN2* mRNA in blood: Blood samples will be collected at the times specified in the SoA 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.

EFFICACY OUTCOME MEASURES

The efficacy outcome measures for this study are as follows:

- Motor Function Measure (32 item version)
- HFMSE
- RULM
- SNIP
- MIP, MEP *(Part 2 only)*
- FVC, FEV1, PCF
- Disease-related Adverse Events
- CGI-C (Part 2 only)
- SMAIS (Part 2, only)
- PedsQL 3.0 Neuromuscular module (Part 1 only)
- PedsQL 4.0 Generic Core scale (Part 1 only)

ADDITIONAL OUTCOME MEASURES

The outcome measures for this study that will be used for economic analyses are as follows:

- EQ-5D-5L
- WPAI:CG-SMA

Other outcome measures for this study include but are not limited to the following:

Taste assessment (taste questionnaire in adults and adolescents, 5-point facial visual hedonic scale in children aged 6−11 years; with the exception of patients to whom study drug is administered via naso-gastric or gastrostomy tube [G-tube]).

INVESTIGATIONAL MEDICINAL PRODUCT(S)

Part 1 Formulation – Powder and solvent for oral solution, 20 mg and 120 mg

Part 1 RO7034067 clinical formulation is a powder and solvent for constitution to an oral solution. Patients will be randomly assigned to one of two possible blinded study drug treatments:

- RO7034067 drug product
- Placebo (containing no active drug substance).

The excipients blend (powder for solvent for reconstitution) bottle is constituted with water for injection and entirely transferred to the drug substance bottle to yield an oral solution containing of 0.25 mg/mL and 1.5 mg/mL of RO7034067, respectively. Matching-placebo oral solutions will be prepared.

The dose administered to the first cohort of patients aged 12−25 years (Group A) will be 3 mg.

Part 2 Formulation – Powder for oral solution, 20 mg and 60 mg

Part 2 RO7034067 clinical formulation is a powder for constitution to an oral solution. Patients will be randomly assigned to one of two possible blinded study drug treatments:

- RO7034067 drug product
- Placebo (containing no active drug substance).

The powder is constituted with purified water to yield an oral solution containing 0.25 mg/mL or 0.75 mg/mL of RO7034067, respectively.

Throughout the study, the study medication (RO7034067 or placebo) 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.

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 will be collected from adult and adolescent patients who give specific consent, and assent if applicable, to participate in this optional RBR.

Collected specimens will be used to achieve the following objectives:

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

The following samples will be collected for identification of dynamic (non-inherited) biomarkers:

- Blood 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 sample collected for DNA extraction may be used for whole genome sequencing (WGS) and other genetic analysis.

PROCEDURES

A Schedule of Assessments (SoA) is provided in Appendices.

STATISTICAL METHODS

The analyses of this study will be structured into two parts; exploratory (Part 1) to select the dose and confirmatory (Part 2) to evaluate the treatment effect of RO7034067. The confirmatory analyses will only include the patients randomized into Part 2 of the study; it will not include the Part 1 patients who will be analyzed to select the dose.

Following the dose selection for Part 2, data from the exploratory Part 1 of this study (and the Part 1 extension phase) may be reported. Data may continue to be locked at intervals in order to analyze and report the safety, PK/PD and exploratory efficacy of those patients enrolled into Part 1 only.

The primary analysis and the analysis of the secondary endpoints in Part 2 will only include data up to the 12-month time-point for each individual.

SAFETY ANALYSES

All patients who receive at least one dose of study medication (RO7034067 or placebo) will be included in the safety population. This population will be the primary safety analysis population to compare RO7034067 to placebo.

The safety endpoints include, but may not be limited to, incidence of adverse events and 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, and incidence of clinically significant findings on neurological examination.

Longer term safety of RO7034067 treatment, including safety data collected in the OLE periods for both parts of the study, will be summarized using the RO7034067 All Exposure Population (i.e., all patients who receive at least one dose of RO7034067 at any dose level during either the double-blinded period or the OLE period).

PHARMACOKINETIC ANALYSES

All patients with at least one time point with a measureable concentration will be included in the PK analysis data set.

Individual and mean plasma concentrations of RO7034067, and metabolites, as appropriate, versus time data will be tabulated and plotted. Assessment of protein binding will be performed on pre-dose samples and results listed. Additional PK analyses will be conducted as appropriate.

PHARMACODYNAMIC ANALYSES

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

EFFICACY ANALYSES

The intent-to-treat (ITT) population will be the primary analysis population for all efficacy analyses. The ITT population is defined as all randomized patients.

The primary endpoint in Part 2 is the change from baseline in the total MFM 32 score at Month 12.

Changes from baseline in the total MFM scores will be summarized descriptively at each time-point by treatment group for the ITT population and a Mixed Model Repeated Measures (MMRM) analysis will be performed to utilize all the data collected in Part 2 up to 12 months. The model will include the absolute change from baseline total MFM score as the dependent variable and as independent variables the baseline total MFM score (continuous), treatment group, time, treatment-by-time interaction and the randomization stratification variable of age (categorical: 2 to 5, 6 to 11, 12 to 17, 18 to 25 years at randomization). An unstructured variance co-variance matrix structure will be applied. The estimated treatment difference in the mean change from baseline in the total MFM score at Month 12 between RO7034067 and placebo will be presented with 95% confidence intervals.

The secondary efficacy endpoints for Part 2 of this study are:

- **Motor Function**, which includes change from baseline in Total score of HFMSE, RULM and in the MFM domain scores of D1, D2, D3 and the total combined score of (D1 + D2), and the proportion of patients who achieve stabilization or improvement on the total MFM score, *total HFMSE score, and total RULM score* at Month 12.

- **Respiratory** with regard to change from baseline in the best SNIP (expressed as a percentage of the predicted value) at Month 12. Additionally, in patients aged 6 to 25 years only: the change from baseline in MIP, MEP, FEV_1, FVC and in PCF at Month 12.

- **Disease-Related Adverse Events**, the proportion of patients who experience at least one disease-related adverse event by Month 12 and the number of disease-related adverse events per-patient year at Month 12.

- **Clinical Global Impression of Change Scale (CGI-C),** with regard to the proportion of patients rated by clinicians as no change or improved, and the proportion of patients rated by clinicians as improved at Month 12.

- **Patient- and Caregiver-Reported Outcomes:** with regard to the change from baseline in the Total score of the caregiver-reported SMAIS and the change from baseline in the Total score of the patient-reported SMAIS (in patients aged 12 to 25 years only) at Month 12.

For continuous endpoints such as the change from baseline in the total score of HFMSE, an MMRM analysis will be performed similar to that specified for the primary efficacy analysis, if appropriate. To control for multiplicity across the different endpoint domains, a hierarchical testing approach will be implemented. *The secondary endpoints to be included in the hierarchy will be specified within the SAP.*

The order of the secondary endpoints in the hierarchy will be specified within the SAP. The first secondary efficacy endpoint will be tested if and only if the primary endpoint has reached the 5% significance level (i.e., p-value ≤ 0.05). The secondary endpoints will be tested at a 5% significance level according to this hierarchy as long as the p-value is ≤ 0.05 for endpoints higher in the hierarchy. Other secondary endpoints not specified in the hierarchy will be simultaneously tested at the 5% significance level without adjustment for multiplicity as they are considered supportive of their endpoint domain or primary endpoint.

Exploratory efficacy endpoints for Part 2 of this study will be summarised at Month 18 and 24 and include, among others, change from baseline in the Total MFM score and its domain scores of D1, D2, D3 and the total combined score of (D1+D2), Total HFMSE and the Total score of RULM, at Month 18 and 24.

OTHER EXPLORATORY ANALYSES

The consistency of the treatment effect for the primary endpoint will be explored for the following baseline subgroups:

- Age group (2 to 5, 6 to 11, 12 to 17, and 18 to 25 years at randomization)
- Age group 2 (2 to 11 and 12 to 25 years at randomization)
- History of scoliosis or hip surgery (yes, no)
- SMA type (2, 3 non-ambulatory)
- Region (US, Rest of World)
- In patients with no major scoliosis or contractures at baseline: Age group 2 (2 to 11 and 12 to 25 years at randomization)

Pharmacoeconomic data analysis and reporting will be handled separately from the clinical study reports of BP39055.

INTERIM ANALYSES

The Sponsor may choose to conduct one interim analysis for efficacy during the confirmatory Part 2 of this study (i.e., if the study [BP39056] in Type 1 SMA achieves its primary efficacy objective earlier than planned or in response to the emerging 12 month results from Part 1 of this study).

If an interim analysis during Part 2 is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the external iDMC.

SAMPLE SIZE JUSTIFICATION

In Part 1, the target sample size is 36 patients, with 6 patients on active treatment in each dose/age group (12 patients on active drug per dose/exposure level) and 3 patients (6 in total across the entire age range) on placebo.

In Part 2, 168 patients will be randomized, 112 patients on RO7034067 and 56 patients on placebo (2:1 randomization). For the primary endpoint of the mean change from baseline in the total MFM score at Month 12, this sample size (allowing for a 10% dropout rate) provides at least 80% power at a two-sided 5% significance level for testing the null hypothesis that the true treatment difference is zero versus the alternative hypothesis, given that the true treatment difference is 3 and assuming that the common standard deviation will be 6.

CONCOMITANT MEDICATIONS

In addition to the study drug treatment, patients may continue to receive concomitant therapy. Concomitant therapy includes any medication used by a patient from 30 days prior to screening until the follow-up visit.

Prohibited therapies include (please see eligibility criteria for additional information):

- Any OCT-2 and MATE substrates.
- <u>Medications intended for the treatment of SMA</u> include riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, nusinersen (SPINRAZA®). 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.
- Patients should not have received the following drugs previously, nor during the study, due to:
    1. Known phototoxicity liabilities: e.g., oral retinoids including over-the-counter formulations, amiodarone, phenothiazines and chronic use of minocycline.
    2. Retinal toxicity effects: quinolines (chloroquine and hydroxychloroquine), thioridazine, retigabin and vigabatrin.
- Desferoxamine, topiramate, latanoprost, niacin, rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon or any other drugs known to cause retinal toxicity, including chronic use of minocycline.

Appendix 2   Schedule of Assessments: Part 1
Screening to Weeks 44–51 (cont. on next page)

Week	Screening[a] D-30 to D-2 / Day 1	Screening Day 2	Week 1 / Day -1[b]	Week 1 / Day 1	Week 1 / Day 7	Week 2 / Day 14	Week 4 / Day 28	Week 6 / Day 42	Week 8 / Day 56	Week 10 / Day 70	Week 12[e] / Day 84	Weeks 13-16	Week 17[a] / Day 119	Week 17 / Day 120	Weeks 18-25	Week 26 / Day 182	Weeks 27-34	Week 35[a] / Day 245	Week 35 / Day 246	Weeks 36-42	Week 43 / Day 301	Weeks 44-51
Visit Window						+/-1	+/-3	+/-3	+/-3	+/-3	+/-3		+/-7			+/-7		+/-7			+/-7	
Assessments																						
Site Visit	X		X	X	X	X	X		X				X			X		X			X	
Follow-up call										X[d]												
Informed Consent	X																					
Randomisation				X																		
Eligibility	X			X																		
Demography	X																					
Medical History	X																					
Physical Examination[f]	X			X		X	X	X	X				X			X		X			x[r]	
Neurological Examination	X												X					X				
SMA History	X																					
Vital Signs	X		X	4h[t]	X	X	X	x[t]	x[t]				X			X		X				
PK Sample[v]				4	X	X	5		5					X							X	
ECG-12 lead[t]	X		X	4h		X	X	x[u]	x[u]				X			X		X				
Substance Use[g]		X	X																			
Significant life events			X			X	X	X	X				X			X		X			X	
Hematology[t]		X	x[n]			X	X		X					X					X			
Blood Chemistry[t]		X	x[n]			X	X		X					X					X			
Coagulation[t]		X	x[n]				X							X					X			
Urinalysis[t]		X	x[n]				X							X					X			
Hormone Panel[h,t]		X												X								
Pregnancy test blood[i]		X					X		X					X					X			
Pregnancy test urine (site)[i]				X												X					X	
Pregnancy test urine (home)[i,o]											X				X		X			X		X
Ophthalmological Exam[j]	X								X				X			X		X			X	
Tanner staging[k]				X																		
Blood Sample for protein binding		X																				

Appendix 2   Schedule of Assessments: Part 1
Screening to Weeks 44–51 (cont. on next page)

Week / Day	Screening D-30 to D-2 Day 1	Screening Day 2	Week 1 Day -1[b]	Week 1 Day 1	Week 1 Day 7	Week 2 Day 14	Week 4 Day 28	Week 6 Day 42	Week 8 Day 56	Week 10 Day 70	Week 12[e] Day 84	Weeks 13-16	Week 17[a] Day 119	Week 17 Day 120	Weeks 18-25	Week 26 Day 182	Weeks 27-34	Week 35[a] Day 245	Week 35 Day 246	Weeks 36-42	Week 43 Day 301	Weeks 44-51
Visit Window						+/-1	+/-3	+/-3	+/-3	+/-3	+/-3		+/-7			+/-7		+/-7			+/-7	
Assessments																						
In vivo mRNA[v]			X	X	X	X[g]	X							X					X			
SMN protein[v]			X		X	X[g]	X							X					X			
MFM[w]	X		X										X					X				
Pulmonary testing[x]	X		X										X					X				
RULM/HMFSE[w]		X												X					X			
C-SSRS[l]	X		X										X					X				
Nutritional Check		X	X				X		X					X		X			X		X	
Serum Biomarkers			X																			
RBR samples[m]			X																			
Clinical Genotyping				X[p]																		
Taste Assessment[l]					X																	
EQ-5D			X										X					X				
WPAI-Caregiver-SMA			X											X					X			
PedsQL neuromuscular module			X											X					X			
PedsQL Core			X											X					X			
Study medication dispensation/return[c]				X	X	X	X	X	X	X	X	X	X			X	X	X			X	X
Administration of Study Medication				X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Diary					X	X	X	X	X	X	X	X	X			X	X	X			X	X
Exercise or Physical Therapy Programs				X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Adverse Events	X[s]		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Previous and Concomitant Treatments	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X
Previous and Concomitant SMA-related Surgeries and Procedures	X		X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X

Appendix 2 Schedule of Assessments: Part 1
Week 52 to Follow-Up (cont. on next page)

Week	Week 52[a] Day 364	Week 52 Day 365	Weeks 53-60	Week 61 Day 427	Weeks 62-69	Week 70 Day 490	Weeks 71-77	Week 78[a] Day 546	Week 78 Day 547	Weeks 79-86	Week 87 Day 609	Weeks 88-95	Week 96 Day 672	Weeks 97-103	Week 104[a] Day 728	Week 104 Day 729	Additional: Every 13 wks	Additional: Every 26 weeks[a] D1	Additional: Every 26 weeks D2	Resupply visit	Early withdrawal[a] D1	Early withdrawal D2	Follow Up Visit 1 EW + 8 weeks	Follow Up Visit 2 EW + 26 weeks	Follow Up Visit 3 EW + 52 weeks
Visit Window	+/-7			+/-7		+/-7		+/-7			+/-7		+/-7		+/-7		+/- 14 days	+/- 14 days					+/-7	+/-14	+/-14
Assessments																									
Site Visit	x			x		x		x			x		x		x		x	x			x		x	x	x
Follow-up call																									
Informed Consent																									
Randomisation																									
Eligibility																									
Demography																									
Medical History																									
Physical Examination [f]	x			x[r]		x		x			x		x[r]		x		x[r]	x			x		x		
Neurological Examination	x							x							x			x			x		x		
SMA History																									
Vital Signs	x[t]					x					x[t]				x			x			x		x		
PK Sample [v]		5				x					5					x			x					x	x
ECG-12 lead [f]	x					x					x[u]				x			x			x		x		
Substance Use [g]																									
Significant life events	x			x		x		x			x		x		x			x			x				
Hematology [t]		x				x					x		x						x					x	x
Blood Chemistry [t]		x				x					x		x						x					x	x
Coagulation [t]		x				x							x						x					x	x
Urinalysis [t]		x				x							x						x					x	x
Hormone Panel [h,t]													x												
Pregnancy test blood [i]		x				x					x		x						x					x	x
Pregnancy test urine (site) [i]				x				x					x				x								
Preganancy test urine (home) [i,o]			x		x		x			x		x		x						x					
Ophthalmological Exam [j]	x			x		x		x			x		x		x		x	x			x		x	x	x
Tanner staging [k]															x						x				
Blood Sample for protein binding																									

Appendix 2   Schedule of Assessments: Part 1
Week 52 to Follow-Up (cont. on next page)

Week	Week 52 [a]		Weeks 53-60	Week 61	Weeks 62-69	Week 70	Weeks 71-77	Week 78 [a]		Weeks 79-86	Week 87	Weeks 88-95	Week 96	Weeks 97-103	Week 104 [a]		Additional visits after Week 104 [q]				Early withdrawal [a]		Follow Up Visit 1	Follow Up Visit 2	Follow Up Visit 3
																	Every 13 wks	Every 26 weeks [a] D1	Every 26 weeks [a] D2	Resupply visit	D1	D2			
Day	Day 364	Day 365		Day 427		Day 490		Day 546	Day 547		Day 609		Day 672		Day 728	Day 729							EW + 8 weeks	EW + 26 weeks	EW + 52 weeks
Visit Window	+/-7			+/-7		+/-7		+/-7		+/-7			+/-7		+/-7		+/- 14 days	+/- 14 days					+/-7	+/-14	+/-14
Assessments																									
In vivo mRNA [v]		X														X						X	X		
SMN protein [v]		X														X			x			X	X		
MFM [w]	X							X							X			x			X		X		
Pulmonary testing [x]	X							X							X			x			X		X		
RULM/HMFSE [w]		X							X							X			x			X		X	
C-SSRS [l]	X							X							X			x			X		X		
Nutritional Check		X		X		X			X		X		X			X			x			X			
Serum Biomarkers		X														X						X			
RBR samples [m]																X						X			
Clinical Genotyping																									
Taste Assessment [i]																									
EQ-5D	X							X							X			x			X				
WPAI-Caregiver-SMA		X							X							X			x			X			
PedsQL neuromuscular module		X																				X			
PedsQL Core		X																				X			
Study medication dispensation/return [c]	X		X	X	X	X	X	X		X	X	X	X	X	X		x	x	x	x	X				
Administration of Study Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	x	x							
Diary		X	X	X	X	X	X	X		X	X	X	X	X	X		x	x	x		X				
Exercise or Physical Therapy Programs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	x	x	x		X		X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	x	x	x		X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	x	x	x		X	X	X	X	X
Previous and Concomitant SMA-related Surgeries and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	x	x	x		X	X	X	X	X

a See protocol Section 4.6.1.26 – Table 2 for order of assessments, which can be conducted over two days.

b Assessments should be performed in the following order: adverse events, previous/concomitant medications, confirmation of eligibility, MFM, pulmonary testing, randomization, physical examination, Tanner staging, ECG, *vital signs,* patient/caregiver reported outcomes and blood samples.

Appendix 2 Schedule of Assessments: Part 1
Week 52 to Follow-Up (cont. on next page)

c   Starting at Week 6 and until Week 17 at the earliest (see below), drug delivery to the patient's home is scheduled every 2 weeks, unless patient has agreed or is scheduled to visit the clinic at these times for drug dispensation, *and* return of unused drug and supplies.
Starting at Week 17 at the earliest, or at one of the following time points: Week 26, Week 35, Week 43, Week 52 (determined according to availability of the Part 2 formulation), patient should start receiving study drug reconstituted in 1 bottle (see Section 4.4.1). Drug dispensation, return of unused drug and supplies will then occur at scheduled site visits. *Ad hoc* resupply site visits, or home visits *will be performed to ensure the patient has adequate drug and supplies between scheduled site visits as necessary*.

d   The Investigator must agree with the patient or parent/ caregiver when to perform the *mandatory* follow-up phone calls at the most appropriate time (day) between the site visits. After Week 12: follow-up phone calls are per investigator decision.

e   The Sponsor or its representative will inform the clinical sites after this time which patients had received placebo. If these patients agree to receive RO7034067, they will begin at Day 1 and perform all scheduled assessments from this day forward in the study. If they have not completed the scheduled visit at Week 17, the placebo patients must complete those assessments prior to beginning Day 1.

f   Body weight *and head circumference in children below 5 years* will be measured at every scheduled physical examination. *At Weeks 43, 61, and 96 weight only should be obtained, not the complete physical examination.* Height (measured or derived from ulna length) at screening, Weeks 17, 35, 52, 78, 104 *and at each physical examination after Week 104* in patients 2-17 years of age. In patients > 17 years of age, height at screening, Weeks 52 and 104, *and at each physical examination after Week 104*. 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.

g   Only patients of ≥ 12 years of age.

h   Free T4 and TSH in all patients; estradiol, follicle-stimulating hormone and luteinizing hormone in female patients aged 12 to 25 years or younger patients who have menses.

i   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 will be confirmed with a blood pregnancy test.

j   See protocol (Table 4, Table 5, Appendix 5, and Appendix 6) for details on required ophthalmology assessments according to the visit and the group.

k   Only in patients 9 to 17 years of age.

l   Only in patients 6 years of age or older.

m   Only in patients ≥ 12 years of age. RBR sampling is optional, requiring additional consent. RBR DNA sample will be collected once, other RBR samples at Day −1 and Week 104.

n   Not required if screening sample < 30 days.

Appendix 2   Schedule of Assessments: Part 1
Week 52 to Follow-Up (cont. on next page)

o   The home pregnancy test must be performed 4 weeks following the last clinic visit *until Week 104. See footnote q for visits after Week 104.* 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.

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

q   Every *13 or* 26 weeks following the Week 104 visit until the conclusion of the open-label extension (OLE). Urine pregnancy tests will be performed at home on Weeks 4 and 8 following the last clinic visit (see footnote o).

r   *Weight only.*

s   Only SAEs.

t   Pre-dose.

u   Matched ECG and PK samples only in patients ≥ 12 years of age (see Appendix 2).

v   Pre-dose except those outlined in Appendix 2.

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

x   SNIP in all patients; spirometry (FCV, FEV1, PCF), MIP and MEP in patients 6 years of age and older.

Appendix 3
Schedule of Assessments: Part 1, Detailed Table

Week	Day	Scheduled Time (h)	ECG-12 Lead	PK Sample	In vivo mRNA	SMN protein
Screening	D-30 to D-2	***	x			
Week 1	Day -1	***	x		x	x
	Day 1	Pre-dose	x			
		1h		x		
		2h		x		
		4h		x	x	
		6h		x		
	Day 7	Pre-dose	x	x	x	x
Week 2	Day 14	Pre-dose	x	x	x [a]	x [a]
Week 4 [b]	Day 28	Pre-dose	x	x		
		1h	x	x		
		2h	x	x		
		4h	x	x	x	x
		6h	x	x		
Week 8 [b]	Day 56	Pre-dose	x	x		
		1h	x	x		
		2h	x	x		
		4h	x	x		
		6h	x	x		
Week 17	Day 119	Pre-dose	x			
	Day 120	Pre-dose		x	x	x
Week 26	Day 182	Pre-dose	x			
Week 35	Day 245	Pre-dose	x			
	Day 246	Pre-dose		x	x	x
Week 52	Day 364	Pre-dose	x			
	Day 365	Pre-dose		x		
		1h		x		
		2h		x		
		4h		x	x	x
		6h		x		
Week 70	Day 490	Pre-dose	x	x		
Week 87 [b]	Day 609	Pre-dose	x	x		
		1h	x	x		
		2h	x	x		
		4h	x	x		
		6h	x	x		
Week 104	Day 728	Pre-dose	x			
	Day 729	Pre-dose		x	x	x
Additional Visits		Pre-dose	x	*x*		*x*
Early withdrawal		***	x	x	x	x
Follow Up Visit		***	x	x	x	x

[a]   Only in patients ≥ 12 years of age.

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

Appendix 4 Schedule of Assessments: Ophthalmology Assessments (Part 1)

Week / Adults and cooperative children	screening	8	17	26	35	43	52	61	70	78	87	96	104	OLE	early withdrawal	FU #1	FU #2	FU #3
Best corrected visual acuity	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	X	X	X	X
Sloan low contrast	X	X	X	X	X	X	X	X	X	X	X	X	X					
Threshold perimetry or other visual field test	X		X		X		X		X		X		X	X[c]	X	X	X	X
Slit Lamp and fundus examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	X	X	X	X
Intraocular pressure (a)	X		X		X		X		X		X		X	X[d]	X	X	X	X
Color fundus photography	X			X			X			X			X	X[c]	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	X	X	X	X
Fundus autofluorescence	X		X		X		X		X		X		X					

Week / Children	screening	8	17	26	35	43	52	61	70	78	87	96	104	OLE	early withdrawal	FU #1	FU #2	FU #3
Visual testing (b)	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	X	X	X	X
Intraocular pressure (a)	X						X						X	X[d]	X			X
Slit Lamp and fundus examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	X	X	X	X
Color Fundus photography	X			X			X			X			X	X[c]	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	X	X	X	X

a Tonometry or digital palpation of the globes.

b Bruckner test, fix and follow test, cover-uncover test, simple visual field test, visual acuity.

c Every 26 weeks after the Week 104 visit until the completion of the open label extension (OLE).

d Every 13 weeks after the Week 104 visit until the completion of the open label extension (OLE).

Appendix 5   Statistical Analysis System (SAS) Code for the MMRM Analysis for the Comparison with External Comparator Data

```
PROC MIXED DATA=data1;
CLASS patient trt visit SMATYPE AMSTAT SCOLIO M5DS SMN2 copy number;
MODEL change = BASE trt visit age SMATYPE AMSTAT M5DS SCOLIO SMN2
copy number trt*visit BASE*visit/DDFM=KR;
REPEATED visit /SUBJECT=patient TYPE=UN ;
LSMEANS trt*visit / DIFFS cl;
WEIGHT attwgt;
RUN;
```

where
data1: dataset which contain data from studies of SUNFISH Part 1, Natural History and WN29836
patient: subject ID
visit: ID of the visit (Week 52, Week 78 and Week 104)
BASE: baseline MFM total score
age: age at enrollment
trt: treatment (risdiplam-SUNFISH Part 1 or from external comparator data)
SMATYPE: SMA Type (Type 2 or Type 3)
AMSTAT: Ambulatory status (Ambulant or Non-ambulant)
M5DS: MFM scale used (MFM32 or MFM20)
SCOLIO: presence of scoliosis at baseline (Yes or No)
change: change from baseline in the total score
attwgt: the weights derived from the propensity scores. (for weighted analyses)
agecat: age categories ($\geq$2 to $<$6 years, $\geq$6 to $<$16 years, $\geq$16 years)

TYPE=UN means the unstructed variance-covariance matrix applied to model the within-patient variability.
If model does not converge, please remove 'age', 'SMATYPE', 'AMSTAT' in the 'MODEL' statement for the analysis. If the model still does not converge, a heterogeneous autoregressive variance-covariance structure will be used (TYPE=ARH(1)) instead. The subgroup analysis by age categories will be done by replace the 'age' variable in the 'MODEL' statement with 'agecat' and also adding in "agecat*trt" and "agecat*trt*visit" in the 'MODEL statement.

STATISTICAL ANALYSIS PLAN (SUNFISH Part 2)

TITLE:	**A TWO-PART SEAMLESS, MULTI-CENTER RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO INVESTIGATE THE SAFETY,TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS, AND EFFICACY OF RO7034067 IN TYPE 2 AND 3 SPINAL MUSCULAR ATROPHY PATIENTS (SUNFISH)**
PROTOCOL NUMBER:	BP39055
STUDY DRUG:	Risdiplam (RO7034067)
VERSION NUMBER:	5
IND NUMBER:	128972
EUDRACT NUMBER:	2016-000750-35
SPONSOR:	F. Hoffmann-La Roche Ltd.
PLAN PREPARED BY:	███████████████ , Ph.D.
DATE FINAL:	Version 1: 27 June 2019
DATES AMENDED:	Version 2: 23 August 2019 Version 3: 21 October 2019 Version 4: 10 November 2020 Version 5: See electronic date stamp below.

STATISTICAL ANALYSIS PLAN AMENDMENT APPROVAL

Date and Time(UTC)	Reason for Signing	Name
12-Mar-2021 18:00:00	Company Signatory	███████████

STATISTICAL ANALYSIS PLAN AMENDMENT RATIONALE

This Statistical Analysis Plan (SAP) Version 5 for Study BP39055 (Part 2) has been amended to incorporate the following changes for reporting events after the primary analysis:

- An additional new section has been added related to the analyses of the comparison of SUNFISH Part 2, 2 years on study data with external control comparator

- All previous medical history results that were collected are reported instead of only previous medical history results up to 30 days prior to screening

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

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1.   BACKGROUND

This Statistical Analysis Plan (SAP) documents the data-handling rules, derivation rules, and statistical methods of summarizing and analyzing safety and efficacy data collected from patients with Type 2 or non-ambulant Type 3 Spinal Muscular Atrophy (SMA) for Part 2, the confirmatory part of Study BP39055. The rules of handling safety and efficacy data from Part 1 patients of Study BP39055 are covered in a separate SAP.

The global population will include all patients enrolled during the global enrollment phase.

Within this SAP, the terms 'placebo group' or 'placebo patients' refer to patients who were randomized to and received placebo treatment for the first 12 months of treatment period. The term 'active' treatment refers to risdiplam treatment. The phrase 'patients initially on active treatment' refers to patients who were randomized to and received risdiplam (RO7034067) treatment for the first 12 months of treatment. In addition, the term 'by treatment group' means by the treatment group the patient was randomized to and received medication during the first 12 months of treatment period.

2.   STUDY DESIGN

This is a seamless, multi-center, randomized, double-blind, placebo-controlled study to investigate the efficacy, safety and tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in adult and pediatric Type 2 and Type 3 SMA patients.

The study consists of two parts:

- An exploratory dose-finding part (Part 1).
- A confirmatory part (Part 2), starting once the dose has been selected in Part 1.

The two parts of the study are independent, have their own objectives and eligibility criteria, and will be analyzed separately. Part 1 patients did not roll over into Part 2.

Part 1 is a double-blinded, placebo-controlled, randomized (risdiplam: placebo [2:1]), exploratory dose-finding study in 51 Type 2 and Type 3 (ambulant and non-ambulant) SMA patients. This is followed by an open-label extension (OLE) phase. Please refer to the protocol for further details about the study design for Part 1 of the study.

Part 2 of Study BP39055 is the confirmatory part of the study to investigate the efficacy and safety of risdiplam in Type 2 and Type 3 (non-ambulatory only) SMA patients of 2 to 25 years of age.

For Part 2, the target sample size was 168 patients and patients were randomized in a 2:1 ratio to receive either risdiplam (at the dose of 5 mg oral daily for patients with a body weight $\geq$20 kg or 0.25 mg/kg for patients with a body weight$<$20 kg) or placebo. Randomization was stratified by age group (2 to 5, 6 to 11, 12 to 17, and 18 to 25 years

at randomization). No more than 30 patients were randomized into the 18 to 25 years of age group. A minimum of 45 patients were randomized into each of the three remaining age groups.

Patients receiving placebo will be switched to risdiplam in a blinded manner after 12 months of treatment (i.e., at their Week 52 visit) and treatment will then continue until Month 24, after which patients will be offered the opportunity to enter the OLE phase in which they will be monitored regularly for safety, tolerability, and efficacy.

As described above, the duration of the study for each patient enrolled in Part 2 (not including the OLE phase) will be up to 25 months as follows:

- Screening: Up to 30 days before the first dose.
- Treatment period: Double-blinded treatment for 12 months, followed by a 12-month risdiplam treatment period.

If a patient withdraws or is withdrawn from the clinical study or study treatment at any time, they will be asked to participate in the follow-up period of the study as described in the schedule of assessment (SoA) tables. All patients will be randomized on Day -1, one day before the first administration of study medication (either placebo or risdiplam) on Day 1.

The study design and the key analysis periods for Part 2 of the study are shown in Figure 1.

Figure 1   Study Design for SUNFISH Part 2
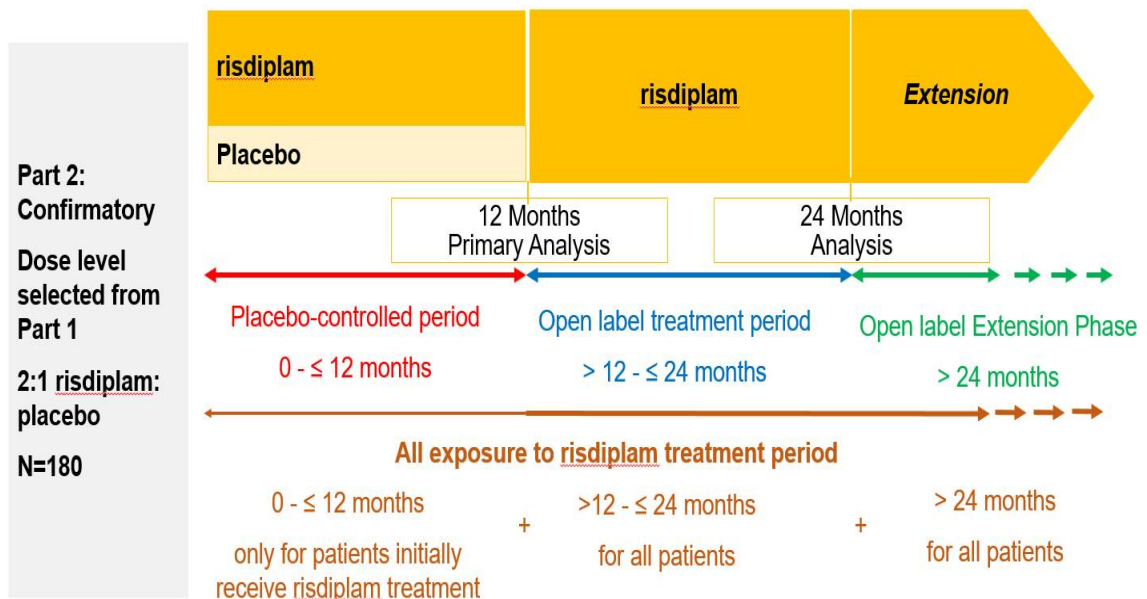
2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the SoA tables for Part 2 of the study in Appendix 2, Appendix 3, and Appendix 4.

2.2 OUTCOME MEASURES

Please refer to the Protocol Synopsis in Appendix 1 for efficacy, safety, pharmacokinetics, pharmacodynamics, and patient-reported outcome measures.

2.3 DETERMINATION OF SAMPLE SIZE

The purpose of the confirmatory Part 2 of this study is to estimate and test the treatment effect of risdiplam at the selected dose from Part 1 relative to placebo. The target sample size was 168 patients with 112 patients randomized to risdiplam and 56 patients randomized to placebo (2:1 randomization).

For the primary endpoint of the mean change from baseline in the total motor function measure (MFM) score at Month 12, the sample size of 168, allowing for a 10% dropout rate, provides at least 80% power at a two-sided 5% significance level for testing the null hypothesis that the true treatment difference is zero versus the alternative hypothesis, that the true treatment difference is 3 and assuming that the common standard deviation will be 6 (twice the value seen in Vuillerot et al. 2012). This corresponds to a hypothesized effect size of 0.5. The minimal detectable treatment difference is approximately 2.03.

The actual number of patients randomized to and enrolled in Part 2 is 180.

2.4 ANALYSIS TIMING

The primary analysis will be conducted once the last patient has completed 12 months of treatment or has been withdrawn early from Part 2 of the study (and all other patients have completed 12 months of treatment or withdrawn from Part 2 of the study); and before all patients have completed 24 months of treatment. For the purpose of the primary analysis and analyses of the 12-month secondary endpoints, a database lock will occur once the last patient in Part 2 has completed his/her 12-month assessment or has been withdrawn.

Another database lock will occur once the last patient in Part 2 has completed 24 months of treatment or withdrawn from Part 2 of the study, for the analyses of the 18-month and 24-month exploratory endpoints.

Following the primary analysis, subsequent locks of the database may occur in order to perform exploratory and safety analyses of the data at further time points during the study. Final database lock will occur at study end when the last patient has completed the OLE phase or has been withdrawn early from Part 2 of the study (and all other patients have completed the OLE phase or withdrawn from Part 2 of the study).

2.4.1   Data Cut Definition for Analysis

For the 12-month primary analysis and reporting event, the clinical data cutoff date is defined as the date when the last patient has completed his/her 12-month assessment which is also the date of the Day 3 pre-dose of his/her Week 52 visit (Day 366). For the 24-month analysis event, the clinical data cutoff date is defined as the date when the last patient has completed his/her 24-month assessment which is also the date of the Day 2 pre-dose of his/her Week 104 visit (Day 729).

Fixed data cuts will be applied for both 12-month and 24-month reporting events. The same clinical data cutoff dates will be applied for all patients.

The primary analysis and the analyses of the secondary endpoints in Part 2 will only include data up to the 12-month time point for each individual. Analyses of the exploratory efficacy endpoints will be performed on all available data up to each of the clinical cutoff dates. All available safety data up to each clinical cutoff date will also be analyzed and reported.

2.4.2   Analysis Period

All efficacy and safety data will be analyzed separately in one of the following study periods of Part 2:

- **Placebo-controlled period (0 to ≤12 months/52 weeks)**. This is the first 12-month treatment (either placebo or risdiplam) period for each individual. The completion time of this period is before dose administration on the third day which is also the last day of each individual's Week 52 visit. Data will be summarized by treatment group.

- **Open-label treatment period (>12 months to ≤24 months/104 weeks)**. This is the treatment period after each individual has completed his/her first 12 months of treatment and up to his/her 24 month of treatment. Note this will be the first 12-month risdiplam treatment period for placebo patients after switching and the second 12-month risdiplam treatment period for patients who have been on risdiplam treatment already. The start time of this period is defined as after dose administration on the third day which is also the last day of his/her Week 52 visit and the completion time is before dose administration on the second day which is also the last of his/her Week 104 visit. Data will be summarized by treatment group, and total for all patients.

- **First 24 months risdiplam treatment period for patients initially on risdiplam treatment (0 to ≤24 months for active patients)**. This is the first 24-month treatment period only for those patients initially randomized to and 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 second day which is also the last day of his/her Week 104 visit. Data will be summarized as total on one treatment group of risdiplam.

- **Open-label extension phase (>24 months)**. This is the treatment period after each individual completes his/her first 24 months of treatment. The start time is defined as after dose administration on the second day which is also the last day of his/her Week 104 visit. Data will be summarized as total for all patients on risdiplam treatment.

- **Follow-up period**. This applies to all patients who discontinue treatment and/or withdraw from the study early at any time during Part 2 of the study or who reach the end of the 24 months' treatment period and do not enter OLE 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 the last treatment the patient received prior to withdrawal.

- **All exposure to risdiplam treatment period**. This is the treatment period after each individual receives his/her first dose of risdiplam. This will include all the risdiplam treatment periods (placebo-controlled period for patients initially on risdiplam treatment, open-label treatment period, and OLE phase for all patients) during Part 2 of the study. For all patients, the start day is the date of first dose of risdiplam. Efficacy data will be summarized at each time point by treatment group for this period. Safety data will be summarized as total for all patients.

- **Whole treatment period**. For all patients, the start time of this period is when the first dose of study medication, either placebo or risdiplam, is administered to each individual. The end day of this period is the date of the corresponding clinical cutoff date. For the primary analysis, the completion/end time of this period is before dose administration on the third day which is also the last day of the Week 52 visit of the last enrolled patients in Part 2. Data presented for this period will be summarized by treatment group.

Note: At each analysis, all available data up to each clinical cutoff date will also be reported. Refer to Figure 1 for details on key analysis periods.

The following Table 1 will provide an overview on which analysis period will be used for each data type.

Table 1 Overview of Analysis Period

Data Type	Placebo-Controlled Period	Open-Label Treatment Period	First 24 Months Risdiplam Treatment Period for Patients Who Initially Received Risdiplam Treatment [*]	Open-Label Extension Phase	All Exposure to Risdiplam Treatment Period	Whole Treatment Period
Disposition	✓	✓		✓		
Analysis populations and enrollment	✓					
Protocol deviation	✓	✓				✓
Previous and concomitant SMA related surgeries and procedure	✓	✓			✓	
Previous and concomitant medical history	✓	✓			✓	
Previous and concomitant medications	✓	✓			✓	
Nutrition check-up						✓
Safety data						
Exposure of study medication	✓	✓	✓		✓	
Adverse events[a] summary	✓	✓	✓		✓	
Laboratory parameters - abnormal values summary tables **for each time point**	✓	✓	✓		✓	
Laboratory parameters – shift tables **for each time point**	✓				✓[b]	
Vital signs – abnormal values summary tables **for each time point**	✓	✓	✓		✓	
Vital signs – shift tables **for each time point**	✓				✓[b]	

Table 1   Overview of Analysis Period (cont.)

Data Type	Placebo-Controlled Period	Open-Label Treatment Period	First 24 Months Risdiplam Treatment Period for Patients Who Initially Received Risdiplam Treatment [*]	Open-Label Extension Phase	All Exposure to Risdiplam Treatment Period	Whole Treatment Period
Electrocardiogram (ECG) – abnormal values summary tables **for each time point**	✓	✓	✓		✓	
ECG – shift table **for each time point**	✓				✓[(b)]	
Suicidality assessment (C-SSRS) – summary tables on number of events	✓	✓	✓		✓	
C-SSRS – shift table **for each time point**	✓				✓[(b)]	
Ophthalmology –overview summary tables (number of clinically significant values or abnormal values)	✓					✓
Ophthalmology – overview summary tables in the last assessment visit (number of clinically significant value or abnormal values)	✓					✓
Ophthalmology – summary table **at each time point** (number of clinically significant value or abnormal values)	✓					✓
Ophthalmology – numerical summary tables **at each time point** (actual numerical values and change from original baseline values)	✓					✓

Table 1 Overview of Analysis Period (cont.)

Data Type	Placebo-Controlled Period	Open-Label Treatment Period	First 24 Months Risdiplam Treatment Period for Patients Who Initially Received Risdiplam Treatment [*]	Open-Label Extension Phase	All Exposure to Risdiplam Treatment Period	Whole Treatment Period
Tanner staging – delayed puberty results **at each time point**	✓				✓	
Anthropometric exam **for each time point**	✓				✓[(b)]	
Efficacy data (only for summary tables)						
Motor function measure (MFM) **for each time point**	✓				✓	
Hammersmith functional motor scale expanded (HFMSE) **for each time point**	✓				✓	
Revised upper limb module (RULM) **for each time point**	✓				✓	
Respiratory data: sniff nasal inspiratory pressure (SNIP), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), peak cough flow (PCF), maximal expiratory pressure (MEP) and maximal inspiratory pressure (MIP) **for each time point**	✓				✓	

Table 1   Overview of Analysis Period (cont.)

Data Type	Placebo-Controlled Period	Open-Label Treatment Period	First 24 Months Risdiplam Treatment Period for Patients Who Initially Received Risdiplam Treatment [*]	Open-Label Extension Phase	All Exposure to Risdiplam Treatment Period	Whole Treatment Period
Disease-related adverse events summary	✓				✓	
Clinical Global Impression of Change Scale (CGI-C) **for each time point**	✓				✓	
Patient reported and parent/caregiver reported SMA Independence Scale (SMAIS) **for each time point**	✓				✓	

[*]Only applied for the 24 months reporting event.

a   The analysis treatment periods for each of the different types of adverse events will be described in Section 4.8.2.

b   Shift tables using adjusted baseline.

3. STUDY CONDUCT

3.1 RANDOMIZATION PROCEDURES

Randomization is performed using an Interactive (voice/web) Response System (IxRS). Separate randomization lists are generated for the exploratory dose-finding Part 1 and the confirmatory Part 2 of the study.

In the confirmatory Part 2 of the study, patients who meet all eligibility criteria after screening will be randomly assigned to either risdiplam or placebo. Patients are randomized to the selected dose of risdiplam from Part 1 or placebo in a 2:1 ratio. The randomization is also stratified by age group (2 to 5, 6 to 11, 12 to 17, and 18 to 25 years at randomization).

Sites should call the IxRS to enter the patient into screening and to register a screen failure. The randomization call to the IxRS should occur on Day −1 after the patient's eligibility (i.e., inclusion/exclusion criteria) has been confirmed. The patient number is allocated by IxRS and is used in the clinical database to record data in the electronic Case Report Form (eCRF).

3.2 INDEPENDENT REVIEW FACILITY

3.2.1 Ophthalmological Examinations

Images obtained from optical coherence tomography (OCT) assessments, fundus photography assessments, fundus auto-fluorescence (FAF) examinations (if performed), and visual field perimetry threshold (if performed) assessments will be sent to the central readers in the Annesley Eye Brain Center (AEBC) for review. This will include an assessment of clinically significant changes from baseline in each of these examinations at each time point (each scheduled assessment). The role and the process of the review of the AEBC will be documented in a separate charter.

3.3 DATA MONITORING

An external independent Data Monitoring Committee (iDMC) was established to monitor patient safety during Part 2 of the study. The iDMC will review safety and PK data for all ongoing Part 1 patients who have continued and been treated in the OLE phase and for all Part 2 patients.

The iDMC will meet on a regular basis, approximately every 3 months over the course of Part 2 of the study to review emerging data and also meet on an ad-hoc basis as required (e.g., if any unexpected safety concerns arise).

Analyses required for the iDMC's safety data review will be performed as described in the iDMC Charter. Data displays will be prepared by an independent Data Coordinating Center (iDCC).

The roles, responsibilities, membership, scope of activities, time of meetings, and communication plans for the iDMC are documented in the iDMC Charter. 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 POPULATIONS

4.1.1 Safety Analysis Population

4.1.1.1 Safety Population

All patients in Part 2, who received at least one dose of the study medication, risdiplam or placebo, whether prematurely withdrawn or not, will be included in the safety population. This population is the primary safety analysis population to compare risdiplam to placebo.

Patients who were not randomized but received study medication in Part 2 will be included in the safety population and will be summarized as follows:

- Patients who receive any risdiplam treatment will be reported under the risdiplam treatment group.

- Patients who receive only placebo will be reported under the placebo group.

For the placebo-controlled period of Part 2, patients who receive study medication different from that to which they were randomized will also be included in the safety population and will be reported as follows:

- Patients who were randomized to placebo and receive any risdiplam treatment will be reported under the risdiplam treatment group.

- Patients who were randomized to risdiplam and receive both placebo and risdiplam treatment will be reported under the risdiplam treatment group.

- Patients who were randomized to risdiplam and receive only placebo will be reported under the placebo group.

4.1.1.2 All Exposure Population

All patients who received at least one dose of risdiplam at any dose level in Part 2 will be included in the risdiplam all exposure population.

For patients randomized to placebo prior to switching to risdiplam, their data will only be included from the date of the first active dose of risdiplam received.

4.1.2 Pharmacokinetic Analysis Population

All patients in Part 2 with at least one time point with a concentration measurement will be included in the PK analysis data set. Patients will only be excluded from the

PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete or not consistent with the treatment received which may influence the PK analysis. Excluded cases will be documented together with the reason for exclusion.

4.1.3 Efficacy Analysis Population

The intent-to-treat (ITT) population defined as all randomized patients in Part 2 will be the primary analysis population for all efficacy analyses. Patients under the ITT population will be reported according to the treatment they were randomized to. Patients who were not randomized but received study medication will be excluded from the ITT population.

4.2 ANALYSIS OF STUDY CONDUCT

4.2.1 Study Enrollment

The number and percentage of patients in each of the ITT and safety populations will be summarized by treatment group and total for all patients. The number and percentage of patients excluded from each of the populations will be summarized by reason for exclusion. The patients excluded from the analysis populations will also be listed. The number and percentage of patients enrolled at each country and site will also be summarized by treatment group and total for all patients.

4.2.2 Patient Disposition

The number and percentage of patients enrolled entered, completed, and discontinued early will be summarized by treatment group for the placebo-controlled period, by treatment group and total for all patients for the open-label treatment period, and total for all patients for the OLE phase, and by last treatment received for the follow-up period. The reasons for early discontinuation during each of the periods will also be summarized and listed.

4.2.3 Protocol Deviations

The major protocol violations will be identified according to the Management of Violations to Protocol Specifications document before database lock for the primary analysis. The number and percentage of patients with major protocol violations categorized by protocol violation criterion will be summarized by treatment group and total for all patients separately for the placebo controlled period and the open treatment period. Major protocol deviations will also be listed and evaluated for their potential effects on the interpretation of study results.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

4.3.1 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the ITT population using descriptive statistics, means, standard deviations, medians, interquartile range, and ranges for continuous variables and number and percentages for categorical

variables, as appropriate. Baseline is defined as the last measurement prior to first dose of study medication (placebo or risdiplam). Data will be presented by treatment group and total for all patients for the following:

- Age at randomization (years)
- Age groups of 2 to 5, 6 to 11, 12 to 17, and 18 to 25 years old
- Sex
- Height (in centimeters [cm]), also summarized by age groups of 2 to 5, 6 to 11, 12 to 17, and 18 to 25 years old
- Height-for-age percentile (inclusively only up to 19 years old) and by age group
- Weight (in kilograms [kg]), also summarized by age groups
- Weight-for-age percentile (inclusively only up to 10 years old, as the WHO data reference data for weight-for-age is only up to 10 years old) and by age group of 2 to 5 and 6 to 10
- Body mass index (BMI), also summarized by age groups
- BMI-for-age percentiles (inclusively only up to 19 years old) and by age group
- Head circumference (in cm) (those aged 5 years or younger at screening)
- Head circumference-for-age percentile (inclusively only up to 5 years old)
- Self/caregiver-reported race
- Self/caregiver reported ethnicity

4.3.2   SMA Disease Characteristics at Baseline

The following SMA disease characteristics at baseline will be summarized by treatment group and total for all patients:

- SMN2 copy number (from genotype analysis)
- SMA type (2 or 3)
- Initial SMA Symptoms, best response
- Ambulatory status (ambulant or non-ambulant)
- Age of onset for initial SMA symptoms, best response in months.
- Duration of disease prior to first dose of study medication (placebo or risdiplam) which is also the time from onset of initial SMA symptoms to first dose of study medication (placebo or risdiplam) in months, defined as

$$\frac{Date\ of\ first\ dose\ of\ study\ medication - Date\ of\ initial\ SMA\ symptom\ onset}{365}\ x\ 12$$

- Duration of disease prior to first dose of risdiplam which is also the time from onset of initial SMA symptoms to first dose of risdiplam in months, defined as

$$\frac{Date\ of\ first\ dose\ of\ risdplam - Date\ of\ initial\ SMA\ symptom\ onset}{365}\ x\ 12$$

- Tracheostomy (yes/no)

- Patient's current level of motor function.

- Highest motor function achieved

- Motor function achieved and maintained, and the corresponding age achieved and/or age lost in months

- Respiratory device(s) used within 2 weeks prior (no pulmonary care, Cough Assist-used daily for therapy, not illness related, Cough Assist-used with an illness, BiPAP Support for less than 16 hours per day, BiPAP Support for more than 16 hours per day, airway clearance through cough assistance)

- Revised upper limb module (RULM) entry item (Item A) score (0, 1, 2, 3, 4, 5, or 6)

- MFM item 9 score. (0, 1, 2, or 3)

- Number and percentage of patient who could or could not sit (sitters and non-sitters)

  Sitting is defined as with a score of ≥ 1 in item 9 of MFM scale and "Could not sit" is defined as with a score of <1 in item 9 of MFM)

- Number and percentage of patients that could or could not stand

  Standing is defined as with a score of ≥ 1 in item 25 of MFM and "Could not stand" is defined as with a score of <1 in item 25 of MFM.

- Number and percentage of patient that could or could not walk (walkers and non-walkers)

  Walking is defined as with a score of ≥ 2 in item 20 of HFMSE and "Could not walk" is defined as with a score of <2 in item 20 of HFMSE

- 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)

4.3.3 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 [PT]") and System Organ Class (SOC) based on the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA). All analyses will be performed using these PT and body systems. Surgeries or procedures performed prior to the first dose date will be summarized separately.

For the coded terms and those surgeries performed prior to first dose date (previous surgeries), the number and percentage of patients who underwent at least one

SMA-related surgery and procedure and the number of surgeries and procedures reported will be summarized by treatment group and total for all patients.

For the coded terms and those surgeries performed after the first dose date (concomitant surgeries), the number and percentage of patients who underwent at least one SMA-related surgery and procedure and the number of surgeries and procedures reported will be summarized by treatment group for the placebo controlled, by treatment group and total for all patients for the open-label treatment period, and total for all patients for the all exposure to risdiplam treatment period. Multiple occurrences of the same procedure for each individual patient (same coded term) will be counted only once.

In addition, 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 similarly for the placebo-controlled period, open-label treatment period and the all exposure to risdiplam treatment period.

For those with tendon release or spinal surgery, data categorized by the following will also be summarized by treatment group and total for all patients:

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

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, surgeries or procedures performed on or after Day 1 and up to Week 52 after study withdrawal/completion will also be summarized similarly.

All SMA related surgeries and procedure results will also be listed which include the investigator reported terms and the corresponding terms by SOC and PT.

4.3.4 <u>Previous and Concomitant Medical History</u>

For all conditions, the term entered by the investigator describing the condition (the "verbatim term") will be assigned to a standardized term (the "PT") and SOC based on

the most up-to-date version of MedDRA. All analyses will be performed using these PT and body systems.

All medical conditions that are recorded in the eCRF from prior to the screening visit will be reported. Previous conditions and concurrent conditions at baseline will be summarized separately. The number and percentage of patients with at least one previous conditions at baseline (including conditions with an onset date prior to screening visit or conditions with an onset date within the 30 days of the screening visit; and the end date is prior to first dose) and the total number of conditions reported will be summarized by treatment group and total for all patient. The number and percentage of patients with at least one concurrent condition at baseline and the number of concurrent conditions reported at baseline (starts prior to the first dose and with no end date or with an end date after the first dose) will be summarized by treatment group for the placebo-controlled period, by treatment group and total for all patients for the open-label treatment period, and for all patients for the all exposure to risdiplam treatment period.

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.

4.3.5   Previous and Concomitant Medications

At the time of primary analysis, for all medications, the term entered by the investigator describing the medications (the 'verbatim term') will be assigned to a standardized term (the 'PT') and drug class on the basis of the International Non-Proprietary Name Drug Terms and Procedure Dictionary. All analyses will be performed using these PT and medication classes.

After the primary analysis for any reporting events, all medications, the term (generic term) entered by the investigator describing the medications will be coded based on the latest version of the WHODrug Global B3 Format Dictionary. The generic term will be coded for 4 Anatomical Therapeutic Chemical (ATC) classes. Each generic term will have one or more ATC classes. The results will be presented in two summary tables:

- by the medication classes and preferred name only for the ATC class 2 and
- by preferred name.

All medications taken by the patients from 30 days prior to the screening visit will be reported for the ITT population. Previous medications (with a start date prior to the screening visit or a with start date within 30 days of the screening visit; and the end date is prior to the first dose date), medications present at baseline (with a start date prior to the first dose and with an end date after the first dose or no end date) and the concurrent medications (with a start date on or after the first dose date up to the date of study withdrawal/completion) will be summarized separately.

The number and percentage of patients taking at least one medication and the total number of medication taken previously will be presented by treatment group and total for all patients. The number and percentage of patients taking at least one medication and the total number of concomitant medication taken will be summarized by treatment group for the placebo controlled period, by treatment group and total for all patients for the open-label treatment period, and total for all patients for the all exposure to risdiplam treatment period. Multiple occurrences of the same medication (same coded term) for an individual will be counted only once.

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

Treatments given for an adverse event (AE) will be summarized separately. Treatments given for prophylaxis will only be summarized at the primary analysis time point but not for any other reporting events after the primary analysis.

4.3.6 Physiotherapy, Occupational Therapy, and Other Forms of Exercise Therapy

All therapies used by patients from 30 days prior to the screening visit are recorded and will be reported.

For multiple records with the same start day and same therapies on the same patient, the record collected as the last schedule time point prior to the clinical cutoff date and marked as "ongoing" or with no end/stop date will be taken for the analysis.

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 treatment group and total for all patients.

4.3.7 Taste Assessment

The taste of the study medication was accessed in patients aged 6 or above after dose administration on Day 7 of the study.

In adults and adolescents (aged 12–25 years), taste was assessed by a taste questionnaire that each patient should complete; entries were reviewed for completeness by the site staff and the patient was asked to complete any blank items. In children aged 6–11 years, taste was assessed using a five-point facial visual hedonic scale; children were encouraged to select the visual face that best reflects how much they liked the taste of the ingested study drug solution.

The taste assessment results will be summarized separately for children age 6–11 years and adult/adolescents aged 12–25 years. The number and percentage of patients within each category for each question on the taste assessments results will be summarized by treatment group and total for all patients at Day 7 on study.

4.3.8   Nutrition Check Up

Nutritional assessment was performed for all patients at the time points as indicated in the SoA. The 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 number and percentage of patients for each meal type (Solid Food, Modified Oral Food Intake, Nasogastric Food Intake, 110% Gastrostomy Tube Fed, Oral Fluid (Milk) Food Intake or Mixed (Fluid/Puréed Food) Oral Food Intake) will be summarized at each time point by treatment group and total for all patients for the whole treatment period.

4.4   EFFICACY ANALYSIS

The ITT population for Part 2 will be the primary analysis population for all efficacy endpoints. The confirmatory efficacy analyses will only include data from patients randomized into Part 2 of the study. The primary efficacy estimand is based on a hypothetical treatment strategy assuming no prohibited medications intended for treatment of SMA are available and patients continue on their randomized treatment until the primary analysis time point. The prohibited medications are defined in the protocol, Section 4.5.2. A treatment policy strategy will also be applied if applicable. For any patients who discontinue study treatment but continue in the study, all data will be included regardless of initialization on prohibited medications.

The baseline/original baseline for Part 2 of the study is defined as the last measurement prior to first dose of the study medication, either placebo or risdiplam. The adjusted baseline is defined as the last measurement prior to the first dose of risdiplam treatment. The adjusted baseline is the same as the original baseline for those patients initially randomized to and receive risdiplam treatment.

Efficacy Data Visit Time Window

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). Results for assessments that are conducted at unscheduled or withdrawal visits will be assigned to the appropriate scheduled study visit with scheduled efficacy assessment 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.

4.4.1   Primary Efficacy Endpoint

The primary endpoint in Part 2 is the change from (original) baseline in the total motor function measure 32 (MFM32) score at Month 12.

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
- 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 $0-100$ 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 across age groups.

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 2 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 (Appendix 5). 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. Patients without a baseline total score derived will not be included in the analysis. If possible, the same assessor should follow the patient throughout the study.

The hypothesis to be tested is that the difference in the mean change from baseline in the total MFM32 score at Month 12 between risdiplam and placebo (δ) is

$$H_0 : \delta = 0 \ \text{ versus } H_1 : \delta \neq 0$$

If the two-sided p-value is ≤5%, then the null hypothesis, of no difference in the mean change from in the total MFM32 score at Month 12 between risdiplam and placebo, will be rejected.

The MFM32 total score and the change from original baseline in the total MFM32 score will be summarized descriptively at each time point (baseline and each post-baseline scheduled assessment visit) for the ITT population 1) by treatment group and 2) by age groups of 2 to 5, 6 to 11, 12 to 17, 18 to 25 years at randomization for the placebo-controlled period. The MFM32 total score and the change from adjusted baseline in the total MFM32 score will also be summarized 1) by treatment group and 2) by age groups of 2–5, 6–11, 12–17, and 18–25 years old at each time point for the all exposure to risdiplam treatment period. The number and percentage of patients with a change from baseline/adjusted baseline MFM32 total score of ≥0, 1, 2, 3, and 4 will also be summarized similarly at each time point for the placebo–controlled period and the all exposure to risdiplam treatment period.

The Mixed Model Repeated Measure (MMRM) analysis will also be performed on the change from baseline in the total MFM32 score using all data collected in Part 2 up to 12 months.

The model can be expressed as the following:
$$Y_i = X_i \beta + Z_i v_i + \varepsilon_t$$
where

- Y_i is the n_i x 1 vector of responses for patient i of the dependent variable.
- X_i is the known n_i x p design matrix of fixed effects.
- β is a p x 1 vector of the unknown population parameters related to the fixed effect.
- Z_i is the known n_i x r random effect design matrix.
- v_i is the r x 1 vector of the unknown parameters for the subject/patient –effect which is distributed as $N(0, \Sigma_v)$.
- ε_i is the random error term for patient i which is a n_i x 1 vector of random residuals distributed independently as $N(0, \Sigma\varepsilon i)$.
- v_i and ε_i are independent.

This is a mixed-effects model which contains components for fixed effects, random effect and the random error term. The dependent variable of this model is the absolute change from baseline total MFM32 score and the fixed effects of the model will include

independent variables of the baseline total MFM32 score, treatment group (placebo or risdiplam), time (i.e., relative to the first dose of randomized study medication in weeks—categorical), treatment-by-time interaction, baseline-by-time interaction and the randomization stratification variable of age (categorical: 2 to 5, 6 to 11, 12 to 17, and 18 to 25 years at randomization). The random effect will include the subject/patient effect. Time will be treated as a repeated variable within a patient (random effects). Patient, treatment, and time will be treated as factor variables and baseline total MFM32 score as covariate.

An unstructured variance–covariance matrix will be applied to model the within-patient variability ($\Sigma\varepsilon i$) in the above model. The components of variance and covariance matrix will be estimated by the restricted maximum likelihood method. Denominator degrees of freedom will be estimated using the Kenward–Roger approximation (2009). If the model does not converge, a heterogeneous autoregressive variance-covariance matrix will then be applied to model the within-patient variability in the above model.
The Statistical Analysis System (SAS) code for the primary repeated measures analysis is included in Appendix 6.

The estimated treatment difference in the mean change from baseline in the total MFM32 score at Month 12 between risdiplam and placebo will be presented with 95% CI.

The individual change from baseline values in the MFM32 total score at Month 12 will be presented in scatter plots for each age group of 2-5, 6-11, 12-17, and 18-25 years old and for each treatment with x-axis by ascending values of 1) age, 2) total MFM32 score at baseline and 3) duration of disease prior to first dose of study medication (placebo or risdiplam).

The mean changes from baseline of the total MFM32 score at each time point up to Month 12 will be plotted for the two treatment groups.

4.4.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are as follows:

Motor Function

- Change from baseline in total score of the Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 12.

- Change from baseline in the total score of the RULM at Month 12.

- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline ≥ 0) on the total MFM score at Month 12.

- Proportion of patients with a change from baseline MFM32 total score of 3 or more (≥ 3) at Month 12.

- Proportion of patients who achieve an improvement of at least one standard error of measurement (SEM; calculated at baseline) on the total MFM score at Month 12.

- Change from baseline in the each of the MFM domain scores of D1, D2, D3, and the total combined score of (D1 + D2) and D2 + D3 at Month 12.

- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline ≥ 0) on the total HFMSE score at Month 12.

- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline ≥ 0) on the total RULM score at Month 12.

- Proportion of patients with a change from baseline HFMSE total score of 2 or more (≥ 2) at Month 12.

- Proportion of patients with a change from baseline RULM total score of 2 or more (≥ 2) at Month 12.

Respiratory

- Change from baseline in the best percentage predicted value of the Sniff Nasal Inspiratory Pressure (SNIP) at Month 12.

In patients aged (at screening) 6 to 25 years only:

- Change from baseline in best percentage predicted value of the forced expiratory volume in 1 second (FEV1) at Month 12.

- Change from baseline in best percentage predicted value of the forced vital capacity (FVC) at Month 12.

- Change from baseline in the best percentage predicted value of the peak cough flow (PCF) at Month 12.

- Change from baseline in the best percentage predicted value of the maximal inspiratory pressure (MIP) at Month 12.

- Change from baseline in the best percentage predicted value of the maximal expiratory pressure (MEP) at Month 12.

Disease-Related Adverse Events

- Proportion of patients who experience at least one disease-related AE by Month 12.

- Number of disease-related AEs adjusted for patient-year (per 100 patient years) at Month 12.

Clinical Global Impression of Change

- The proportion of patients rated by clinicians as no change or improved (i.e., rated as "no change", "minimally improved", "much improved", or "very much improved") in the Clinical Global Impression of Change (CGI-C) Scale at Month 12.

- The proportion of patients rated by clinicians as improved (i.e., rated as "minimally improved", "much improved", or "very much improved") in the CGI-C at Month 12.

Patient- and Caregiver-Reported Outcomes

- Change from baseline in the total score of the caregiver-reported SMA independence scale (SMAIS) at Month 12.

In patients aged 12 to 25 years only

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

All analysis of the secondary efficacy endpoints will be performed on data in Part 2 up to 12 months for each individual. The secondary endpoints will be summarized descriptively at each time point (at each scheduled assessment visit) by treatment group using the ITT population.

4.4.2.1　　Motor Function

Hammersmith Functional Motor Scale Expanded

The HFMSE was developed to assess the motor function ability of individuals aged two years or older, with Type 2 and 3 SMA (O'Hagen et al. 2007). The scale contains 33 items which 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.

Revised Upper Limb Module

The RULM is a scale that assesses specifically the motor performance of the upper limbs in SMA patients. It consists of twenty items that test proximal and distal motor functions of the arm in patients with SMA. The first entry item, used to determine study eligibility 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) with lower scores indicating greater impairment.

4.4.2.1.1　　Analysis of the Motor Function Measures

For items recorded as "Not Done" for both the HFMSE and RULM 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 HFSME. 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.

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.

For the MFM total score, domain score and combined score, please refer to Section 4.1.1 for further details on handling missing items and missing total scores.

Patients without a total score derived at baseline will not be included in the analysis.

The total score and the change from baseline total score of HFMSE, RULM, MFM domain score of D1, D2, D3, the combined score of D1+ D2 and D2 + D3 will be summarized descriptively at each time point for the ITT population by treatment group for the placebo-controlled period. The total score and change from adjusted baseline score of HFMSE, RULM, MFM domain score of D1, D2, D3, the combined score of D1+ D2 and D2 + D3 will also be summarized by treatment group at each time point for the all exposure to risdiplam treatment period. In addition, the total score and the change from baseline or the change from adjusted baseline total score of HFMSE, RULM, MFM domain score of D1, D2, D3, and the total combined score of D1+D2 and D2 + D3 will also be summarized at each time point by age groups of 2–5, 6–11, 12–17, and 18–25 years at randomization for the placebo-controlled period and the all exposure to risdiplam treatment period. The proportion of patients with a change from baseline/adjusted baseline HFMSE and RULM total score of ≥0, 1, 2, and 3 will also be summarized by treatment group at each time point for the placebo-controlled period and the all exposure to risdiplam treatment period.

For continuous endpoints, the change from baseline in the total score of HFMSE at Month 12, the change from baseline in the total score of the RULM at Month 12, the change from baseline in the MFM domain scores of D1, D2, D3, and the total combined score of D1+D2 at Month 12; an MMRM analysis will be performed for each of the endpoints similar to that specified for the primary efficacy analysis. The estimated treatment difference in the mean change from baseline in the score at Month 12 between risdiplam and placebo will be presented with 95% CI.

Three responder analyses will be performed as secondary analyses on the primary efficacy measure (total MFM32 score). For the endpoints of the proportion of patients with a change from baseline MFM32 total score of ≥ 0 and ≥ 3 on the total MFM32 score at Month 12, the responders are defined as those patients who achieve a change from baseline in the total MFM32 score of greater or equal to 0 or to 3, respectively at Month 12. For the endpoint of the proportion of patients who achieve an improvement of at least one SEM on the total MFM score at Month 12, the responders are defined as those patients who achieve an increase in the total MFM32 score by at least one unit of the SEM on the total MFM score at Month 12. The SEM is the standard deviation of the error of measurement of the MFM32 scores.

The SEM to be used will be calculated at baseline with the following equation:

$$\text{SEM} = s \sqrt{1-r}$$

where s is the standard deviation of the MFM32 total scores collected at baseline and r is the reliability. Reliability will be estimated using Cronbach's alpha.

The equation to calculate the Cronbach's alpha (α) (Cronbach 1951) is as follows:

$$\alpha = \frac{K}{K-1}\left(1 - \frac{\sum_{i=1}^{K} \sigma_{I_i}^2}{\sigma_T^2}\right)$$

The Cronbach's alpha (α) is calculated based on the 1) number of items K which is 32 items for the MFM scale, 2) the variance of the MFM32 total score σ_T^2, estimated by all MFM total scores collected at baseline and 3) the variance of each of the MFM 32 items scores at baseline ($\sigma_{I_i}^2$ is the variance of the score of item i which is estimated from all item i scores at baseline)

Cronbach's alpha has a value ranging from 0 to 1. The greater the value of the Cronbach's alpha, the higher the inter-correlation among the MFM items, the more reliable the MFM test is. The higher the reliability estimate will give a smaller SEM estimate; that is, a smaller value of SEM implies a more reliable MFM test.

Patients who withdraw or have missing total MFM32 scores at Month 12 will be classified as a non-responder in the above analyses.

The proportion of patients with a change from baseline ≥ 0 and ≥ 3 on the total MFM score at Month 12 will be analyzed using logistic regression models. The logistic regression model will include the baseline total score, treatment and age group.

The estimated odds ratio for stabilization or improvement at Month 12 for patients treated with risdiplam compared to placebo will be presented with 95% CI. Similar analysis will be performed for the proportion of patients who achieve an improvement of at least one SEM on the total MFM32 score at Month 12.

A cumulative distribution plot will be presented to show the proportion of responders when each possible cutoff point of the MFM32 total score is used as the definition of response. The proportion of patients in each treatment group with each unit of improvement or worsening will be presented in a cumulative plot. At a particular change from baseline MFM32 score X, the proportion of patients with a change of baseline value ≥x will be presented in the cumulative plot. The cutoff points to present in the plot will include the value at 0 (no change), −3, +3, and at one unit of SEM improvement and at one unit of SEM worsening.

Similar cumulative plots for the proportion of responders of HFMSE and RULM will also be presented including cutoff points at the values of 0, −2 and + 2 in the plot.

Individual change from baseline in the HFMSE and RULM total score at Month 12 will be presented in scatter plots for each age group of 2–5, 6–11, 12–17 and 18–25 years old and for each treatment group with x-axis by ascending values of 1) age, 2) total HFMSE/RULM score at baseline and 3) duration of disease prior to first dose of study medication (placebo or risdiplam).

4.4.2.2   Analysis of Respiratory Measures

The respiratory tests for Part 2 of the study include the SNIP, spirometry, MIP, and MEP tests. The SNIP test will be performed for all patients and the spirometry, MIP, and MEP tests will only be performed for patients aged 6 − 25 years old at screening.

The respiratory measurements obtained will include the SNIP, MIP, MEP, FVC, FEV1, and PCF of which FVC, FEV1, and PCF are results obtained from the spirometry tests.

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

A MMRM analysis will be performed on the change from baseline in the best percentage predicted values for each of the respiratory measurements similar to that specified for the primary efficacy analysis. The estimated treatment difference in the best predicted values for each of the respiratory measurements at Month 12 between risdiplam and placebo will be presented with 95% CI.

The change from baseline in best value and in the best percentage predicted value for each of the respiratory measurements will also be summarized by treatment group at each time point for the placebo-controlled period. In addition, the change from adjusted baseline in the best value and in the best percentage predicted value for each of the respiratory parameters will be summarized by treatment group for the all exposure to risdiplam treatment period.

4.4.2.3   Disease-Related Adverse Events

The disease-related AEs and the disease-related AE rate adjusted for patient years (AE rate per 100 patient-years) will be presented.

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 (LLT basket). 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). The lowest level terms included in each basket, coded using the latest version of MedDRA.

- Broad prospectively defined basket with events selected at PT level from all AEs reported in ongoing clinical trials up to January 2019, i.e., prior to unblinding of Part 2 of Study BP39055 (Preferred Term [PT] basket).

For both LLT and PT baskets, terms have been defined for each of the following medical concepts: disease-related AE overall basket, gastro-intestinal disorders, lower respiratory tract infections, respiratory impairment, neuro-musculo-skeletal and connective tissues, nutrition and growth, cardiac not elsewhere classified (NEC), and other NEC.

Note: the same LLT/PT 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 by treatment group for the placebo controlled period and as total for all patients for the all exposure to risdiplam treatment period. Percentages will be based on the number of patients included in the safety population.

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

$$\text{Disease-related AE rate} = (\text{number of disease-related AEs observed} \div \text{total patient-years at risk}) \times 100.$$

where the total patient-years at risk is defined as

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

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

The disease-related AE rate ratio per 100 patient-years is defined as

Disease-related AE rate ratio=(The disease-related AE rate per 100 patient-years for patients treated on risdiplam)÷(The disease-related AE rate per 100 patient-years for patients treated on placebo)

A rate ratio with value less than 1 suggests that the average number of disease-related AEs per 100 patients-years observed in the risdiplam treatment group is less than the average number of disease-related AEs per 100 patient-years observed in the placebo group.

For the placebo-controlled period, the disease-related AE rate results for the Broad prospectively defined basket will be presented by time unit for every 6 months of 0 to ≤6 months, >6 to ≤12 months, and for the whole placebo controlled period of 0 to ≤12 months. For the all exposure to risdiplam treatment period, the disease-related AE rate results for the LLT basket will also be presented by time unit for every 6 months of 0 to ≤6 months, >6 to ≤12 months, >12 to ≤18 months, etc., for every 12 months of 0 to ≤12 months, >12 to ≤24 months, etc., 0 to ≤18 months and 0 to ≤24 months and for the whole all exposure to risdiplam treatment period, where appropriate up to the clinical cutoff date.

4.4.2.4   Clinical Global Impression of Change

The CGI-C is a single item measure of change in global health, using seven response options: "very much improved", "much improved", "minimally improved", "no change", "minimally worse", "much worse", and "very much worse". Clinicians will score patients using this scale based on their impression of change in the patient's global health since baseline.

The proportion of patients rated by clinicians as no change or improved (i.e., rated as "no change", "minimally improved", "much improved" or "very much improved") in the CGI-C Scale at Month 12 will be analyzed using a logistic regression model, including the treatment group and age group. The estimated odds ratio for no change or improved at Month 12 for patients treated with risdiplam compared to placebo will be presented with 95% CI.

Similar analysis will be performed for the proportion of patients rated by clinicians as improved (i.e., rated as "minimally improved", "much improved" or "very much improved") in the CGI-C Scale at Month 12.

Patients who withdraw or have missing CGI-C responses at Month 12 will be classified as non-responders in both of the analyses.

The number and percentage of patients in each category of the response of the CGI-C including missing response will also be summarized by treatment group at each time point during the placebo-controlled period and for the all exposure to risdiplam treatment period.

4.4.2.5 Patient- or Caregiver-Reported Outcomes

For Part 2 of the study, the patient-reported and caregiver-reported (a parent or caregiver, if no parent is available) SMAIS data will be scored. The SMAIS is developed specifically for SMA patients in order to assess function-related independence. The SMAIS contains 29 items, assessing the amount of assistance required from another individual to perform daily activities such as eating, or transferring to/from their wheelchair. Each item is scored on a 0-4 scale (with an additional option to indicate that an item is non-applicable). Lower scores indicate greater dependence on another individual. Calculation of the total score will follow the user manual in Appendix 7. The SMAIS will be completed by patients aged ≥12 years and caregivers of patients aged 2-25 years.

Missing data will be handled according to the user manual in Appendix 7 (including the minimum number of completed items required for calculating 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 MMRM analysis will be performed for each of the patient–reported and caregiver-reported SMAIS total scores similar to that specified for the primary efficacy analysis. The estimated treatment difference in the mean change from baseline in the patient–reported or caregiver-reported total SMAIS score at Month 12 between risdiplam and placebo will be presented with 95% CI.

The actual value and the change from baseline value for the patient-reported and the caregiver-reported total SMAIS scores will be summarized by treatment group at each time point for the placebo controlled period. The actual value and the change from adjusted baseline value for the patient-reported and the caregiver-reported total SMAIS scores will also be summarized by treatment group for the all exposure to risdiplam

treatment period. Results will also be presented similarly by age group of 2–5, 6–11, 12–17, and 18–25 years old at each time point.

Cumulative distribution function plots will also be presented by treatment group for the patient-reported and caregiver-reported change from baseline total SMAIS score.

4.4.2.6 Adjustment for Multiple Testing

To control the Type I error rate due to multiple testing of risdiplam versus placebo for the primary and the six key secondary efficacy endpoints in the ITT population of Part 2 of the study, a gatekeeping approach will be applied to the seven null hypotheses which are grouped into six families. Hypotheses to be tested are ordered hierarchically and the truncated Hochberg procedure will be used in the family which contains more than one hypothesis. The following shows the seven null hypotheses and the six families of the testing for Part 2.

- Family 1 includes the hypothesis for the primary endpoint on the change from baseline total MFM32 score at Month 12 comparing risdiplam versus placebo:

    H_{11} (MFM32)

- Family 2 includes the hypothesis for the proportion of patients who achieve a change from baseline ≥ 3 on the total MFM32 score at Month 12 comparing risdiplam versus placebo:

    H_{21} (Prop. MFM32 ≥ 3)

- Family 3 includes the hypothesis for the change from baseline total score of RULM at Month 12 comparing risdiplam versus placebo:

    H_{31} (RULM)

- Family 4 includes the hypothesis for the change from baseline total score of HFMSE at Month 12 comparing risdiplam versus placebo and also the hypothesis for the change from baseline best percentage predicted value in FVC at Month 12 comparing risdiplam versus placebo:

    H_{41} (HFMSE)

    H_{42} (FVC)

- Family 5 includes the hypothesis for the change from baseline in total score of caregiver/parent reported SMAIS at Month 12 comparing risdiplam versus placebo:

    H_{51} (SMAIS)

- Family 6 include the hypothesis for the proportion of patients rated by clinician as "Improved" in the CGI-C scale at Month 12 comparing risdiplam versus placebo:

    H_{61} (CGI)

Figure 2 Decision Tree for Part 2 Key Efficacy Endpoints for Hierarchical Testing

Family 1: Primary analysis	H_{11} MFM32
Family 2	H_{21} Prop MFM32 $\geq$ 3
Family 3	H_{31} RULM
Family 4	H_{41} HFMSE H_{42} FVC
Family 5	H_{51} SMAIS
Family 6	H_{61} CGI
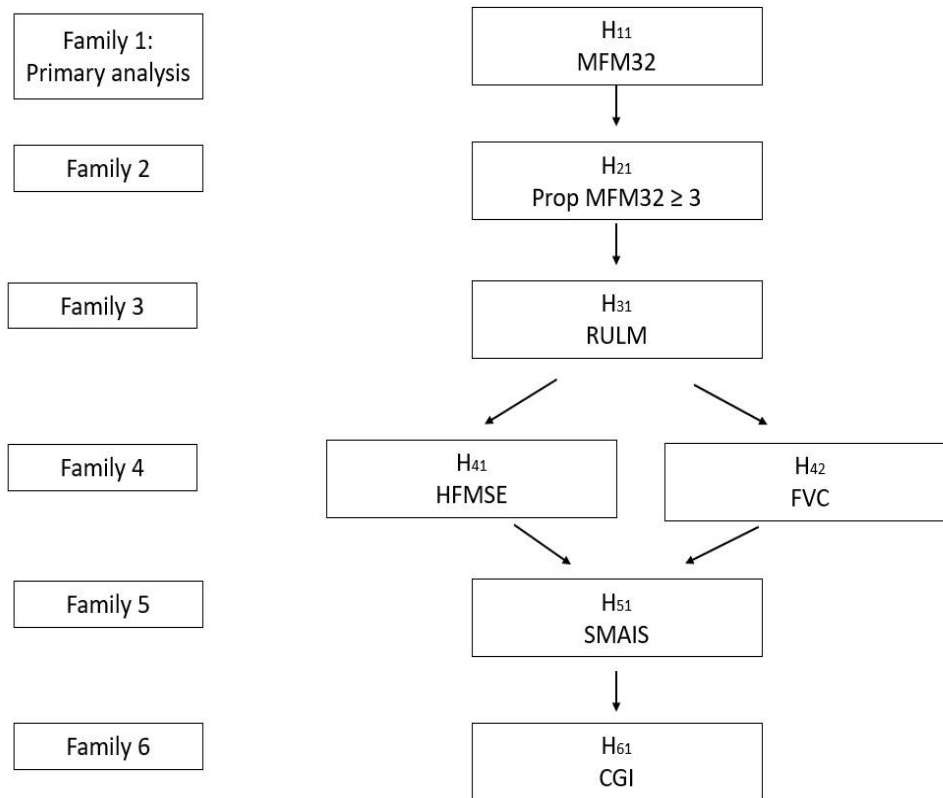
CGI= Clinical Global Impression; FVC=forced vital capacity; HFMSE=Hammersmith Functional Motor Scale Expanded; MFM=Motor Function Measure; RULM=Revised Upper Limb Module; SMAIS=Patient Reported and Parent/Caregiver reported SMA Independence Scale.

The decision tree of the hierarchical hypothesis testing procedure is shown in the above figure. The hypothesis H_{21} is tested if and only if H_{11}, the hypothesis for the primary analysis is rejected. The hypothesis H_{31} is tested if and only if H_{21} is rejected. The hypotheses H_{41} and H_{42} are tested if and only if H_{31} is rejected. The hypothesis H_{51} is tested if and only if one or both of the hypotheses H_{41} and H_{42} are rejected. The hypothesis H_{61} is tested if and only if H_{51} is rejected.

The Hochberg procedure is a stepwise procedure with a data-driven testing sequence. For Part 2 of the study, the truncated Hochberg procedure will only be used in Family 4. The truncation fraction which lies between 0 and 1 ensures the method is separable and allows a positive error rate to be carried over to the next family if at least one null hypothesis in Family 3 is rejected. In this study, the truncation fraction is set to 0.95 to allow a relatively higher weight to Family 4 than to subsequent families (Family 5 and Family 6). As there are only two null hypotheses in Family 4, the truncated Hochberg procedure is equivalent to the truncated Hommel procedure with equivalent stepwise form.

The p-values for each hypothesis will be computed using the MMRM as described in Section 4.4.1. Each of the p-values for the seven hypotheses will be assessed for statistical significance in the following sequence on the basis of the specified threshold α level two-sided for all hypotheses.

- For Family 1 the primary analysis, the nominal p-value of H_{11} will be tested at the 0.05 level, two-sided. When the p-value of H_{11} is ≤ 0.05, the null hypothesis H_{11} will be rejected. If the p-value of H_{11} is >0.05, the null hypothesis H_{11} will be not be rejected, and there will be no further testing for the rest of the families, i.e., no further testing of all the secondary endpoints included in this hierarchy and their corresponding hypotheses (i.e., all hypotheses in Family, 2, 3, 4, 5, and 6 are also not rejected). In this case, the testing of the secondary endpoints will then only be considered as for exploratory purpose and each of these secondary endpoints will be tested at the 5% significance level without adjustment for multiplicity as they are considered as supportive.

- If H_{11} is rejected, hence for Family 2, the p-value of H_{21} will be tested at the 0.05 level, two-sided. When the p-value of H_{21} is ≤ 0.05, the null hypothesis H_{21} will be rejected. If the p-value of H_{21} is >0.05, the null hypothesis H_{21} will not be rejected, and testing stops (i.e., all hypotheses in Family 3, 4, 5, and 6 are also not rejected).

- If H_{21} is rejected, hence for Family 3, the p-value of H_{31} will be tested at the 0.05 level, two-sided. When the p-value of H_{31} is ≤ 0.05, the null hypothesis H_{31} will be rejected. If the p-value of H_{31} is >0.05, the null hypothesis H_{31} will not be rejected, and testing stops (i.e., all hypotheses in Family 4, 5, and 6 are also not rejected).

- If H_{31} is rejected, hence for Family 4, the two hypotheses H_{41} and H_{42} will be tested via the truncated Hochberg procedure in the following sequence:

    The largest p-value will be tested at the 0.04875 level.

    - When the largest p-value is ≤ 0.04875, both null hypotheses of H_{41} and H_{42} will be rejected.

    - If the largest p-value is > 0.04875, the corresponding null hypothesis will not be rejected and the smaller p –value will be tested at 0.025 level.

        If the smaller p-value is ≤ 0.025, the corresponding null hypothesis will be rejected. If the smaller p-value is >0.025, the corresponding null hypothesis will not be rejected and testing stops (i.e., all hypotheses in Family 5 and 6 are also not rejected)

- If both hypotheses H_{41} and H_{42} in Family 4 are rejected, the hypothesis H_{51} in Family 5 will be tested at 0.05 level.

    - If the p-value of H_{51} is ≤ 0.05, the null hypothesis of H_{51} will be rejected. Hence the hypothesis H_{61} in Family 6 will be tested at 0.05 level. If the p-value of H_{61} in Family 6 is ≤ 0.05, the null hypothesis of H_{61} will be rejected. If the p-value of H_{61} is >0.05, the hypothesis H_{61} will not be rejected.

- If the p-value of H_{51} is >0.05, the null hypothesis of H_{51} will not be rejected and testing stops (i.e., hypothesis H_{61} in Family 6 will also not be rejected)

- If only one of the hypothesis of H_{41} or H_{42} in Family 4 is rejected, the hypothesis H_{51} will be tested at 0.00125 level.

  - If the p-value of H_{51} is ≤0.00125, the null hypothesis of H_{51} will be rejected. Hence H_{61} will be tested at 0.00125 level. If the p-value of H_{61} is ≤0.00125, the null hypothesis of H_{61} will be rejected. If the p-value of H_{61} is >0.00125, the null hypothesis of H_{61} will not be rejected.

  - If the p-value of H_{51} is >0.00125, the null hypothesis of H_{51} will not be rejected and testing stops (i.e., hypothesis H_{61} in Family 6 will also not be rejected).

Other secondary endpoints not specified in the above hierarchical testing procedure will be simultaneously tested at the 5% significance level without adjustment for multiplicity as they are considered as supportive.

4.4.3   Exploratory Efficacy Endpoints

The exploratory efficacy endpoints after Month 12 in Part 2 of the study include, but may not be limited to, the following:

Motor Function

- Change from baseline in the total MFM32 score and its domain scores of D1, D2, D3, and the total combined score of D1 + D2 and D2+ D3 at Months 18 and 24.

- Proportion of patients who achieve a change from baseline ≥ 0 on the total MFM32 score at Months 18 and 24.

- Proportion of patients who achieve a change from baseline ≥ 3 on the total MFM32 score at Months 18 and 24.

- Change from baseline in total score of HFMSE at Months 18 and 24.

- Proportion of patient with a change from baseline ≥ 2 on the total HFMSE score at Months 18 and 24.

- Change from baseline in the total score of the RULM at Months 18 and 24.

- Proportion of patients with a change from baseline ≥ 2 on the total RULM score at Months 18 and 24.

Respiratory

- Change from baseline in the best percentage predicted value of the SNIP at Months 18 and 24.

In patients aged (at screening) 6 to 25 years only:

- Change from baseline in best percentage predicted value of the FEV_1 at Months 18 and 24.

- Change from baseline in the best percentage predicted value of the FVC at Months 18 and 24.

- Change from baseline in the best percentage predicted value of the PCF at Months 18 and 24.

- Change from baseline in the best percentage predicted value of the MIP at Months 18 and 24.

- Change from baseline in the best percentage predicted value of the MEP at Months 18 and 24.

Patient/Caregiver-Reported Outcomes

- Change from baseline in the total score of the caregiver-reported SMAIS at Months 18 and 24.

In patients aged 12 to 25 years only

- Change from baseline in the total score of the patient-reported SMAIS at Months 18 and 24.

The adjusted baseline will be used for all patients for the exploratory analyses. For patients initially on active treatment, the actual value (total score or best value of the respiratory measurements) and the change from baseline value at Month 18 and Month 24 will be summarized. For patients initially on placebo treatment, the actual value and the change from adjusted baseline values for placebo patients at Month 18 (i.e., at Month 6 on risdiplam treatment) and at Month 24 (i.e., at Month 12 on risdiplam treatment) will be summarized. Based on the rules of handling MFM, RULM, and HFMSE missing items (defined in Sections 4.4.1 and 4.4.2.1, respectively), patients who have a valid total score calculated at a time point will be included in the analysis for each of the corresponding time point. For the proportion summary tables of responders defined as above for MFM32, HFMSE, and RULM for the all exposure to risdiplam treatment period, the proportion or percentage of responders will be calculated based on the number of patients with a valid total score at the adjusted baseline (i.e., the number of patients with valid results at the adjusted baseline will be used as the denominator value to derive the proportion of responders at each post adjusted baseline time point). Patients who withdraw or have missing total scores post adjusted baseline at Month 18 and at Month 24 on the study (at Month 6 and at Month 12 for those initially receive placebo) will be classified as a non-responder in the above analyses.

Data will be summarized at each time point by treatment group for the all exposure to risdiplam treatment period.

The mean change from original baseline in the total scores of MFM32, RULM, and HFMSE will be plotted over time at each schedule efficacy assessment time point by treatment group up to Month 24 on study.

4.4.4   Sensitivity Analyses

As a supportive analysis to assess the robustness of the primary analysis results based on the MMRM, sensitivity analyses will be performed on the primary efficacy endpoint, the change from baseline in MFM32 at Month 12.

Based on previous clinical studies experiences on SMA Type 2 and 3 patients, the dropout rate is expected to be low. Depending on the amount of missing data due to withdrawal from the study, a tipping point analysis will be performed for the primary hypothetical efficacy estimand. Depending on the number of patients who discontinue treatment, a tipping point analysis may also be performed for the treatment policy estimand.

Tipping Point Analysis

The sensitivity of departures from the missing-at-random (MAR) assumption will be explored using a tipping point analysis. The departures from MAR in the risdiplam arm will be assessed assuming that patients who have monotone (not intermittent missing data) missing data pattern have, on average, the missing monotone efficacy outcomes that are worse by some amount of δ compared to similar patients with observed data, i.e., compared to a value which would have been assumed under the MAR model. The reason for having monotone missing MFM32 total scores in patients are 1) the total MFM32 scores could not be calculated after applying the rule stated in Section 4.4.1 on missing items on the MFM scale and/or 2) patient discontinue the study treatment (or the study).

A series of analyses will be performed with increasing value of δ until the analysis conclusion of statistically significant treatment effect no longer holds. The value of δ that overturns the primary results will represent a tipping point.

Mean change from baseline in MFM32 total score at Month 12 will be analyzed based on data observed while the patient remains on study treatment (or study) with total MFM32 total scores that could be calculated at post-baseline time points as well as data imputed using multiple imputation methodology for time points at which no value is observed. Multiple imputation will be performed using SAS. Intermittent (non-monotone) missing data will be imputed first based on the MAR assumption. This will be based on a multivariate joint Gaussian imputation model using Markov Chain Monte Carlo (MCMC) method. The imputation will be by treatment group. The imputation will include variables of the fixed, categorical effects of age group at randomization and all MFM32 total score at each visit up to Week 52. The MCMC method in the multiple imputation (MI) procedure in SAS will be used with single chain, with 200 burn-in iteration for each chain and 100 iterations between imputations in a chain. A random seed will be chosen for this MCMC stage.

After the imputation for non-monotone data, the remaining monotone missing data will be imputed using sequential regression multiple imputation assuming MAR. A separate

regression model will be estimated for imputation of the MFM32 total score at each time point. At each time point, a regression model will be fitted based on all patients who have observations (imputed or observed) available. The regression model will include the covariates of treatment, age group at randomization and all previous (baseline and all previous visits) values of MFM32 total score. No rounding or range restriction will be applied to imputed continuous values. A random seed different from the MCMC stage will be used here for the sequential imputation stage. The imputed data will consist of 5 imputed datasets.

Multiple imputation of placebo arm will assume MAR as described above. Otherwise, the imputed values in the risdiplam arm will be first sampled based on the above sequential MAR imputation model and then $\delta-$ adjusted as described below.
The MAR-based imputation will be generated for the total MFM32 score at each time point, and then a value of δ, the same value of δ at each time point will be added to all imputed values in the risdiplam arm prior to analyzing multiply imputed data.
This approach assumes that the marginal mean of imputed patients' MFM32 total score is worse by the same δ at each time point after discontinuation of study treatment (or study) compared to the marginal mean of patients with observed data at the same time point. A range of δ s will be used to adjust the post dropout of risdiplam (or study) MAR-imputed data in the risdiplam arm. The size of the δ will be chosen based on the treatment effect of the risdiplam arm generated from the primary repeated measure analysis.

Each of the five datasets (obtained after MAR sequential imputation for placebo arm and after MAR sequential imputation and δ - adjusted for risdiplam arm) will be analyzed as follows: change in MFM total score from baseline to each post-baseline visit will be calculated based on observed and imputed and/or δ - adjusted data. Each dataset will then be analyzed with the same analysis of covariance (ANCOVA) model.
The ANCOVA model will include treatment group and age group as factors, and baseline MFM32 total score as a covariate. The estimated treatment differences in the change from baseline in the total MFM32 score at Month 12 will be calculated as the difference of the least squares means of each treatment group estimated from the ANCOVA model. A treatment difference and its corresponding variances will be calculated for each dataset. The estimates from analyses of each dataset will be combined based on Rubin's imputation rule (1987) to obtain the pooled least square mean estimates for the treatment difference, the corresponding 95% CI, and pooled p-value to test the null hypothesis of no treatment effect.

Analyses will be conducted with a range of values of δ until the null hypothesis can no longer be rejected.

Imputation on Missing MFM Items

The MFM assessments of Part 2 are performed approximately every 4 months during the placebo–controlled period of the study. If 5% or more of the ITT population are excluded from the primary analysis (i.e., patients are excluded based on the rule for

handling MFM missing items defined in Section 4.4.1), a sensitivity analysis will be performed for the primary endpoint by imputing scores in missing MFM items for all patients based on the method defined as follows:

- If an item is "Not Done" at the original baseline, the value of this item at baseline will be imputed by the same value of the same item from the screening visit if available.

- If an item is "Not Done" at the post baseline time point of Week 17 or Week 35, the value of the item will be imputed by the mean value of the previous and next visit of the same item.

- If an item is "Not Done" at Week 52 or at the patient's last visit, a last observation carried forward imputation will be applied. The value of this item at Week 52 will be imputed by the same value of the same item from a previous visit.

After applying these rules, if there are still 3 or more items missing in D1, 3 or more items missing in D2, or 2 or more missing items in D3; the total score will be treated as missing. If there are ≤2 missing items in D1, or ≤2 missing items in D2, or ≤1 missing item in D3; these missing items will be imputed to "0" as described in Section 4.4.1.

Efficacy Responder Analysis for the All Exposure to Risdiplam Period

Sensitivity analyses will be performed on MFM32 and RULM assuming patients who withdraw or have missing total scores at any post adjusted baseline time point will be classified as having missing results, but not as non-responders. In this analysis, the proportion or percentage of responders will be calculated based on the number of patients with a valid total score at both the adjusted baseline and at each corresponding post adjusted baseline time point (i.e., at Month 24 on study, the number of patients with valid results at both adjusted baseline and at Month 24 on study will be used as the denominator value to derive the proportion of responders).

4.4.5 Subgroup Analyses

The consistency of the treatment effect for the primary endpoint will be explored for the following baseline age, region and measures of disease severity subgroups:

- Age group (2−5, 6−11, 12−17, 18−25 at randomization)

- Disease severity (Patient with MFM32 baseline total score below and equal to the first quartile ≤**Q1** (i.e., ≤25th percentile), above the first quartile and below or equal to the third quartile >**Q1** to ≤**Q3** (i.e., >25th percentile and ≤75th percentile) and above the third quartile >**Q3** (i.e., >75th percentile)

- SMA type (Type 2, Type 3)

- Region (North America, Europe, China, Japan, rest of the world)

- SMN2 copy number (<2, 2, 3, ≥4 copies, unknown) from genotype analysis

For the age subgroup analysis, an additional interaction term of treatment-by-age group will be added into the primary model. For the other subgroups, the additional subgroup and treatment-by-subgroup terms will be added into the primary model. The estimated

treatment difference in the mean change from baseline in the total MFM score between risdiplam and placebo will be presented with 95% CI for each subgroup category. p-values will be interpreted in an exploratory manner. The change from baseline in the MFM32 total score at Month12 will be presented in a forest plot by subgroup with the corresponding 95% CI confidence interval of the mean change of baseline in the MFM32 total score at Month 12.

For the secondary endpoints for the proportion of patients with a change from baseline in the total MFM32 score of ≥3,the change from baseline in the total RULM and HFMSE score and the change from baseline in the best percentage predicted value in FVC; all subgroup analyses as defined above will also be performed.

For reporting events after the primary analysis, analyses will be performed for all the subgroups defined above with results summarized by treatment group at each time point for the all exposure to risdiplam treatment period. The total score and the change from adjusted baseline total scores in MFM32, RULM, HFMSE, and SMAIS, and the proportion of patients with a change from adjusted baseline in the total MFM32 score of ≥0 and ≥3 will be summarized by subgroups at each time point. The corresponding 95% CI of the mean total score and mean change from adjusted baseline total score will also be presented at each time point.

In addition, for the subgroup

- HFMSE total score at original baseline (with total score <10 or ≥10)

The change from adjusted baseline in total score of MFM32, RULM, and HFMSE; and the proportion of patients with a change from adjusted baseline in the total MFM32 score of ≥3 will also be summarized for this above subgroup for the all exposure to risdiplam treatment period by treatment group at each time point.

4.5 PHARMACOKINETIC ANALYSES

Patient exposure to risdiplam and the following parameters will be assessed (if possible, based on the available data):

- Concentration per time point listed.
- C_{max}
- AUC_{0-24h}
- 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 SoA in the protocol for all Part 2 patients (Appendix 2, Appendix 3, and Appendix 4).

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

Individual and mean plasma concentration of risdiplam and metabolite(s) versus time data will be plotted.

Nonlinear mixed effects modeling (software NONMEM) will be used to analyze the sparse samples of concentration-time data of risdiplam (and its metabolites if deemed necessary). Population and individual PK parameters will be estimated and the influence of various covariates (such as age, gender, body weight, etc.) 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 parameters 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.

The details of the modeling and exploratory analyses may be reported in a document separate from the Clinical Study Report (CSR).

4.6 PHARMACODYNAMIC ANALYSES

The PD parameters collected from Part 2 of the study include the in vivo SMN mRNA and SMN protein in blood. The PD samples are collected as per the SoA in the protocol for all Part 2 patients (Appendix 2, Appendix 3, and Appendix 4).

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, including, for example, scatterplots of absolute SMN protein level and percent change from baseline in SMN protein level versus change from baseline in the total MFM score, change from baseline in the total score of HFMSE, change from baseline in total score of RULM, and the change from baseline in the best percentage predicted value in FVC at Months 12 by treatment group.

The details of the modeling and exploratory analyses may be reported in a document separate from the CSR.

4.7 PHARMACOECONOMIC ANALYSIS

Analysis of pharmacoeconomic (PE) data (EQ-5D-5L, WPAI: CG-SMA) and the production of a final PE report will be handled separately from the clinical reports of this study.

Information obtained in this study may be combined with other data such as cost data or other clinical parameters in the production of a final PE report.

4.8 SAFETY ANALYSES

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

- Incidence of AEs (overall, by severity and by relationship to study medication)

- Incidence of serious AEs (SAEs)

- Incidence of treatment discontinuations due to AEs

- Incidence of deaths

- Incidence of laboratory abnormalities.

- Incidence of ECG abnormalities

- Incidence of vital sign abnormalities

- Incidence of suicidal ideation or behavior (C-SSPS)

- Incidence of clinically significant findings on ophthalmological examination

- Incidence of clinically significant findings on neurological examination

All patients who receive at least one dose of risdiplam or placebo will be included in the safety population. This population will be the primary analysis population to compare the safety of risdiplam to placebo.

For Part 2 of the study, all available safety data up to the clinical cutoff date for the respective analysis will be reported. The safety data will be summarized descriptively by treatment group for the first 12-month placebo-controlled period (i.e., 0 to $\leq$12 months of treatment for each individual) and by treatment group and total for all patients for the open-label treatment period (i.e., >12 months to $\leq$24 months of treatment for each individual).

The safety data for patients initially on active treatment will also be summarized for their first 24-month treatment period. Longer term safety of risdiplam treatment (all exposure to risdiplam treatment period), including safety data collected in the OLE period (post 24 months of treatment), will also be summarized using the risdiplam all exposure population.

Safety Data Visit Time Window

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). 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 (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.

4.8.1 Exposure of Study Medication

For the placebo-controlled period, the extent of exposure to study medication, either risdiplam or placebo, will be summarized by treatment group using descriptive statistics. The extent of exposure to risdiplam will also be summarized by treatment group, and total for all patients, for the open-label treatment period. For patients initially on active treatment, the extent of exposure to risdiplam will also be summarized for the first 24 months of treatment. For the all exposure to risdiplam treatment period, the extent of exposure on risdiplam will be summarized as total for all patients.

The following extent of exposure of study medication will be included in each of the summary tables:

- Duration of study medication, which will be calculated from the first day of the study medication to the last day of study medication **for each period**, and is calculated by

  Duration of study medication $=$ Date of the last dose $-$ Date of first dose $+1$ (day).

- 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 missed dose(s)

- Number of over dose(s)

- Number of partial dose(s) taken

- Dose intensity in percentage, which is calculated by

  Dose intensity $\% = $ (number of non-missing doses $\div$ number of doses expected for the duration the patient is already on the study) $\times 100$

  The number and percentage of patients with dose intensity $<80\%$ and $\geq 80\%$

Note: Any available study medication exposure data available during the open-label treatment period and the OLE phase at the time of each clinical cutoff date will also be reported. 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.

4.8.2 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 "PT") based on the most up-to-date version of MedDRA. All data displays of AEs will be performed using the SOC and PT. 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 SAEs, AEs by greatest intensity/severity according to the 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 who receive any treatment 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 adjusted for patient years for all occurrences will also be summarized overall for all System Organ Classes (SOC), for each SOC and for each preferred term (PT). The AE and SAE rate per 100 patient-years which is also the average number of events per 100 patient-years is calculated by

$$\text{AE rate} = (\text{number of AEs observed} \div \text{total patient-years at risk}) \times 100.$$

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% CI of the 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 AE rate.

The AE rate ratio per 100 patient-years defined as

AE Rate ratio = (the AE rate per 100 patient -years for patients initially on risdiplam treatment)/(the AE rate per 100 patient-years for placebo patients)

A rate ratio with value less than 1 suggests that the average number of AEs per 100 patient-years observed in the risdiplam treatment group is less than the average number of AEs per 100 patient-years observed in the placebo group. The AE rate ratios will be summarized.

For the placebo-controlled period, the AE/SAE rate will be presented every 6 months of 0 to $\leq$ 6 months, >6 to $\leq$12 months and for the whole 0 to $\leq$12 months placebo

controlled period. For the open-label treatment period, the AE/SAE rate will also presented for every 6 months for >12 to ≤18months and >18 to ≤24 months and the whole >12 to ≤24 months open-label treatment period. Similarly for the first 24 months treatment period for patients initially on active treatment and for the all exposure to risdiplam treatment period, the AE/SAE rate results will be presented by time unit for every 6 months of 0 to ≤ 6 months, >6 to ≤12 months, >12 to ≤18months, etc., for every 12 months of 0 to ≤12 months, >12 to ≤24 months, etc., 0 to ≤18 months, and 0 to ≤24 months and for the whole corresponding treatment period where as appropriate up to the clinical cutoff date.

The AE by greatest intensity/severity rate adjusted per 100 patient years and the AE related to study drug rate adjusted per 100 patient years will also be presented for the placebo controlled period in terms of every 6 months of 0 to ≤ 6 months, >6 to ≤12 months and for the whole 0 to ≤12 months placebo controlled period.

AEs of special interest (AESIs) will also be listed. The AESI rate adjusted per 100 patient years will also be presented for the all exposure to risdiplam treatment period. The following AESIs, as defined in the protocol, are:

- Cases of potential drug induced liver injury that includes an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 x Upper Limit of Normal [ULN]) in combination with either an elevated total bilirubin > 2 x 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.

The overall number of patients experiencing at least one AE/SAE, the total number of AEs/SAEs reported and AEs by PT will also be summarized separately for the age groups of 2 to 5, 6 to 11, 12 to 17, and 18 to 25 years old.

For reporting event after the primary analysis, the results for AEs and SAEs will also be summarized for the all exposure to risdiplam treatment period as total for all patients on all relevant preferred terms which are defined within each of the following 6 categories/baskets in MedDRA.

- Lower respiratory tract infection (LRTI)
- Upper respiratory tract infection (URTI)
- Urinary tract infection (UTI)
- Rash
- Nausea and vomiting
- Oral mucosal ulceration including cheilitis

The number of AEs and SAEs and the number of patients with at least one AE/SAE will be summarized for each of the above 6 baskets for the all exposure to risdiplam treatment period. In addition, the AEs and SAEs rates adjusted per 100 patient years will be summarized for each of the above 6 baskets for the all exposure to risdiplam treatment period by time unit for every 6 months of 0 to ≤6 months, > 6 to ≤12 months, >12 to ≤18months, etc., for every 12 months of 0 to ≤12 months, >12 to ≤24 months, etc., and 0 to ≤24 months and for the whole corresponding treatment period where as appropriate up to the clinical cutoff date.

Table 2 provides an overview of the treatment periods that will be used to summarize AEs as described above.

Table 2 Overview of Analysis Periods of Adverse Events

	Placebo-controlled (0 to ≤ 12 months)	Open-label treatment (> 12 months to ≤ 24 months)	#First 24 months risdiplam treatment period for patients initially on risdiplam (0 to ≤ 24 months)	All exposure to risdiplam treatment	Follow-up period
*Overview summary of AEs/SAE	✓	✓	✓	✓	✓
*AEs/SAEs by PT	✓	✓	✓	✓	✓
AEs by intensity (Grade)	✓	✓	✓	✓	✓
AEs/SAEs related to study medication	✓	✓	✓	✓	✓
AEs leading to study medication adjustment	✓			✓	
AEs leading to withdrawal of study treatment	✓			✓	
AE outcomes	✓	✓	✓	✓	
Most common AEs reported in ≥ 5 % of patients who receive any treatment	✓	✓	✓	✓	
AE rate/SAE rate per 100 patient years	✓	✓	✓	✓	
AE of special Interest rate per 100 patient years				✓	
AEs by intensity rate per 100 patient years	✓				

Table 2   Overview of Analysis Periods of Adverse Events (cont.)

	Placebo-controlled (0 to ≤ 12 months)	Open-label treatment (> 12 months to ≤ 24 months)	#First 24 months risdiplam treatment period for patients initially on risdiplam (0 to ≤ 24 months)	All exposure to risdiplam treatment	Follow-up period
AEs related to study drug rate per 100 patient years	✓				
AEs/SAEs based on the 6 baskets defined in MedDRA				✓	
AE/SAE rate per 100 patient years based on the 6 baskets defined in MedDRA				✓	

AE=adverse event; PT=Preferred Term; SAE=serious adverse event.

*Summary tables that will also be presented by age groups.

#Only for the 24-month reporting event.

Note: All available data at the time of the clinical cutoff date will be reported. All AE records with a start date on or before the clinical cutoff date will be included in the data cut.

- **Placebo-controlled period** (0 to ≤12 months). For all patients, this will include the AEs with onset during the placebo-controlled period or existing AEs which worsen in intensity during the placebo-controlled period, specifically:

  – with onset date on or after the first day of administration of the study medication (placebo or risdiplam) (Day 1); OR

  – with onset date prior to the first dose day (Day 1), is unresolved, and the most extreme intensity is worse than the initial intensity;

  and up to the earliest date of study withdrawal during the placebo-controlled period or before dose administration on Day 3 of Week 52 visit (Day 366) for each individual. AE results for the placebo controlled period will be summarized by treatment group.

- **Open-label treatment period** (>12 to ≤24 months). For all patients, this includes the AEs with onset during the open-label treatment period or existing AEs which worsen in intensity during the open-label treatment period, specifically:

  – with onset after dose administration in the third day which is also the last day of the Week 52 visit (Day 366); OR

- with onset during the placebo-controlled period, is unresolved, and the most extreme intensity is greater, i.e., worse than the initial intensity;

and up to the earliest date of study withdrawal during the open-label treatment period or before dose administration on the second day also the last day of their Week 104 (Day 729) visit. AE results for the open-label treatment period will be summarized by treatment group and total for all patients.

- **First 24 months risdiplam treatment period for patients initially on risdiplam treatment** (0 to ≤24 months for active patients). This will only include patients who were initially randomized to and received risdiplam treatment. This includes the AEs with onset during their first 24 months of treatment period or existing AEs which worsen in intensity during their first 24 months of treatment period, specifically:
    - with onset date on or after the first day of risdiplam administration; OR
    - with onset prior to first risdiplam dose, is unresolved, and the most extreme intensity is greater than the initial intensity;

  and up to the earliest date of study withdrawal during their first 24 months of treatment period or before dose administration on the second day also the last day of their Week 104 (Day 729) visit. AE results in this period will be summarized as total for patients initially on risdiplam treatment.

- **All exposure to risdiplam treatment period.** For all patients, this will include the AEs with onset during their risdiplam treatment period or existing AEs which worsen in intensity during their risdiplam treatment period, specifically:
    - with onset date on or after the first dose of risdiplam; OR
    - with onset date before the first risdiplam dose, is unresolved and the most extreme intensity is greater than the initial intensity.

  AE results for the all exposure to risdiplam treatment period will be summarized as total for all patients

- **Follow-up period.** This only applies to any patient who discontinues treatment and/or withdraws from the study early at any time during Part 2 of the study. This includes the AEs for which
    - the onset date is from 1 day (Day 1 follow up) and up to 52 weeks after study withdrawal/completion; OR
    - the onset date is before Day 1 follow up, is unresolved and the most extreme intensity is greater than the initial intensity during their follow-up period.

  AE results for the follow up period will be summarized by the last treatment received.

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, AE

related to study medication, AE by intensity and AEs resulting in death. Listing will also be presented for AEs of special interest. The AESI rate by patient year will also be presented for the all exposure to risdiplam treatment period.

All AEs results during the follow-up period will be listed.

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.

4.8.3   Deaths

Individual patient listings will be presented with all the details for patients who died at any time during Part 2 of the study and up to 52 weeks after study withdrawal/completion. 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.

4.8.4   Clinical Laboratory Test Results

All clinical laboratory data will be stored on the database in the units in which they were reported. Data will be presented using the International System of Units (SI units; Système International d'Unités). Laboratory data not reported in SI units will be converted to SI units before processing. The normal ranges of all laboratory parameters are based on central laboratory ranges. 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 range and will be labeled "H" for high or "L" for low. The number and percentage of patients with abnormality results (in the direction of abnormality) will also be summarized at each time point for each laboratory parameter by treatment group for the placebo-controlled period, by treatment group and total for all patients for the

open-label treatment period; and as total for all patients for all the exposure to risdiplam treatment period.

For the 24-month reporting event, the abnormality results of the patients initially on risdiplam treatment will also be summarized at each time point for their first 24-month risdiplam treatment period.

The change from baseline values for parameters of hematology, creatinine phosphokinase, creatinine, blood urea nitrogen, and transaminase will be summarized by treatment group at each time point.

A shift table to compare the status at original baseline to each time point (each scheduled assessment visit) post-baseline for the placebo-controlled period will be summarized by treatment group. A shift table will also be presented to compare the status at the adjusted baseline to each time point during the all exposure to risdiplam treatment period with results summarized as total for all patients.

Patients with elevated post-baseline AST or ALT levels results at baseline and at post baseline time points will be summarized by treatment group for the placebo-controlled period, and by treatment group and total for the open-label treatment period, and summarized as total for all patients for all the exposure risdiplam treatment period.

Data collected during safety follow-up will be summarized similarly by their last treatment group prior to withdrawal.

4.8.5 Vital Signs

Vital signs measured throughout the study will include systolic and diastolic blood pressure (SBP and 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 the patient at the time of assessment. The vital signs data will be listed for patients with abnormal values or values outside the normal ranges. The number and percentage of patients with abnormal values (in the direction of abnormality) will also be summarized at each time point by treatment group for each vital sign parameter for the placebo-controlled period and by treatment group and total for all patients for the open-label treatment period. The abnormal value results on risdiplam treatment will also be summarized as total for all patients for the all exposure to risdiplam treatment period.

For the 24-month reporting event, the abnormality results of patients initially on risdiplam treatment will also be summarized for the overall first 24-month risdiplam treatment period.

A shift table to compare the status at original baseline to each time point post baseline (each scheduled assessment visit) for the placebo controlled period will be summarized by treatment group. A shift table will also be presented to compare the status at the

adjusted baseline to each time point during the all exposure to risdiplam treatment period with results summarized as total for all patients.

Data from the follow-up period will also be summarized similarly by their last treatment group prior to withdrawal.

Table 3 shows the normal ranges of each vital sign parameters by age group.

Table 3   Normal Ranges of Vital Signs Parameters by Age Group

	Age (years)			
	2 to ≤6	**6 to ≤8**	**8 to ≤12**	**>12**
Vital signs parameters				
Diastolic blood pressure (mmHg)	60-80			40-90
Systolic blood pressure (mmHg)	90-125			90-140
Pulse rate (beats/min)	70-130	60-110	55-100	50-100
Respiratory rate (breaths/min)	18-30			12-20
Temperature (°C)	35.5-37.8			36.5-37.5

4.8.6   Electrocardiogram Data Analysis

The 12-lead ECG recordings are obtained in triplicate pre-dose at each scheduled assessment time point for Part 2 of the study. The ECG measured throughout this study includes the heart rate (per minute), the PQ or PR interval, QRS interval, QT interval, QTcB (the QT interval corrected by Bazett's formula), QTcF (the QT interval corrected by Fridericia's formula) and the RR interval.

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 or values outside the normal ranges. The number and percentage of patients with abnormality results (in the direction of abnormality) will also be summarized at each time point for each ECG parameter by treatment group for the placebo-controlled period, by treatment group and total for all patient for the open-label treatment period; and summarized as total for all patient on risdiplam treatment for the all exposure risdiplam treatment period.

For the 24-month reporting event, the abnormality results of patients initially on risdiplam treatment will also be summarized at each time point for their first 24-month risdiplam treatment period.

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

A shift table 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 original baseline to each time point post baseline for the placebo controlled period will be summarized by treatment group. A shift table will also be presented to compare the status at the adjusted baseline to each time point during the all exposure to risdiplam treatment period with results summarized as total for all patients.

Table 4 shows the normal ranges of each ECG variable by age group.

Table 4 Normal Ranges of ECG Parameters by Age Group

	Age (years)			
	2 to ≤6	6 to ≤8	8 to ≤12	>12
ECG Parameters				
Heart rate (beats/min)	70–130	60–110	55–100	50–100
PR duration (ms)	80–160			120–200
QT duration (ms)	260–390			200–500
QRS duration (ms)	40–90			80–120
RR duration (ms)	460–860	450–1000	600–1090	600–1500
QTcF (ms)	380–450			300–450
QTcB (ms)	380–450			300–450

ECG= electrocardiogram; PR=time from the onset of the P wave to the start of the QRS complex; QRS=Q wave, R wave, S wave; RR=time between two successive R-waves of the QRS signal; QTcB= corrected QT interval by Bazett; QTcF=corrected QT interval by Fridericia.

The number and percentage of patients with ECG parameter values within each of the ranges given in Table 5 will be summarized by treatment group for the placebo-controlled period and by treatment group and total for all patients for the open-label treatment period. Data will also be summarized as total for all patients for the all exposure to risdiplam treatment period.

For the 24-month reporting event, data will also be summarized for the first 24-month risdiplam treatment period for patients initially on risdiplam treatment.

The actual numerical values and the change from baseline values for each of the ECG parameters will be summarized at each time point by treatment group for the placebo-controlled period. The actual numerical values and the change from adjusted baseline values for each of the ECG parameters will also be summarized as total for all patients for the all exposure to risdiplam treatment period.

Data collected from the follow-up period will be summarized similarly by their last treatment group prior to withdrawal.

Table 5   Ranges of ECG Parameters for Summary Tables

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

ECG= electrocardiogram; PR=time from the onset of the P wave to the start of the QRS complex; QRS=Q wave, R wave, S wave; RR=time between two successive R-waves of the QRS signal; QTcB= corrected QT interval by Bazett; QTcF=corrected QT interval by Fridericia.

4.8.7   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 is used for children (aged 6-11 years). The C-SSRS assessments results are collected at baseline and at time points specified as per the SoA 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.

The number and percentage of patients with

- 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

will be summarized for all patients with at least 1 post-baseline measurement regardless of whether they have a baseline measurement or not. Results will be summarized by treatment group for the placebo-controlled period and by treatment group and total for all patients for the open-label treatment period, and summarized as total for all patients for the all exposure risdiplam treatment period.

For the 24-month reporting event, patients initially on risdiplam treatment will also be summarized for the overall first 24-month risdiplam treatment period.

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 and reach 6 years old at any time during the study, all available post-baseline C-SSRS assessment results will be listed.

Shift tables will be presented to demonstrate the change in C-SSRS endpoints (suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent) for all patients with a baseline measurement and at least one post-baseline measurement.

A shift table using the original baseline will be presented by treatment group at each time point post baseline for the placebo controlled period. A shift table will also be presented to compare the status at the adjusted baseline to each time point during the all exposure to risdiplam treatment period with results summarized as total for all patients.

Results for those patients with suicidal ideation, suicidal behavior, or self-injurious behavior without suicidal intent will be listed. 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 will be summarized similarly.

4.8.8   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, the Sloan Low Contrast Test, visual field threshold perimetry assessment and the simple visual field tests.

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 treatment group for the placebo-controlled period and the whole treatment period. 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 or 4) the end of study date, 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 visit will be summarized. Results will be summarized by treatment group for the placebo-controlled period and the whole treatment period.

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 treatment group for the placebo

controlled period and the whole treatment period. 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 2 months throughout the study up to Month 24 and always comprised SD-OCT assessments. The number and percentage of patients with at least one abnormal or potentially clinically significant SD-OCT results and the total number of abnormal or potentially clinically significant SD-OCT results will be summarized at each time point (presented at least for every 2 months up to Month 24) by treatment group for the placebo controlled period and the whole treatment period. The number of patient 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 (original baseline) values will be summarized under each ophthalmology assessment for each parameter for each eye at each time point by treatment group for the placebo-controlled period and the whole treatment period.

Data collected in any of the ophthalmological assessments (see Section 4.8.8.1 to Section 4.8.8.3) during safety follow-up will be summarized similarly by the last treatment group prior to withdrawal.

Listings will also be presented for all patients with an abnormal or potentially clinically significant result in any of the ophthalmology tests.

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

4.8.8.1   Ophthalmological Examination

This will include the slit-lamp examination, fundus examination, visual testing (including the Bruckner red reflex, corneal reflex, cover/uncover examination) and the intraocular pressure assessment.

4.8.8.1.1   Ocular Examination (Slit-Lamp)

The slit-lamp examination will be performed in all patients across all age groups.

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.

4.8.8.1.2 Fundus Examination

The fundus examination assessment will be performed in all patients across all age groups.

An abnormal or potentially clinically 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 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.

4.8.8.1.3 Ocular Examination (Visual Testing)

This assessment will be performed in patients aged 10 years or younger.

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.

4.8.8.1.4 Intraocular Pressure Assessment

The intraocular pressure assessment will be performed in all patients across all age groups. 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 visual testing 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 $\leq$ - 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; for the method of "digital palpation", the parameter, and actual result for each parameter will be listed, for methods other than "digital palpation", the actual numerical results and the baseline value and the change from baseline values will be listed.

4.8.8.2 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.

4.8.8.2.1 Optical Spectral Domain-Optical Coherence Tomography (SD-OCT)

The SD-OCT will be performed in all patients across all age groups.

An abnormal or potentially clinically significant result in the SD-OCT assessment is defined as:

- A clinically significant change from baseline (as assessed by 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.

4.8.8.2.2 Fundus Photography

The fundus photography or the funduscopy will be performed in all patients across all age groups.

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.

4.8.8.2.3 Fundus Auto-Fluorescence

The FAF examination was introduced when Part 1 of the study was initiated and performed in all patients across all age groups. Since Protocol Version 3 (rest of the world), the FAF examination has been removed and is not required to be performed in patients in the rest of the world population which includes all patients enrolled in countries other than the United States (US). The FAF examination will still be performed in the US study population. 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.

4.8.8.3 Visual Function

This will include the best corrected visual acuity (BCVA) test, the fix and follow test, and the Sloan low contrast test, visual field threshold perimetry assessment and the simple visual field test.

4.8.8.3.1 Best Corrected Visual Acuity and Fix and Follow Tests

The BCVA test will be performed in all patients across all age groups. For those aged 10 years or under and 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 "ETDRS" or "Patti Pics", a decrease of more than or equal to 9 optotypes (i.e., letters or symbols) that could be read compared to baseline. (i.e., change from baseline in the number of optotypes that could be read of $\leq$ -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 $\geq$ 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) 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 method used (EDTRS, Patti Pics, Off chart), the parameter, the actual result of each parameter; for EDTRS and Patti Pics, the total number of 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.

4.8.8.3.2 Sloan Low Contrast Test

The Sloan low contrast test was introduced when Part 1 of the study was initiated and performed in all patients across all age groups. Since Protocol Version 3 (rest of the world), the Sloan low contrast test has been removed and is not required to be performed in patients in the rest of the world population which includes all patients enrolled in countries other than the United States (US). The Sloan low contrast test will still be performed in the US study population. 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 $\leq$ -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 $\geq$ 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.

4.8.8.3.3   Visual Field Threshold Perimetry

The visual field threshold perimetry assessment will be performed in all adults, adolescents and cooperative children >10 years of age.

An abnormal or potentially clinically 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.

4.8.8.3.4   Simple Visual Field Test

This assessment will be performed in all patients aged 10 years or younger, or in other patients who cannot perform the visual field threshold perimetry assessment.

An abnormal or potentially clinically significant results 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.

4.8.9   <u>Anthropometric Examination</u>

The 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 treatment group and by age groups (age at screening) of 2-5, 6-11, 12-17, and 18-25 years old for the placebo–controlled period. The actual value and the change from adjusted baseline values for body weight, height, ulna length (if available), and BMI will be summarized at each time point as total for all patients and by age groups (age at adjusted baseline) of

2-5, 6-11, 12-17, and 18-25 years old during the all exposure to risdiplam treatment period.

For patients aged up to 5 years, the actual value and the change from baseline/adjusted baseline of head circumference values at each time point will also be summarized by treatment group for the placebo controlled period and as total for all patients for the all exposure to risdiplam treatment period.

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

- In patients aged 2–18 years, formulae 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

- In patients aged 19–25 year old, MUST formulae (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)]

The WHO child growth standards (2006) will be used to summarize the percentile and the change from baseline percentile for the weight-for-age, length/height-for-age, head circumference–for-age and BMI-for-age for patients aged 2 up to 5 years old inclusively. In addition, the WHO growth reference data (2007) will also be used to summarize the percentile and the change from baseline/adjusted baseline percentile for the length/height-for-age, BMI-for-age for patients aged above 5 to 19 years old, and for the weight-for-age in patients aged above 5 up to 10 years old.

Since the WHO growth reference data for weight-for-age is not available for patients above 10 years old and also not available for patients above 19 years old for length/height-for-age, BMI-for-age, 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, and the percentile for head circumference-for-age will only be presented up to 5 years old.

The percentile and the change from baseline percentile for the weight-for-age, length/height-for-age and BMI for age will be summarized at each time point by treatment and by age group of 2–5, 6–11 (6–10 for weight-for-age), 12–17, and 18-19 years for all patients aged 19 years old (at screening) or below, by treatment group for the placebo controlled period. The percentile and the change from adjusted baseline percentile for the weight-for-age, length/height-for-age and BMI for age will be summarized at each time point as total for all patient and by age group (age at adjusted baseline) of 2–5, 6–11 (6-10 for weight-for-age), 12–17, and 18-19 years for the all exposure to risdiplam treatment period.

For the head circumference for age, the percentile and the change from baseline/adjusted baseline percentile will be summarized at each time point by treatment group for the placebo controlled period and as total for all patients for the all exposure to risdiplam treatment period.

For the weight-for-age length/height-for-age, head circumference–for-age, and BMI-for–age, the number and percentage of patients within each of the category of percentiles ($<$3rd, $\geq$ 3rd to $<$ 5th, $\geq$ 5th to $<$ 10th, $\geq$ 10th to <25th, $\geq$ 25th to $<$ 50th, and $\geq$ 50th) will be summarized at each time point by treatment group for the placebo controlled period, and summarized as total for all patients for the all exposure to risdiplam treatment period.

Shift table for 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$10th to <25th, and$\geq$25th to$<$50th, $\geq$50th) to each time point post-baseline will be summarized by treatment group for the placebo controlled period. The shift table for weight–for-age, length/height-for-age, head circumference–for-age and BMI-for-age to compare the percentile at the adjusted baseline ($<$3rd, $\geq$3rd to$<$5th, $\geq$5th to$<$10th, $\geq$10th to<25th and$\geq$25th to$<$50th, $\geq$50th) to each time point during the all exposure to risdiplam treatment period will be summarized as total for all patients.

4.8.10   Neurological Examination

Examination will be performed by asking questions to the patient and his/her 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, friend, activities, job, as appropriate), memory (e.g., with short word recall), reasoning and language, drawing, etc.

Individual patient listings will be provided which contain all results for patients who have "Neurological condition not expected with SMA".

4.8.11   Tanner Staging

Tanner staging will be determined at baseline and at scheduled post baseline time points in all patients aged 9−17 years of age at time of enrollment.

The tanner staging results at baseline and at post baseline time points will be summarized separately by gender. The number and percentage of patients who performed the tanner staging assessment at baseline and at post baseline time points and the number and percentage of patients with tanner staging results within each stage (categorized by Stage I to Stage V) at baseline and post baseline time points will be presented for all applicable patients. Similar results will also be summarized at baseline for patients aged 12 years or above at enrollment.

The median ages and the age ranges of patients within each stage of the staging assessment results at baseline and post baseline time points will also be presented by treatment and total for all applicable patients.

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

- Girls: age at assessment $\geq$13 years old with a tanner stage of $<$2
- Boys: age at assessment $\geq$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 treatment group for the placebo controlled period and as total for patients for the all exposure to risdiplam treatment period.

Results of the tanner staging, including the stage of the staging assessment results and any delayed puberty results, will be listed for the whole treatment period.

4.9　　　MISSING DATA

No imputation will be applied for missing data for any of the safety variables.

For the MFM, HFMSE, and RULM, all assessments up to Month 12 will be included in the MMRM analyses. The handling of missing data for the efficacy variables is described in the corresponding sections within this SAP.

To understand the pattern and mechanism of missing data observed during Part 2 of the study, the following will be summarized:

- Time point of discontinuation by treatment group
- The reason for discontinuation by treatment group and time point

4.10　　　INTERIM ANALYSES

No interim analysis will be performed prior to the primary analysis of Part 2 of the study.

4.11　　　ANALYSES 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.

SUNFISH Part 2 had the first patient enrolled in October 2017 and the last patient enrolled in September 2018. When the pandemic occurred, the study was fully enrolled and all patients had completed at least 12 months on study and all placebo patients had been switched to risdiplam treatment. The primary analysis of SUNFISH Part 2 which includes all analyses of the primary endpoint and all secondary endpoints at Month 12 for had also been completed before the pandemic occurred. Therefore, the following COVID-19 related analyses will be performed for reporting events after the primary analysis.

4.11.1 <u>Disposition</u>

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 4.2.2 for the open-label treatment period and/or for the OLE phase if applicable. 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 4.2.2.

4.11.2 <u>Protocol Deviations</u>

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 as total for all patients. The reason for major protocol deviations related to the COVID-19 pandemic will also be summarized as total for all patients. The COVID-19-related major protocol deviations with descriptions and reasons for each corresponding protocol deviation will also be listed.

4.11.3 <u>Safety Analysis</u>
4.11.3.1 Confirmed or Suspected COVID-19 Infection and Associated Adverse Events

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

- Narrow AE search strategy: This search strategy is using the "Roche Standard AE Group Terms (AEGT)–COVID-19" as defined as in Table 6 below.

Table 6   Roche AEGT "COVID-19" Preferred Terms for All Cases (Confirmed and Suspected)

Coronavirus Infection
Coronavirus Test Positive
COVID−19
Coronavirus Test Negative
Sars-CoV−2 Test Positive
Sars-CoV−2 Test Negative
Coronavirus Test
Sars-CoV−2 Test
COVID-19 Pneumonia
Occupational Exposure to Sars-CoV−2
Suspected COVID−19
Exposure to Sars-CoV-2
COVID-19 Immunisation
COVID-19 Prophylaxis
Asymptomatic COVID−19
COVID−19 Treatment
Sars-CoV−2 Carrier
Quarantine
Sars-CoV−2 Test False Negative

AEGT = AE group terms; COVID-19=Coronavirus Disease 2019; Sars-CoV-2=Severe acute respiratory syndrome coronavirus 2.

The 19 PTs of this AEGT allow for the assessment of COVID-19 diagnoses, infections, treatment and carrier status. AEs identified with this search strategy are considered "AEs of suspected or confirmed COVID-19 infections", and patients for whom these AEs are reported are named "Patients with confirmed or suspected COVID-19".

- Broad search strategy: This search strategy includes all AEs of the confirmed/suspected AEs from the "Roche Standard AEGT—COVID-19" in Table 6 above plus any AEs reported in patients with confirmed COVID-19 infection or positive polymerase chain reaction (PCR) test. Confirmed COVID-19 infection or positive PCR test is defined as the 5 preferred terms in Table 7. The additional AEs for the confirmed cases are included if they occurred within ≤7 days before and ≤30 days after start date of any of the AEs in Table 7.

Table 7 Roche AEGT "COVID-19" Preferred Terms for Confirmed Cases

Coronavirus Infection
Coronavirus Test Positive
COVID-19
Sars-CoV-2 Test Positive
COVID−19 Pneumonia

AEGT = AE group terms; COVID-19=Coronavirus Disease 2019; Sars-CoV-2=Severe acute respiratory syndrome coronavirus 2.

With this analysis concept, the impact of COVID-19 infection on the AE profile of patients with a positive COVID-19 diagnosis can be assessed including any complications that may have occurred in patients with a positive COVID-19 diagnosis.

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.

4.11.4 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.

4.12 STATISTICAL ANALYSIS FOR COMPARISON OF SUNFISH PART 2 2 YEARS ON STUDY RESULTS WITH EXTERNAL CONTROL COMPARATOR

4.12.1 Background

This section documents the data-handling rules, derivation rules, and statistical methods of summarizing and analyzing the efficacy data from Part 2 patients of Study BP39055 (SUNFISH) in comparison with the external control comparator group of patients.

Comparison analyses will be performed to compare the Motor Function Measure (MFM) total score results at Month 24 from Study BP39055 (SUNFISH) Part 2 patients randomized to risdiplam with the results of the NatHis SMA study and the placebo arm of Study WN29836. This will include:

- Comparison of Study BP39055 (SUNFISH) Part 2 with the external control population (i.e. all patients from NatHis-SMA study and from the placebo arm of Study WN29836 combined)

- Comparison of Study BP39055 (SUNFISH) Part 2 with the NatHis-SMA study

- Comparison of Study BP39055 (SUNFISH) Part 2 with the placebo arm of Study WN29836

The statistical analysis methods applied to compare the results of Study BP39055 (SUNFISH) Part 2 with the external control population or with each of the NatHis-SMA study and placebo arm of Study WN29836 groups separately will be the same. Both weighted and unweighted analyses will be conducted for each of the three comparisons.

Additional analysis will also be performed to compare the MFM total score results from Study BP39055 (SUNFISH) Part 2 patients randomized to placebo after they have switched to risdiplam (following 12 or 24 months of treatment).

Throughout this Section 4.12, SUNFISH Part 2 patients who were initially randomized to and received risdiplam treatment are called the risdiplam treated patients. For Part 2 patients who initially were randomized and received placebo treatment and after 12 months on study switched to and received risdiplam are called the placebo- risidiplam treated patients. The treated group are patients from SUNFISH Part 2. The untreated group are patients from the external comparator sources.

4.12.2 Analyses to Compare SUNFISH Part 2 Data with External Comparators

The main analyses will be undertaken to compare the change from baseline in MFM total score at Month 24 for the risdiplam treated patients (the treated group) to changes observed in patients from the external control population (the untreated group). Same analyses will be performed to compare the risidplam treated patients (treated group) with patients from each of the individual external comparator sources (each of the untreated groups).

Additional analyses will also be performed to compare the change from baseline in MFM total score at Month 12 or at Month 24 on risdiplam treatment for the placebo-risdiplam treated patients (treated group) to changes observed in patients from external control population (the untreated group).

The analyses results on the comparisons will be documented separately from the Clinical Study Report (CSR).

4.12.2.1 Data Sources for External Comparators

The external comparator will be selected from:

Natural History Study (BP29540)

The NatHis-SMA study is a European, prospective, multicenter, longitudinal natural history study of Type 2 and Type 3 SMA patients conducted at 9 reference centers for neuromuscular diseases in France, Belgium and Germany between May 2015 and May 2018. The study is an investigator-sponsored, Roche-supported study run by the French Institute of Myology (BP29540; NCT02391831). The primary objective of this study is to characterize the disease course in SMA Type 2 and Type 3 patients using standardized evaluations, including the MFM. The study included 81 patients aged

between 2 and 29 years. The maximum duration for participation for each patient was 24 months and all patients were evaluated every 6 months.

Olesoxime Study (WN29836)

Study WN29836 was a Phase II, placebo-controlled, randomized, adaptive, parallel group, double-blind, multicenter study, designed to assess the efficacy and safety of olexosime 10 mg/kg q.d. over a period of 2 years (104 weeks), in 3- to 25-year-old patients with Type 2 or non-ambulant Type 3 SMA. Only the placebo arm of this study will be utilized in this analysis.

The study enrolled 165 patients (57 randomized to placebo) aged between 3 and 25 years from sites in Belgium, France, Germany, Italy, the Netherlands, Poland, and the United Kingdom.

4.12.2.2   Analysis to Compare Risdiplam Treated Patients With External Control Population

For the risdiplam treated patients (the treated group), the baseline is defined as the last measurement prior to first dose of risdiplam treatment. For the patients from external control population (untreated group), the baseline is defined as the last measurement prior to enrollment to the corresponding studies, which is the measurements taken at the baseline visit, at Visit 1 for the NatHist study or at Visit 0 for the placebo arm patients in Study WN29836.

4.12.2.2.1   Statistical Methods
4.12.2.2.1.1 Analysis Population
4.12.2.2.1.1.1   External Comparator Analysis Population and the SUNFISH Part 2 Risidiplam Treated Analysis population

Patients from the external control population will be selected to match the SUNFISH Part 2 risdiplam treated patients based on key inclusion/exclusion criteria. In addition, only patients with a baseline MFM assessment and with at least one post baseline assessment at or beyond Month 12 will be included in the analysis.

Based on the this , the external comparator analysis population includes all Type 2 and Type 3 non-ambulant patients that are enrolled in NatHis-SMA study and from the placebo arm of Study WN29836 with a baseline and at least one post baseline MFM assessment at or beyond Month 12. Similarly, the SUNFISH Part 2 risdiplam treated analysis population included all Type 2 and Type 3 non-ambulant patients that are initially randomized to and received risidiplam treatment with a baseline and at least one post baseline MFM assessment at or beyond Month 12.

4.12.2.2.1.1.2   Unweighted Population – Patients Eligible for Weighting

This is the main analysis population for all the unweighted analyses. Based on the following criteria, patients from the external comparator analysis population and the

SUNFISH Part 2 risdiplam treated analysis population will be excluded from the unweighted population or the group of patients eligible for weighting if:

- There is **Unknown covariate information/prognostic factor.**

    The following covariates: age at baseline, SMA type, baseline MFM score, presence of scoliosis at baseline and SMN2 copy number, are the covariates that are included in the logistic regression model to estimate the propensity score. Patients with unknown information from any of these covariates will not be included in the unweighted population. e.g. patients with unknown status of scoliosis at baseline will be excluded

- **Covariate information is only available in either the treated or untreated group.**

    For a particular category within each covariate (those specified in the above bullet to be used in the logistic regression model for propensity score), if the information is only available from patients in either of the treated or untreated group, then patients having the same characteristics as for this particular category of covariate will not be included in the unweighted population. e.g., if no patient has SMA copy number 2 in the untreated group, but there are some patients with SMA copy number 2 in the treated group. Those treated patients with SMA copy number 2 will not be included in the unweighted population.

- **Outside the overlapping distribution area of the propensity scores between the treated and untreated groups**

    Trimming (Please refer to Section 4.12.2.2.1.2 for details about trimming), will be applied so that patients with propensity scores that are not within the overlapping distribution area of the propensity score between the treated and the untreated group will not be included in the unweighted population.

4.12.2.2.1.1.3   Weighted Population

This is the main analysis population for all the weighted analyses. This is the population obtained after a weight is applied to each of the patients using the inverse probability treatment weighting approach (Section 4.12.2.2.1.2). This weighted Population is a pseudo-population where the covariate profile will be similar between the treated and the untreated groups.

4.12.2.2.1.2 Inverse Probability of Treatment Weighting

Inverse probability of treatment weighting (IPTW) will be used to create a pseudo-population with similar covariate distributions in the treated and untreated groups. A propensity score will be estimated for each patient from the unweighted population using logistic regression incorporating potential predictors of treatment assignment (risdiplam vs no risdiplam) as independent variables. The potential predictors to be included in the model will be age at baseline (years), SMA type (Type 2 and Type 3), baseline MFM total score, presence of scoliosis at baseline (Y/N),

SMN2 copy number (2,3,4) and the MFM scale used in this analysis (MFM32 for aged ≥ 6 years, MFM20 for aged <6 years). Patients with missing data for at least one prognostic factor are excluded from the analysis (as also defined under the unweighted population section). In addition, patients with missing total MFM score at baseline and in at least one post-baseline timepoint at or beyond Month 12 will be excluded.

Trimming will be applied prior to weighting to include only patients with an overlapping distribution of propensity scores.

IPTW will be applied to the propensity scores to derive weights only in the external control group based on the average effect for treated patients (ATT) approach. Let the propensity score of the jth patient in the external comparator group be p_j. A weight of 1 will be given to each of the patients in the risdiplam treated group and a weight of $\frac{p_j}{1-p_j}$ will be given to each of the jth patient in the untreated external comparator group.

To control for too much influence of patients with very low propensity scores, weights will be truncated at the 99th percentile.

4.12.2.2.1.3 Variable Balance Assessment

The variance balance between the treated and untreated groups will be assessed pre and post-weighting. Pre- and post-weighted propensity scores will be presented graphically and standardized mean differences (SMDs) will be computed for all covariates and will be summarised and presented graphically. Adequate balance will be assumed if all SMDs are less than 0.25 (Stuart 2010), but the impact of variables with SMDs >0.1 will be assessed.

If adequate balance is not achieved (at least 1 SMD >0.25), an alternative approach such as matching SUNFISH Part 2 risdiplam patients to the external comparator group using coarsened exact matching may be applied to explore whether better balance can be obtained.

4.12.2.2.1.4 Statistical Analysis

The main analysis will be based on a comparison of SUNFISH Part 2 risdiplam treated patients with the external control population.

Patients that are not included in the unweighted population (i.e. those from the external comparator analysis population and the SUNFISH Part 2 risdiplam treated analysis population that are excluded) will be listed including patients' covariate information and the reason for exclusion.

The baseline characteristics will be summarized for the external comparator analysis population and the SUNFISH Part 2 risidiplam treated analysis population, and the weighted and unweighted populations by the treated and untreated group. For the

untreated group, results will also be presented separately by each source of the external comparator.

All patients in SUNFISH Part 2 were to be assessed using MFM32 regardless of age. In NatHis-SMA study and the placebo group of Study WN29836, patients under the age of 6 were assessed using MFM20 and patients aged 6 and over were to perform MFM32. In order to use the MFM data from all patients and to enable MFM scores to be compared to external controls across all ages, data from patients who completed the MFM32 and those who completed the MFM20 need to be placed onto the same scale. The change from baseline in the MFM total score will be derived based on 1) MFM32 for all patients aged 6 years or above and 2) MFM20 for all patients aged less than 6 years old. All items scores from the 1) MFM32 or the 2) MFM20 scales will be summed up and then transformed onto a 0-100 scale to form the 1) MFM32 or 2) MFM20 total scores and the resulting score is defined as the MFM Total Score. (Of note, 1 point change on the item will be equivalent of 1.04 change in the MFM32 total score and 1.67 change in the MFM20 total score). For visits where the MFM32 was used in patients aged less than 6 years, the 12 additional items will not count towards the scoring algorithm.

A missing item rule on the MFM scale will be applied prior to the calculation of the MFM32 or MFM20 total score. The MFM32 or MFM20 total 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. For the MFM32 scale, in domains D1 and D2, scores will only be calculated if there is a maximum of 2 items missing in each domain, and for domain D3, if a maximum of 1 item missing. For the MFM20 scale, in domains D1 and D2, score will only be calculated if there is a maximum of 1 item missing in each domain, and for domain D3, if no item is 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 1) two missing items in either D1 or D2, and/or one missing item in D3 in the MFM32 scale or 2) 1 missing item in either D1 or D2 for the MFM20 scale; 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 due to missed assessments will not be imputed.

Descriptive statistics will be presented for the change from baseline in MFM total score at Months 12, 18 and 24 for the weighted and unweighted population. In addition, the change from baseline in the MFM total score at Month 24 will be analyzed using the Mixed Model Repeated Measure (MMRM) model. For this MMRM analysis, patients with baseline and at least one post-baseline timepoint at or beyond Month 12 MFM total score will be included in the analysis. This mixed-effect model will contain components for fixed effects, random effects and the random error term. The dependent variable of this model is the absolute change from baseline in the total MFM score.
The independent variables will include baseline MFM total score, treatment, time (time of assessment, i.e., the study visits in weeks [Weeks 17, 26, 35, 52, 78, and 104 –

categorical], treatment –by-time interaction, baseline-by-time interaction, age at baseline, SMA Type, SMN2 copy number, MFM scale used and presence of scoliosis at baseline. The random effect will include the subject/patient effect. Time will be a repeated variable within a patient. Patient, treatment, time, SMA Type, SMN2 copy number, MFM scale used and presence of scoliosis at baseline will be treated as factors variables, and baseline MFM total score and age at baseline as covariates. The schedule of assessments for the NatHist Study and study WN29836 are provided in Appendix 8 and Appendix 9, respectively.

If the model does not converge by including all the independent variables as described above, only selective independent variables will be included in the MMRM model. These selective variables are those included in the primary analysis model for SUNFISH Part 2 which includes the baseline MFM total score, treatment, time, age, treatment –by-time interaction and the baseline-by-time interaction.

An unstructured variance-covariance matrix will be applied to model the within-patient variability in the MMRM model. The components of variance and covariance matrix will be estimated by the restricted maximum likelihood method. Denominator degrees of freedom will be estimated using the Kenward–Roger approximation (2009). If the model which includes selective covariates does not converge, a heterogeneous autoregressive variance-covariance matrix will then be applied to model the within-patient variability in the MMRM model. The Statistical Analysis System (SAS) code for this MMRM analysis is included in Appendix 10.

The least square mean (LS mean) change from baseline in MFM total score, treatment difference and 95% CI at Months 12, 18 and 24 will be presented for the weighted and unweighted populations. The LS means and the corresponding 95% CI on the change from baseline in MFM total score at Month 12, 18 and 24 will also be plotted by treated or untreated groups for the weighted and unweighted populations.

Descriptive summary statistics for the proportion of patients who achieved an improvement which is also a change from baseline of ≥ 0, ≥ 1, ≥ 2, ≥ 3, ≥ 4 in the total MFM score at Month 12, 18 and 24 will be presented for the weighted and unweighted populations. The proportion will be derived based on the number of patients with available MFM total score at baseline and at the corresponding post-baseline timepoint. The number of patients with no MFM change from baseline results at each timepoint will also be presented.

The proportion of patients who achieve an improvement of change from baseline of ≥ 0 and ≥ 3 in the total MFM score at Month 12 and at 24 will be analyzed using a logistic regression model. This model will include treatment, MFM total baseline score and age at enrollment as covariates, and SMA type, SMN2 copy number, MFM scale and presence of scoliosis as factors. The odds ratio and 95% CI will be reported. The logistic regression analysis at Month 12 and 24 will be based on patients with available

MFM total score at 1) both baseline and Month 12 or at 2) both baseline and Month 24, respectively.

4.12.2.2.1.5 Subgroup Analyses

Subgroup analysis will also be performed for the change from baseline in the MFM total score at Month 12 and Month 24 for the following age groups based on age at baseline:

- 2 to 5 years ($\geq$ 2 years to < 6 years)
- 6 to 11 years ($\geq$ 6 years to <12 years)
- 12 to 17 years ($\geq$ 12 years to < 18 years)
- 18 years or above ($\geq$ 18 years)

The results including the treatment differences and corresponding 95% CIs for the overall (all patients) and for each of the subgroups will be presented in forest plots for the weighted population.

4.12.2.2.1.6 Comparison with each of the External Comparator Source

Analysis will also be performed as described in Section 4.12.2.2.1.4 and Section 4.12.2.2.1.5 by comparing the SUNFISH Part 2 risdiplam treated patients results with each of the external comparator sources separately for the unweighted and weighted population, that is, for:

- SUNFISH Part 2 risdiplam patients versus NatHis-SMA study
- SUNFISH Part 2 risdiplam patients versus placebo arm of Study WN29836

4.12.2.2.1.7 Sensitivity Analysis: Missing Results as non-Responders

Responder analyses will also be performed by considering patients with missing MFM total score as non-responders. The proportion and percentage of patients who achieved an improvement of a change from baseline of ≥0, ≥1, ≥2, ≥3, ≥4 in the total MFM score at Month 12, 18 and 24 will be summarized for the weighted and unweighted populations.

The proportion of patients who achieve an improvement of a change from baseline of $\geq$0 and $\geq$3 in the total MFM score at Month 12 and 24 will also be analyzed using the same logistic regression model as defined in Section 4.12.2.2.1.4. The odds ratio and 95% CI will be reported. These analyses will be performed by comparing results in SUNFISH Part 2 risdiplam treated patients based on the external control population, and also by comparing results in SUNFISH Part 2 risdiplam treated patients separately with NatHis-SMA study (Study BP29540) or with placebo arm of Study WN29836 study for the weighted and unweighted populations.

4.12.2.3 Analysis to Compare SUNFISH PART 2 Placebo-Risidplam Treated Patients on Risidiplam Treatment to External Control Population

This analysis will include only the placebo-risdiplam treated patients from SUNFISH Part 2 (treated group) to compare the mean change from baseline in MFM total score at Month 12 or Month 24 on risdiplam treatment to changes observed in the external control population (untreated group). For this analysis, the data sources for the external comparator group are the same as those defined in Section 4.12.2.1.

4.12.2.3.1 Statistical Methods

For the placebo-risdiplam treated patients (treated group), the baseline used which is also called the adjusted baseline which is defined as the last measurement prior to first dose of risdiplam treatment. The original baseline is also defined as the last measurement prior to first dose of study medication, placebo or risdiplam, in SUNFISH Part 2.

For the patients from external control population (untreated group), the same baseline definition will be used from Section 4.12.2.2.

4.12.2.3.1.1 Analysis Population
4.12.2.3.1.1.1 External Comparator Analysis Population and the SUNFISH Part 2 placebo Risidiplam Treated Analysis Population

Patients from the external control population will be selected to match the SUNFISH Part 2 placebo-risdiplam treated patients based on key inclusion/exclusion criteria of which will include all non-ambulatory Type 2 and Type 3 SMA patients. In addition, only patients with a (adjusted) baseline MFM assessment and with at least one post (adjusted) baseline assessment at or beyond Month 12 will be included in the analysis.

The external comparator analysis population is the same as defined in Section 4.12.2.2.1.1.1. The SUNFISH Part 2 placebo-risdiplam treated analysis population will include all Type 2 and 3 non-ambulant patients that are initially randomized to placebo with a (adjusted) baseline and at least one post (adjusted) baseline MFM assessment at or beyond Month 12.

4.12.2.3.1.1.2 Unweighted Population – Patients eligible for weighting

The unweighted population for this analysis is the same as defined in Section 4.12.2.2.1.1.2.

4.12.2.3.1.1.3 Weighted Population

The weighted population is the same as defined in Section 4.12.2.2.1.1.3.

4.12.2.3.1.2 Inverse Probability of Treatment Weighting

The same approach will be applied as described in Section 4.12.2.2.1.2 using the inverse probability of treatment weighting (IPTW) to create a pseudo-population with similar covariate distributions in the treated and untreated groups.

The propensity score will be estimated for each patient in the unweighted population using logistic regression which includes potential predictors of age at (adjusted) baseline (in years) which is the age after 1 year of enrollment for the SUNFISH Part 2 placebo-risdiplam treated patients, SMA type (Type 2 and Type 3), (adjusted) baseline MFM total score, presence of scoliosis at (original) baseline (Y/N), SMN2 copy number (2,3,4) and the MFM scale used in this analysis (MFM32 for aged $\geq$ 6 years, MFM20 for aged < 6 years) in the model. Patients with missing data for at least one prognostic factor will be excluded from the analysis (as also defined under the unweighted population section). In addition, patients with missing total MFM score at (adjusted) baseline and in at least one post (adjusted) baseline timepoint at or beyond Month 12 will be excluded.

Trimming will also be applied to include only patients with an overlapping distribution of propensity scores.

IPTW will be applied to the propensity scores to derive weights only in the external control group as described in Section 4.12.2.2.1.2.

Weights will be truncated at the 99th percentile.

4.12.2.3.1.3 Variable Balance Assessment

The variance balance between the treated and untreated groups will be assessed pre and post-weighting as described in Section 4.12.2.2.1.3. Pre - and post-weighted propensity scores will be presented graphically and standardized mean differences (SMDs) will be computed for all covariates and will be summarized and presented graphically.

4.12.2.3.1.4 Statistical Analysis

The main analysis will be based on a comparison of SUNFISH Part 2 placebo-risdiplam treated patients with the external control population.

Patients that are not included in the unweighted population (i.e. those from the external comparator analysis population and the SUNFISH Part 2 placebo-risdiplam treated analysis population that are excluded) will be listed including patients' covariate information and the reason of exclusion.

The (adjusted) baseline characteristics will be summarized for the external comparator analysis population and the SUNFISH Part 2 placebo risidiplam treated analysis population, and the weighted and unweighted populations by treated and untreated groups. For the untreated group, results will also be presented separately by each external comparator sources.

The MFM total score as defined in Section 4.12.2.2.1.4 will be used for the analysis.

Descriptive statistics will be presented for the change from (adjusted) baseline in MFM total score at Month 12, 18 and 24 for the weighted and unweighted groups. In addition,

the change from (adjusted) baseline in the MFM total score at Month 12 and at Month 24 will be analyzed using the Mixed Model Repeated Measure (MMRM) model. For this MMRM analysis, patients with (adjusted) baseline and with at least one post- (adjusted) baseline results at or beyond Month 12 will be included in the analysis. This MMRM will contain components for fixed effects, random effects and the random error term. The dependent variable of this model is the absolute change from (adjusted) baseline in the total MFM score. The independent variables will include treatment, (adjusted) baseline MFM total score, time (time of assessment, i.e., the study visits in weeks), treatment – by-time interaction, (adjusted) baseline-by-time interaction, age at (adjusted) baseline, SMA Type, SMN2 copy number, MFM scale used and presence of scoliosis. The random effect will include the subject/patient effect. Time will be a repeated variable within a patient. Patient, treatment, time, SMA Type, SMN2 copy number, MFM scale used and presence of scoliosis at original baseline will be treated as factor variables, and (adjusted) baseline MFM total score and age at (adjusted) baseline as covariates.

If the model does not converge by including all the independent variables as described above, only selected independent variables will be included in the MMRM model. These selected variables are those included in the primary analysis model for SUNFISH Part 2 which includes the (adjusted) baseline MFM total score, treatment, time, age, treatment –by-time interaction and the (adjusted) baseline-by-time interaction.

An unstructured variance-covariance matrix will be applied to model the within-patient variability in the MMRM model as described in Section 4.12.2.2.1.4. If the model which includes selected covariates does not converge, a heterogeneous autoregressive variance-covariance matrix will then be applied to model the within-patient variability in the MMRM model.

The least square mean (LS mean) change from (adjusted) baseline in MFM total score, treatment difference and 95% CI at Month 12, 18 and 24 will be also be presented for the weighted and unweighted population. The LS means and the corresponding 95% CI on the change from (adjusted) baseline in MFM total score at Month 12 (for the Month 12 analysis) or at Month 12, 18 and 24 (for the Month 24 analysis) will also be plotted by the treated and untreated groups for the weighted and unweighted groups.

Descriptive statistics for the proportion of patients who achieved an improvement which is also a change from (adjusted) baseline of ≥ 0, ≥ 1, ≥ 2, ≥ 3, ≥ 4 in the total MFM score at Month 12, 18 and 24 will be presented for the weighted and unweighted populations.

The proportion of patients who achieve an improvement of change from (adjusted) baseline of ≥ 0 and of ≥ 3 in the total MFM score at Month 12 and at Month 24 will be analyzed using a logistic regression model. This model will include treatment, MFM total (adjusted) baseline score and age at baseline as covariates, and SMA type, ambulatory status, SMN2 copy number, MFM scale and presence of scoliosis as factors. The odds ratio and 95% CI will be reported. The proportion of the responders for summary table

and the logistic regression analysis above at Month 12 or at Month 24 will be based on all patients with available MFM total score at both 1) baseline and Month 12 or 2) baseline and Month 24, respectively.

4.12.2.3.1.5 Subgroup Analyses

Subgroup analysis will also be performed for the change from (adjusted) baseline in the MFM total score at Month 12 for the following age groups based on age at (adjusted) baseline:

- 2 to 5 years ($\geq$ 2 years to < 6 years)
- 6 to 11 years ($\geq$ 6 years to <12 years)
- 12 to 17 years ($\geq$ 12 years to < 18 years)
- 18 years or above ($\geq$ 18 years)

The results including the treatment differences and corresponding 95% CIs for the overall (all patients) and for each of the subgroups will be presented in forest plots for the weighted population.

4.12.2.3.1.6 Comparison with each of the external comparator sources

Sensitivity analysis will also be performed as described in Section 4.12.2.3.1.4 and Section 4.12.2.3.1.5 by comparing results in SUNFISH Part 2 placebo risdiplam treated patients on risdiplam treatment with each of the external comparator sources separately for the unweighted and weighted population, that is, for

- SUNFISH Part 2 placebo patients versus NatHis-SMA study
- SUNFISH Part 2 placebo patients versus placebo arm of Study WN29836

4.12.2.3.1.7 Sensitivity Analysis: Missing results as non-responders

Responder analyses will also be performed by considering patients with missing MFM total score at Month 12 or at Month 24 as non-responders. The proportion and percentage of patients who achieved an improvement of a change from (adjusted) baseline of ≥0, ≥1, ≥2, ≥3, ≥4 in the total MFM score at Month 12, 18 and 24 will be summarized for the weighted and unweighted populations. The proportion of patients who achieve an improvement of a change from (adjusted) baseline of $\geq$0 and $\geq$3 in the total MFM score at Month 12 and at Month 24 will also be analyzed using the same logistic regression model as defined in Section 4.12.2.2.1.4. The odds ratio and 95% CI will be reported. These analyses will be performed by comparing the SUNFISH Part 2 results for the placebo patients based on the external control population, and also by comparing the SUNFISH Part 2 results for the placebo patients separately with NatHis-SMA study (Study BP29540) or with placebo arm of Study WN29836 study for the weighted and unweighted populations.

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Appendix 1
Protocol Synopsis

TITLE:	A TWO PART SEAMLESS MULTI-CENTER RANDOMIZED PLACEBO-CONTROLLED, DOUBLE-BLIND STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND EFFICACY OF RISDIPLAM (RO7034067) IN TYPE 2 AND 3 SPINAL MUSCULAR ATROPHY PATIENTS

PROTOCOL NUMBER:	BP39055
VERSION:	6
EUDRACT NUMBER:	2016-000750-35
IND NUMBER:	128972
TEST PRODUCT:	Risdiplam
PHASE:	II
INDICATION:	Type 2 and 3 spinal muscular atrophy
SPONSOR:	F. Hoffmann-La Roche Ltd

OBJECTIVES

Primary Objectives:

The primary objectives for the study are as follows:

Part 1

- To evaluate the safety, tolerability, PK and PD of risdiplam in patients with Type 2 and Type 3 (ambulant or non-ambulant) spinal muscular atrophy (SMA), and to select the dose for Part 2 of the study.

Part 2

- To evaluate efficacy of risdiplam compared to placebo in terms of motor function in Type 2 and non-ambulant Type 3 SMA patients, as assessed by the change from baseline in the total score of the motor function measure (MFM) at 12 months.

Secondary Objectives

There are no secondary objectives for Part 1 of this study.

Secondary objectives for Part 2 are as follows:

- To investigate the PK/PD relationship of risdiplam by PK/PD modeling (PD to include *SMN2* mRNA and survival of motor neuron [SMN] protein).
- To investigate the efficacy of 12-month treatment with risdiplam in terms of motor function as assessed by the Hammersmith functional motor scale expanded (HFMSE) and the revised upper limb module (RULM)

- To investigate the efficacy of 12-month treatment with risdiplam in terms of responder analyses of the MFM, HFMSE, and RULM
- To investigate the efficacy of 12-month treatment with risdiplam in terms of respiratory function as assessed by sniff nasal inspiratory pressure (SNIP) and, in patients aged 6 years and older, by maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and peak cough flow (PCF).
- To investigate the proportion of patients who experience a pre-specified disease-related adverse event by Month 12.
- To investigate the efficacy of 12-month treatment with risdiplam in terms of global health status as assessed by the Clinical Global Impression of Change (CGI-C).
- To investigate the efficacy of 12-month treatment with risdiplam in terms of patient-reported and caregiver-reported independence, as measured by the SMA Independence Scale (SMAIS).
- To investigate the safety and tolerability of risdiplam treatment.

Exploratory Objectives

The exploratory objectives for this study are as follows:

Part 1
- To investigate the PK/PD relationship of risdiplam by PK/PD modeling (PD to include *SMN2* mRNA and SMN protein).
- To explore the effect of risdiplam on motor function, respiratory function, and pre-specified adverse events (in terms of proportion of patients experiencing them) and patient-reported QOL measures, in line with the secondary objectives of Part 2.

Part 2
- To investigate efficacy of risdiplam treatment beyond 12 months in terms of motor function as assessed by the MFM, the HFMSE and the RULM.
- To investigate efficacy of risdiplam treatment beyond 12 months in terms of respiratory function as assessed by SNIP, MIP, MEP, FVC, FEV1 and PCF.
- To investigate the proportion of patients who experience pre-specified disease-related adverse events beyond Month 12 of treatment.
- To investigate the efficacy of risdiplam beyond 12 months in terms of patient-reported and caregiver-reported independence, as measured by the SMA Independence Scale (SMAIS).

Other exploratory objectives of the study include:
- To assess the impact of risdiplam treatment and conduct economic modeling on caregiver resource use and health-related quality of life using the Work Productivity and Activity Impairment: Caregiver (WPAI:CG) and the EQ-5D-5L, respectively.
- To explore the correlation of motor function, and pulmonary function measures (as appropriate) with in vivo *SMN2* mRNA and SMN protein in blood.
- To assess the taste of the risdiplam oral solution.

STUDY DESIGN

Description of Study

The study consists of two parts:

Part 1 is a double-blinded, placebo-controlled, dose-finding part. Patients will be randomized to risdiplam active treatment or placebo (2:1 ratio), administered once daily.
- Enrollment will start with the first cohort of Group A (i.e., adult and adolescent patients [age 12–25 years]).

- Once risdiplam at the first dose level has been shown to be safe and well-tolerated for at least 4 weeks in a minimum of 3 adolescent patients (age 12-17 years) on active treatment, enrollment will be opened to the first cohort of younger patients (Group B, age 2-11 years). The first dose administered to both age groups will target an $AUC_{0-24h,ss}$ of 700 ng • h/mL.

- Safety and tolerability at this first dose level will be confirmed for the respective age groups based on at least 4-week treatment duration in all patients of the cohort (i.e., patients enrolled first will have longer treatment duration). Once safety and tolerability of the first dose level is confirmed, enrollment will be opened to another cohort of 9 patients each in the respective age groups, at a higher dose level. This higher dose level will be determined such as to achieve maximum SMN protein increase, with the corresponding target exposure not exceeding the exposure cap (C_{max} 400 ng/mL; $AUC_{0-24h,ss}$ 2000 ng• h/mL).

- Once the last patient of the last cohort in Part 1 (higher dose level in either of the two age groups, depending on recruitment) has completed 4 weeks of treatment, all available safety, tolerability, PK and PD data will be reviewed by an Internal Monitoring Committee (IMC) which will recommend the dose for Part 2 of the study.

- Once Part 1 patients have completed the 12-week double-blinded treatment period and the Part 2 dose has been selected, all Part 1 patients will then be switched to the Part 2 dose and followed up for safety, tolerability and efficacy as part of the open-label extension (OLE) phase of the study.

Part 2, the confirmatory part, will start once the dose has been selected in Part 1 by the IMC and has been confirmed by the iDMC.

- Part 2 of Study BP39055 will investigate the efficacy and safety of R07034067 over a 24-month treatment period, in Type 2/3 (non-ambulant only) SMA patients of 2 to 25 years of age.

- A total of 168 patients will be randomized (2:1) to receive either risdiplam at the dose of 5 mg once daily (o.d.) for patients with a body weight (BW) $\geq$20kg and 0.25 mg/kg for patients with a BW <20 kg, or placebo. Randomization will be stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years at randomization). No more than 30 patients will be randomized into the 18 to 25 years of age group. A minimum of 45 patients will be randomized into each of the other 3 age groups. Patients from Part 1 will not be included in Part 2.

- The primary analysis will be conducted and the Sponsor unblinded once the last patient completes 12 months of treatment (i.e., before all patients have completed 24 months of treatment).

- Patients receiving placebo will be switched to risdiplam in a blinded manner after 12 months of treatment and treatment will then continue until Month 24, after which patients will be offered the opportunity to enter the OLE phase where they will be monitored regularly for safety, tolerability and efficacy.

NUMBER OF PATIENTS

In Part 1, at least 36 patients will be randomized in a 2:1 ratio to risdiplam or placebo. If required, to enable the dose selection for Part 2, up to an additional 36 patients may be enrolled, for a total number of a maximum of 72 patients.

In Part 2 of the study 168 patients will be randomized 2:1 to risdiplam or placebo (i.e., 112 patients on risdiplam and 56 patients on placebo).

TARGET POPULATION

Part 1 will enroll patients with Type 2 and 3 SMA (ambulant and non-ambulant) aged 2-25 years.

Part 2 of the study will include Type 2 and non-ambulant Type 3 SMA patients aged 2–25 years.

INCLUSION/EXCLUSION CRITERIA

Inclusion criteria:

Patients must meet the following criteria for study entry:

1. Males and females 2 to 25 years of age inclusive (at screening).

2. For Part 1: Type 2 or 3 SMA ambulant or non-ambulant.

   For Part 2: Type 2 or 3 SMA non-ambulant. Non-ambulant is defined as not having the ability to walk unassisted (i.e., without braces, assisted devices such as canes, crutches or calipers, or person/hand-held assistance) for 10 m or more.

3. 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 symptoms attributable to Type 2 or Type 3 SMA.

4. For non-ambulant patients in Part 2 (at screening):
   - RULM entry item A (Brooke score) ≥2 (i.e., "Can raise 1 or 2 hands to the mouth, but cannot raise a 200 g weight in it to the mouth").
   - Ability to sit independently (i.e., scores a ≥1 on item 9 of the MFM 32 "with support of one or both upper limbs maintains the seated position for 5 seconds").

5. Able and willing to provide written informed consent and to comply with the study protocol according to International Conference on Harmonisation (ICH) and local regulations. Alternatively, a legally authorized representative must be able to consent for the patient according to ICH and local regulations and assent must be given whenever possible.

6. Negative blood pregnancy test at screening (all women of childbearing potential, including those who have had a tubal ligation), and agreement to comply with measures to prevent pregnancy and restrictions on egg and sperm donation, as below:

   a) <u>For women</u> who are not prematurely menopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent (refrain from heterosexual intercourse) or to 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 last dose of study drug. Women must refrain from donating eggs during this same period. The reliability of sexual abstinence needs to 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. Barrier methods must always be supplemented with the use of a spermicide.

   b) 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. 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.

   c) <u>For men</u>: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:

   d) With female partners 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 last 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 spermatogenic cycle duration and drug elimination process.

   e) With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 28 days after the last dose of study drug. The reliability

of sexual abstinence needs to 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.

Exclusion criteria:

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

1. Inability to meet study requirements.

2. Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening, or 5 half-lives of the drug, whichever is longer.

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

4. Any history of cell therapy.

5. Hospitalization for a pulmonary event within the last 2 months or planned at time of screening.

6. Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 months.

7. Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases as considered to be clinically significant by the Investigator.

8. Pregnant or lactating women.

9. Suspicion of regular consumption of drug of abuse.

10. Positive urine test for drugs of abuse or alcohol at screening or baseline visit (adolescents and adults only).

11. Cardiovascular, blood pressure, and heart rate:

    a. 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.

    b. Adolescents (12−17 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate <50 bpm or >100 bpm.

    c. Children (6−11 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate <60 bpm or >120 bpm.

    d. Children (2−5 years of age): SBP and/or DBP outside the 95th percentile for age; resting heart rate <70 bpm or >140 bpm.

12. Presence of clinically significant ECG abnormalities before study drug administration (e.g., second or third degree AV block, confirmed QTcF >460 ms for patients age >10 years or QTcB >460 ms for children up to age 10 years as Bazett's correction is more appropriate in young children) from average of triplicate measurement 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 patients as determined by the Investigator.

13. History of malignancy if not considered cured.

14. Significant risk for suicidal behavior, in the opinion of the Investigator as assessed by the C-SSRS (>6 years of age).

15. Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration.

16. 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).

17. Use of the following medications within 90 days prior to randomization: riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth

hormone, anabolic steroids, probenecid, agents anticipated to increase or decrease muscle strength, agents with known or presumed histone deacetylase (HDAC) inhibitory effect, and medications with known phototoxicity liabilities (e.g., oral retinoids including over the counter formulations, amiodarone, phenothiazines and chronic use of minocycline). (Patients who are on inhaled corticosteroids, administered either through a nebulizer or an inhaler, will be allowed in the study)

18. Recently initiated treatment (within <6 months prior to randomization) 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 months before randomization 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.

19. 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 (12 months) prior to randomization is not allowed.

20. 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 creatine kinase and LDH. Out of range creatine kinase levels should be reviewed in light of the underlying SMA pathology of the patient; elevated levels *per se* do not disqualify the patient from the study. In the case of uncertain or questionable results, tests performed during screening may be repeated before randomization to confirm eligibility.

21. Donation or loss of blood ≥10% of blood volume within three months prior to screening.

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

23. 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.

24. Recent history (less than one 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) must be discussed with the Investigator, ophthalmologist, and with the Sponsor, who will jointly make the decision if the patient may be enrolled in the study. Patients in whom OCT measurement of sufficient quality cannot be obtained at screening will not be enrolled.

25. Patients requiring invasive ventilation or tracheostomy.

26. Any inhibitor or inducer of FMO1 or FMO3 taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing.

END OF STUDY

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 OLE phase of the study, which will include regular monitoring of safety, tolerability and efficacy. Unless the development of the drug is stopped, the patient's treatment in the OLE may continue for an additional 3 years (patients will be treated for a total duration of at least 5 years). Thereafter, treatment will continue until the drug is available commercially 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 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.

LENGTH OF STUDY

For each subject the study will consist of:

- A screening visit, up to 30 days prior to the first dose of study drug.

- A minimum of 12-week double-blind treatment period for patients enrolled in Part 1.

- 12-month double-blind treatment period followed by 12-month active treatment period for patients enrolled in Part 2.

- Thereafter patients will be given the opportunity to enter the open-label extension (OLE) phase of the study (for both Parts 1 and 2*). Unless the development of the drug is stopped, the patient's treatment in the OLE may continue for an additional 3 years (patients will be treated for a total duration of at least 5 years). Thereafter, treatment will continue until the drug is available commercially in the patient's country.*

If a patient is withdrawn from study treatment, the patient will be requested to attend *a study completion/ early withdrawal* visit, as described in the Schedule of Assessments (SoA).

OUTCOME MEASURES

SAFETY OUTCOME MEASURES

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events.

- Incidence and severity of serious adverse events.

- Incidence of treatment discontinuations due to adverse events.

- Incidence of abnormal laboratory values.

- Incidence of abnormal ECG values.

- Incidence of abnormal vital signs (body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate).

- Physical examination

- Height, weight and head circumference.

- Incidence of emergence or worsening of items of 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*

- Tanner staging for pubertal status *as appropriate for age.*

PHARMACOKINETIC OUTCOME MEASURES

Patient exposure to risdiplam will be assessed and the following parameters calculated (if possible, based on the available data):

- Concentration per timepoint listed.

- C_{max} (maximum plasma concentration)

- AUC (area under the concentration-time curve)

- Concentration at the end of a dosing interval (C_{trough}) to assess steady-state.

- Other PK parameters as appropriate.

PHARMACODYNAMIC OUTCOME MEASURES

The pharmacodynamics outcome measures for this study are as follows:

- *SMN2* mRNA in blood: Blood samples will be collected at the times specified in the SoA 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.

EFFICACY OUTCOME MEASURES

The efficacy outcome measures for this study are as follows:

- Motor Function Measure (32 item version)
- HFMSE
- RULM
- SNIP
- MIP, MEP (Part 2 only)
- FVC, FEV1, PCF
- Disease-related Adverse Events
- CGI-C (Part 2 only)
- SMAIS (Part 2, only)
- PedsQL 3.0 Neuromuscular module (Part 1 only)
- PedsQL 4.0 Generic Core scale (Part 1 only)

ADDITIONAL OUTCOME MEASURES

The outcome measures for this study that will be used for economic analyses are as follows:

- EQ-5D-5L
- WPAI:CG-SMA

Other outcome measures for this study include but are not limited to the following:

- Taste assessment (taste questionnaire in adults and adolescents, 5-point facial visual hedonic scale in children aged 6–11 years; with the exception of patients to whom study drug is administered via naso-gastric or gastrostomy tube [G-tube]).

INVESTIGATIONAL MEDICINAL PRODUCT(S)

Part 1 Formulation – Powder and solvent for oral solution, 20 mg and 120 mg

Part 1 risdiplam clinical formulation is a powder and solvent for constitution to an oral solution. Patients will be randomly assigned to one of two possible blinded study drug treatments:

- risdiplam drug product
- Placebo (containing no active drug substance).

The excipients blend (powder for solvent for reconstitution) bottle is constituted with water for injection and entirely transferred to the drug substance bottle to yield an oral solution containing of 0.25 mg/mL and 1.5 mg/mL of risdiplam, respectively. Matching-placebo oral solutions will be prepared.

The dose administered to the first cohort of patients aged 12-25 years (Group A) will be 3 mg.

Part 2 Formulation – Powder for oral solution, 20 mg and 60 mg

Part 2 risdiplam clinical formulation is a powder for constitution to an oral solution. Patients will be randomly assigned to one of two possible blinded study drug treatments:

- risdiplam drug product
- Placebo (containing no active drug substance).

The powder is constituted with purified water to yield an oral solution containing 0.25 mg/mL or 0.75 mg/mL of risdiplam, respectively.

Throughout the study, the study medication (risdiplam or placebo) 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.

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 will be collected from adult and adolescent patients who give specific consent, and assent if applicable, to participate in this optional RBR.

Collected specimens will be used to achieve the following objectives:
- To study the association of biomarkers with efficacy, adverse events, or disease progression.
- To increase knowledge and understanding of disease biology.
- To study drug response, including drug effects and the processes of drug absorption and disposition.
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays.

The following samples will be collected for identification of dynamic (non-inherited) biomarkers:
- Blood 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 sample collected for DNA extraction may be used for whole genome sequencing (WGS) and other genetic analysis.

PROCEDURES

A Schedule of Assessments (SoA) is provided in Appendices.

STATISTICAL METHODS

The analyses of this study will be structured into two parts; exploratory (Part 1) to select the dose and confirmatory (Part 2) to evaluate the treatment effect of risdiplam. The confirmatory analyses will only include the patients randomized into Part 2 of the study; it will not include the Part 1 patients who will be analyzed to select the dose.

Following the dose selection for Part 2, data from the exploratory Part 1 of this study (and the Part 1 extension phase) may be reported. Data may continue to be locked at intervals in order to analyze and report the safety, PK/PD and exploratory efficacy of those patients enrolled into Part 1 only.

The primary analysis and the analysis of the secondary endpoints in Part 2 will only include data up to the 12-month time-point for each individual.

SAFETY ANALYSES

All patients who receive at least one dose of study medication (risdiplam or placebo) will be included in the safety population. This population will be the primary safety analysis population to compare risdiplam to placebo.

The safety endpoints include, but may not be limited to, incidence of adverse events and 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, and incidence of clinically significant findings on neurological examination.

Longer term safety of risdiplam treatment, including safety data collected in the OLE periods for both parts of the study, will be summarized using the risdiplam All Exposure Population (i.e., all patients who receive at least one dose of risdiplam at any dose level during either the double-blinded period or the OLE period).

PHARMACOKINETIC ANALYSES

All patients with at least one time point with a measureable concentration will be included in the PK analysis data set.

Individual and mean plasma concentrations of risdiplam, and metabolites, as appropriate, versus time data will be tabulated and plotted. Assessment of protein binding will be performed on pre-dose samples and results listed. Additional PK analyses will be conducted as appropriate.

PHARMACODYNAMIC ANALYSES

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

EFFICACY ANALYSES

The intent-to-treat (ITT) population will be the primary analysis population for all efficacy analyses. The ITT population is defined as all randomized patients.

The primary endpoint in Part 2 is the change from baseline in the total MFM 32 score at Month 12.

Changes from baseline in the total MFM scores will be summarized descriptively at each time-point by treatment group for the ITT population and a Mixed Model Repeated Measures (MMRM) analysis will be performed to utilize all the data collected in Part 2 up to 12 months. The model will include the absolute change from baseline total MFM score as the dependent variable and as independent variables the baseline total MFM score (continuous), treatment group, time, treatment-by-time interaction and the randomization stratification variable of age (categorical: 2 to 5, 6 to 11, 12 to 17, 18 to 25 years at randomization). An unstructured variance co-variance matrix structure will be applied. The estimated treatment difference in the mean change from baseline in the total MFM score at Month 12 between risdiplam and placebo will be presented with 95% confidence intervals.

The secondary efficacy endpoints for Part 2 of this study are:

- **Motor Function**, which includes change from baseline in Total score of HFMSE, RULM and in the MFM domain scores of D1, D2, D3 and the total combined score of (D1 + D2), and the proportion of patients who achieve stabilization or improvement on the total MFM score, total HFMSE score, and total RULM score at Month 12.

- **Respiratory** with regard to change from baseline in the best SNIP (expressed as a percentage of the predicted value) at Month 12. Additionally, in patients aged 6 to 25 years only: the change from baseline in MIP, MEP, FEV_1, FVC and in PCF at Month 12.

- **Disease-Related Adverse Events**, the proportion of patients who experience at least one disease-related adverse event by Month 12 and the number of disease-related adverse events per-patient year at Month 12.

- **Clinical Global Impression of Change Scale (CGI-C),** with regard to the proportion of patients rated by clinicians as no change or improved, and the proportion of patients rated by clinicians as improved at Month 12.

- **Patient- and Caregiver-Reported Outcomes:** with regard to the change from baseline in the Total score of the caregiver-reported SMAIS and the change from baseline in the Total score of the patient-reported SMAIS (in patients aged 12 to 25 years only) at Month 12.

For continuous endpoints such as the change from baseline in the total score of HFMSE, an MMRM analysis will be performed similar to that specified for the primary efficacy analysis, if appropriate. To control for multiplicity across the different endpoint domains, a hierarchical testing approach will be implemented. The secondary endpoints to be included in the hierarchy will be specified within the SAP.

The order of the secondary endpoints in the hierarchy will be specified within the SAP. The first secondary efficacy endpoint will be tested if and only if the primary endpoint has reached the 5% significance level (i.e., p-value ≤0.05). The secondary endpoints will be tested at a 5% significance level according to this hierarchy as long as the p-value is ≤0.05 for endpoints higher in the hierarchy. Other secondary endpoints not specified in the hierarchy will be simultaneously tested at the 5% significance level without adjustment for multiplicity as they are considered supportive of their endpoint domain or primary endpoint.

Exploratory efficacy endpoints for Part 2 of this study will be summarised at Month 18 and 24 and include, among others, change from baseline in the Total MFM score and its domain scores of D1, D2, D3 and the total combined score of (D1+D2), Total HFMSE and the Total score of RULM, at Month 18 and 24.

OTHER EXPLORATORY ANALYSES

The consistency of the treatment effect for the primary endpoint will be explored for the following baseline subgroups:

- Age group (2 to 5, 6 to 11, 12 to 17, and 18 to 25 years at randomization)
- Age group 2 (2 to 11 and 12 to 25 years at randomization)
- History of scoliosis or hip surgery (yes, no)
- SMA type (2, 3 non-ambulatory)
- Region (US, Rest of World)
- In patients with no major scoliosis or contractures at baseline: Age group 2 (2 to 11 and 12 to 25 years at randomization)

Pharmacoeconomic data analysis and reporting will be handled separately from the clinical study reports of BP39055.

INTERIM ANALYSES

The Sponsor may choose to conduct one interim analysis for efficacy during the confirmatory Part 2 of this study (i.e., if the study [BP39056] in Type 1 SMA achieves its primary efficacy objective earlier than planned or in response to the emerging 12 month results from Part 1 of this study).

If an interim analysis during Part 2 is conducted, the Sponsor will remain blinded. The interim analysis will be conducted by an external statistical group and reviewed by the external iDMC.

SAMPLE SIZE JUSTIFICATION

In Part 1, the target sample size is 36 patients, with 6 patients on active treatment in each dose/age group (12 patients on active drug per dose /exposure level) and 3 patients (6 in total across the entire age range) on placebo.

In Part 2, 168 patients will be randomized, 112 patients on risdiplam and 56 patients on placebo (2:1 randomization). For the primary endpoint of the mean change from baseline in the total MFM score at Month 12, this sample size (allowing for a 10% dropout rate) provides at least 80% power at a two-sided 5% significance level for testing the null hypothesis that the true treatment difference is zero versus the alternative hypothesis, given that the true treatment difference is 3 and assuming that the common standard deviation will be 6.

CONCOMITANT MEDICATIONS

In addition to the study drug treatment, patients may continue to receive concomitant therapy. Concomitant therapy includes any medication used by a patient from 30 days prior to screening until the follow-up visit.

Prohibited therapies include (please see eligibility criteria for additional information):

- *Any administration of nusinersen (SPINRAZA®) either in a clinical study or for medical care at any time prior to or during the study is strictly prohibited*
- Any OCT-2 and MATE substrates.
- *Any inhibitor or inducer of FMO1 or FMO3.*

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- Medications intended for the treatment of SMA include riluzole, valproic acid, hydroxyurea, sodium phenylbutyrate, butyrate derivatives, creatine, carnitine, growth hormone, anabolic steroids, probenecid, nusinersen (SPINRAZA®). 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 retinal toxicity liabilities: Amiodarone, phenothiazines, and chronic use of minocycline*

- Patients should not have received the following drugs previously, nor during the study: quinolines (chloroquine and hydroxychloroquine), thioridazine, retigabin and vigabatrin.

- 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, including chronic use of minocycline.

Appendix 2   Schedule of Assessments: Part 2 Screening to Weeks 44–51

Week	Screening[a]		Week 1			Week 2	Week 4	Week 6	Week 8	Weeks 9-16	Week 17[a]		Weeks 18-25	Week 26	Weeks 27-34	Week 35[a]		Weeks 36-42	Week 43	Weeks 44-51
Day	D-30 to D-2 Day 1	Day 2	Day -1[b]	Day 1	Day 7	Day 14	Day 28	Day 42	Day 56		Day 119	Day 120		Day 182		Day 245	Day 246		Day 301	
Visit Window						+/-1	+/-3	+/-3	+/-3		+/-7			+/-7		+/-7			+/-7	
Assessments																				
Site Visit	x		x	x	x	x	x		x		x			x		x			x	
Follow-up call							x[d]													
Informed Consent	x																			
Randomisation			x																	
Eligibility	x		x																	
Demography	x																			
Medical History	x																			
Physical Examination[f]	x		x			x	x	x	x		x			x		x			x	
Neurological Examination	x										x			x						
SMA History	x																			
Vital Signs	x		x	4h	x	x	x[t]		x[t]		x			x		x				
PK Sample[u]				4	x	x	5		x			x					x			
ECG-12 lead[t]	x		x	4h	x	x	x		x		x			x		x				
Substance Use[g]		x	x																	
Significant life events			x		x	x	x		x		x			x		x			x	
Hematology[t]		x	x[n]			x	x		x			x					x			
Blood Chemistry[t]		x	x[n]			x	x		x			x					x			
Coagulation[t]		x	x[n]				x					x					x			
Urinalysis[t]		x	x[n]				x					x					x			
Hormone Panel[h,t]		x										x								
Pregnancy test blood[i]		x					x		x		x					x				
Pregnancy test urine (site)[i]			x											x					x	
Pregnancy test urine (home)[i,o]										x			x		x			x		x
Ophthalmological Exam[j]	x								x		x			x		x			x	
Tanner staging[k]			x																	

Appendix 2   Schedule of Assessments: Part 2 Screening to Weeks 44–51 (cont. on next page)

Week	Screening[a]		Week 1			Week 2	Week 4	Week 6	Week 8	Weeks 9-16	Week 17[a]		Weeks 18-25	Week 26	Weeks 27-34	Week 35[a]		Weeks 36-42	Week 43	Weeks 44-51
Day	D-30 to D-2 — Day 1	Day 2	Day -1[b]	Day 1	Day 7	Day 14	Day 28	Day 42	Day 56		Day 119	Day 120		Day 182		Day 245	Day 246		Day 301	
Visit Window						+/-1	+/-3	+/-3	+/-3		+/-7			+/-7		+/-7			+/-7	
Assessments																				
In vivo mRNA[u]			X	X	X	X						X					X			
SMN protein[u]			X		X	X						X					X			
MFM[v]	X		X								X					X				
Pulmonary testing[l]	X		X								X					X				
RULM/HMFSE[v]		X										X					X			
C-SSRS[e]	X		X								X					X				
Nutritional Check		X	X				X		X		X			X		X			X	
Serum Biomarkers			X																	
RBR samples[m]			X																	
Clinical Genotyping				X[p]																
Taste Assessment[e]					X															
EQ-5D			X								X					X				
WPAI-Caregiver-SMA			X									X					X			
CGI-C																				
SMAIS			X									X					X			
Study medication dispensation/return[c]				X	X	X	X	X	X	X	X		X	X	X	X		X	X	X
Administration of Study Medication				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diary					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Exercise or Physical Therapy Programs				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X[s]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant SMA-related Surgeries and Procedures	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Appendix 2   Schedule of Assessments: Part 2 Week 52 to Completion (cont. on next page)

Week	Week 52 [a,w]			Weeks 53-60	Week 61	Weeks 62-69	Week 70	Weeks 71-77	Week 78 [a]		Weeks 79-86	Week 87	Weeks 88-95	Week 96	Weeks 97-103	Week 104 [a]		Additional visits after Week 104 [q]				Completion / Early Withdrawal [a]		Phone call
																		Every 13 wks	Every 26 weeks [a]		Resupply visit			
Day	Day 364	Day 365	Day 366		Day 427		Day 490		Day 546	Day 547		Day 609		Day 672		Day 728	Day 729		D1	D2		D1	D2	Comp/EW + 30 days
Visit Window	+/-7				+/-7		+/-7		+/-7			+/-7		+/-7		+/-7		+/- 14 days	+/- 14 days					+/-7
Assessments																								
Site Visit	x				x		x		x			x		x		x		x	x			x		
Follow-up call																								
Informed Consent																								
Randomisation																								
Eligibility																								
Demography																								
Medical History																								
Physical Examination [f]	x				x		x		x			x		x		x		x[r]	x			x		
Neurological Examination	x								x							x			x			x		
SMA History																								
Vital Signs	x[t]						x					x[t]				x			x			x		
PK Sample [u]			5				x					5					x			x			x	
ECG-12 lead [t]	x						x					x				x			x			x		
Substance Use [g]																								
Significant life events	x				x		x		x			x		x		x			x			x		
Hematology [t]		x					x					x							x				x	
Blood Chemistry [t]		x					x					x							x				x	
Coagulation [t]		x					x					x							x				x	
Urinalysis [t]		x					x					x							x				x	
Hormone Panel [h,t]																x								
Pregnancy test blood [i]		x					x					x							x				x	
Pregnancy test urine (site) [i]					x				x					x				x						
Preganancy test urine (home) [i,o]				x		x		x			x		x		x						x			
Ophthalmological Exam [j]	x				x		x		x			x		x		x			x			x		
Tanner staging [k]																x			*x*			x		

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Appendix 2   Schedule of Assessments: Part 2 Week 52 to Completion (cont. on next page)

Week	Week 52 [a,w]			Weeks 53-60	Week 61	Weeks 62-69	Week 70	Weeks 71-77	Week 78 [a]		Weeks 79-86	Week 87	Weeks 88-95	Week 96	Weeks 97-103	Week 104 [a]		Additional visits after Week 104 [q]				Completion / Early Withdrawal [a]		Phone call
Day	Day 364	Day 365	Day 366		Day 427		Day 490		Day 546	Day 547		Day 609		Day 672		Day 728	Day 729	Every 13 wks	Every 26 weeks [a] D1	D2	Resupply visit	D1	D2	Comp/EW + 30 days
Visit Window	+/-7				+/-7		+/-7		+/-7			+/-7		+/-7		+/-7		+/- 14 days	+/- 14 days					+/-7
Assessments																								
In vivo mRNA [u]			X														X						X	
SMN protein [u]			X														X			X			X	
MFM [v]	X								X							X			X			X		
Pulmonary testing [l]	X								X							X			X			X		
RULM/HMFSE [v]		X								X							X			X			X	
C-SSRS [e]	X								X							X			X			X		
Nutritional Check		X			X		X		X			X		X		X				X			X	
Serum Biomarkers		X														X							X	
RBR samples [m]																X							X	
Clinical Genotyping																								
Taste Assessment [e]																								
EQ-5D	X								X							X			X			X		
WPAI-Caregiver-SMA		X								X						X				X			X	
CGI-C		X																						
SMAIS		X								X						X				X		X		
Study medication dispensation/return [c]		X		X	X	X	X	X	X		X	X	X	X	X	X		X	X		X		X	
Administration of Study Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		x x		
Diary		X		X	X	X	X	X	X		X	X	X	X	X	X		X	X				X	
Exercise or Physical Therapy Programs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Previous and Concomitant Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Previous and Concomitant SMA-related Surgeries and Procedures	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Appendix 2   Schedule of Assessments: Part 2 Footnotes (cont. on next page)

a   See protocol Section 4.6.1.26 – Table 2 for order of assessments, which can be conducted over two days.

b   Assessments should be performed in the following order: adverse events, previous/concomitant medications, confirmation of eligibility, MFM, pulmonary testing, randomization, physical examination, Tanner staging, ECG, vital signs, patient/caregiver reported outcomes and blood samples.

c   Drug dispensation, return of *used and* unused *study* drug *bottles* and supplies will occur at scheduled site visits. Ad hoc resupply site visits, or delivery to the patient's home will be performed to ensure the patient has adequate drug and supplies between scheduled site visits as necessary. *At completion/early withdrawal visit, no study drug dispensation and used and unused study drug bottles to be returned to sites.*

d   The Investigator must agree with the parent/caregiver when to perform the mandatory follow-up phone calls at the most appropriate time (day) between the site visits. After Week 12: follow-up phone calls are per investigator decision.

e   Only in patients 6 years of age and older.

f   Body weight and head circumference in children below 5 years will be measured at every scheduled physical examination. At Weeks 43, 61, and 96 weight only should be obtained, not the complete physical examination. Height (measured or derived from ulnar length) at screening, Weeks 17, 35, 52, 78, 104, and at each physical examination after Week 104 in patients 2-17 years of age. In patients > 17 years of age, height at screening, Weeks 52 and 104, and at each physical examination after Week 104. Body Mass Index (BMI) will be derived from the last height recorded in patients > 17 years of age, and from the last known height in patients 2-17 years of age.

g   Only patients of ≥ 12 years of age.

h   Free T4 and TSH in all patients; estradiol, follicle-stimulating hormone and luteinizing hormone in female patients aged 12 to 25 years or younger patients who have menses.

i   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 will be confirmed with a blood pregnancy test.

j   See protocol (Table 4, Table 5, Appendix 5, and Appendix 4) for details on required ophthalmology assessments according to the visit and the group.

k   *Tanner staging will be determined at the 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.*

l   SNIP in all patients; MIP, MEP and spirometry (FVC, FEV1, and PCF), MIP and MEP in patients 6 years of age and older.

m   Only in patients ≥ 12 years of age. RBR sampling is optional, requiring additional consent. RBR DNA sample will be collected once, other RBR samples at Day −1 and Week 104.

n   Not required if screening sample < 30 days.

o   The home pregnancy test must be performed 4 weeks following the latest clinic visit until Week 104. See footnote q for visits after Week 104. 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 2   Schedule of Assessments: Part 2 Footnotes

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

q   Every 13 or 26 weeks following the Week 104 visit until the conclusion of the open-label extension (OLE). Urine pregnancy tests will be performed on Weeks 4 and 8 following the last clinic visit (see footnote o).

r   Weight only.

s   Only SAEs.

t   Pre-dose.

u   Pre-dose except those outlined in Appendix 4.

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

w   At this visit, patients should be switched to newly-assigned medication (in a blinded manner, patients initially randomized to placebo are being switched to active treatment at this visit) in the morning of Day 3.

x   *Final dose of study drug to be administered on day of study completion visit. At the investigator's discretion and if appropriate, study drug may be administered on the day of early withdrawal visit.*

Appendix 3   Schedule of Assessments: Part 2, Detailed Table

Week	Day	Scheduled Time (h)	PK Sample	In vivo mRNA	SMN protein
Week 1	Day -1	***		x	x
	Day 1	Pre-dose			
		1h	x		
		2h	x		
		4h	x	x	
		6h	x		
	Day 7	Pre-dose	x	x	x
Week 2	Day 14	Pre-dose	x		
Week 4	Day 28	Pre-dose	x		
		1h	x		
		2h	x		
		4h	x	x	x
		6h	x		
Week 8	Day 56	Pre-dose	x		
Week 17	Day 120	Pre-dose	x	x	x
Week 35	Day 246	Pre-dose	x	x	x
Week 52	Day 366	Pre-dose	x		
		1h	x		
		2h	x		
		4h	x	x	x
		6h	x		
Week 70	Day 490	Pre-dose	x		
Week 87	Day 609	Pre-dose	x		
		1h	x		
		2h	x		
		4h	x		
		6h	x		
Week 104	Day 729	Pre-dose	x	x	x
Additional Visits		Pre-dose	x		x
Completion / Early Withdrawal		***	x	x	x

Appendix 4 Schedule of Assessments: Ophthalmology Assessments (Part 2)

Week **Adults and cooperative children**	Screening	8	17	26	35	43	52	61	70	78	87	96	104	OLE[c]	Completion / Early Withdrawal
Best corrected visual acuity	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Threshold perimetry or other visual field test	X			X			X			X			X	X	X
Slit Lamp and fundus examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure (a)	X		X		X		X		X		X		X		
Color fundus photography	X			X			X			X			X		
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Week **Children**	Screening	8	17	26	35	43	52	61	70	78	87	96	104	OLE[c]	Completion / Early Withdrawal
Visual testing (b)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Intraocular pressure (a)	X						X						X		
Slit Lamp and fundus examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Color Fundus photography	X			X			X			X			X		
SD-OCT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

a   Tonometry or digital palpation of the globes
b   Bruckner test, fix and follow test, cover-uncover test, simple visual field test, visual acuity
c   Every 26 weeks after the week 104 visit until the completion of the open label extension (OLE)

Appendix 5   Letter from ███████████████ on the Rules of Handling Missing Items on the MFM Scale

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SERVICE CENTRAL DE
REEDUCATION
PEDIATRIQUE
Centre de référence Maladies
Neuromusculaires
Centre de référence Troubles des
Apprentissages
Centre de Compétence Spina
Bifida

Unité l'Escale
Aile A1, 3ème étage

(Accueil : ███████
Fax : ███████
Rendez-vous
Adresse mail :
███████████

███████████
Hospitalier-MPR
███████████
Secrétariat : ███████

Bron, May 10th, 2019

To whom it concerns

Dear Madam, Dear Sir,

As part of the team that is developping the Motor Function Measure, I was asking by Roche Team about the most optimal approach to handling missing data on MFM-32 in the Roche Sunfish clinical trial.

After discussion with the professionals involved in the development and validation of the scale ███████ Methodologist, ███████ and ███████ trainers and ███████ Clinical research assistant), we confirm that a score of 0 has to be allocated to each item with a missing data.

Regarding the score calculation by domain (D1, D2 and D3), it is only possible to calculate a score by domain if there is less than 15% of missing data. In others words, for D1 and D2 a maximum of 2 missing items and for D3 a maximum of 1 missing item. In addition, to calculate a Total score, it is imperative to have calculated a score for D1, for D2 and for D3. It seems also mandatory to quantify the number of patients with missing data.

Sincerely,

███████████████

Appendix 6   SAS Code for Primary Analysis

```
PROC MIXED DATA=data1;
  CLASS patient trt visit agecat;
  MODEL change = basval trt visit agecat trt*visit basval*visit/DDFM=KR;
  REPEATED visit /SUBJECT=patient TYPE=UN R RCORR;
  LSMEANS trt*visit / DIFFS cl;
  ODS OUTPUT DIFFS=_DIFFS LSMEANS=_LSMEANS;
RUN;
```

where

data1: data from SUNFISH Part 2;
patient: subject ID
visit: ID of the visit
basval: baseline MFM32 score
agecat: age of patient in groups of 2-5, 6-11, 12-17 and 18-25 years
change: change from baseline in the total MFM32 score
trt: randomized treatment (1="risdiplam" or 0="placebo")

This assumes an unstructured variance–covariance matrix will be used (TYPE=UN).
If the primary repeated measures model does not converge, a heterogeneous
autoregressive variance-covariance structure will be used (TYPE=ARH(1)) instead.

Appendix 7   Spinal Mpmauscular Atropy Independence Scale (SMAIS) User Manual

⟨Roche⟩

Spinal Muscular Atrophy Independence Scale (SMAIS) User Manual

Prepared by:

Dylan Trundell, Hannah Staunton, Stephanie Le Scouiller

Patient-Centered Outcomes Research, Roche Products Limited

Version 1.0

2nd October, 2019

Risdiplam—F. Hoffmann-La Roche Ltd
109/Statistical Analysis Plan BP39055

Table of Contents

Version History

Version Number	Summary/Reason for changes	Date Issued
1.0	N/A	30th September 2019

Risdiplam—F. Hoffmann-La Roche Ltd
111/Statistical Analysis Plan BP39055

1 Background

The SMA Independence Scale (SMAIS) was developed to assess the degree of support needed to perform basic functions or Activities of Daily Living (ADLs). Independence is a key determinant of health-related quality of life in this population (Rouault et al. 2017). The SMAIS is intended to be used in conjunction with motor function measures such as the Motor Function Measure (Bérard et al. 2005), Hammersmith scales (O'Hagen et al. 2007), and/or the Revised Upper Limb Module (Mazzone et al. 2017), to provide complementary information regarding how changes in motor function impact the individual's level of independence.

The SMAIS was developed through an examination of existing measures focused on functioning and functional independence, a review of the qualitative articles focused on SMA, results from a survey that collected data about ADLs in individuals with SMA, internal review of the draft measure, and a qualitative interview study with patients and caregivers exploring SMA symptoms and how they impact levels of independence when performing daily activities. A patient-reported outcome (PRO) self-report version has been developed for use by SMA patients (type 2 and non-ambulatory type 3 SMA) aged 12 years and older. A caregiver-completed observer-reported outcome (ObsRO) measure has been developed for use by caregivers of SMA patients (non-ambulatory type 2 and 3 SMA) aged 2 years and older.

An overview of the characteristics of the SMAIS is included below in Table 1.

Table 1. Overview of SMAIS

Objective	To assess the level of functional independence in individuals with Type 2/3 non-ambulatory SMA
Clinical Outcome Assessment type	PRO or ObsRO
Concept of interest	ADL-related independence
Number of items	29
Population for intended use	PRO – Type 2/3 non-ambulatory SMA aged 12+ years ObsRO – Type 2/3 non-ambulatory SMA aged 2+ years
Mode of administration	Paper (no electronic version currently available)
Recall period	Past 7 days
Time to complete	5-10 minutes
Available translations	• Bulgarian for Bulgaria • Chinese for Taiwan and China • Croatian for Croatia, Czech for Czech Republic • Dutch for Belgium and the Netherlands • English for Australia, Canada, UK, US • French for Belgium, Canada and France • German for Switzerland and Germany • Italian for Switzerland and Italy • Polish for Poland

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	• Portuguese for Brazil
	• Romanian for Romania
	• Russian for Ukraine and Russia
	• Serbian for Serbia
	• Spanish for Argentina, Spain and USA
	• Swedish for Sweden
	• Turkish for Turkey
	• Ukrainian for Ukraine

2 Content validity

Following a review of the literature, a qualitative, cross-sectional study involving semi-structured, individual telephone interviews with eight patients with type 2 or non-ambulatory type 3 SMA, and 15 caregivers of individuals with type 2 or non-ambulatory type 3 SMA was conducted. The interviews contained two sections:

- Concept elicitation: open-ended questions focused on SMA symptoms and how they impact an individual's level of independence when performing daily activities.
- Cognitive interviews: assessing the content of the draft SMAIS, including the clarity of wording and whether or not the items were relevant and comprehensive of the individual's experience of ADL-related independence.

The interviews were conducted in two phases to permit evaluation of interim changes. Several items were adapted (e.g., revision of the toileting item) and new content was added (e.g., a separate item focused on hand washing). Results from this qualitative study provided support for the content validity of the SMAIS among SMA patients and caregivers. Overall, participants provided positive feedback on the SMAIS and found the measure to be relevant, straightforward, easy to understand, and comprehensive of their SMA experience with independence. The majority of participants found the SMAIS to be clear, and demonstrated a good understanding of the instructions, items, and recall periods.

3 Scoring

3.1 Item scoring

Each item is scored using a 5-point ordinal scale, with higher scores indicating greater independence:

- 0: I [He/she] cannot do this at all without help
- 1: I [He/she] need a lot of help
- 2: I [He/she] need a moderate amount of help
- 3: I [He/she] need a little bit of help
- 4: I [He/she] do not need help

Items rated as non-applicable are given a score of zero.

3.2 Total score calculation

The SMAIS total score combines 22 of the 29 items into a single upper-limb summary score. Items 1-18 and 26-29 are included in the SMAIS scoring algorithm. Items 19-25 (mobility/strength and chores items) should not be included in the total score but can be interpreted as stand-alone items.

Based on results from a Rasch analysis, items should be rescored prior to calculation of the total score:

Current item score	Revised item score
0	0
1	1
2	1
3	2
4	2

Items are then summed, to create a total score ranging from 0 to 44.

3.3 Missing data

For the total score, missing data item responses can be handled by either:

1. Setting the value to zero (i.e., assume individual is unable to perform the activity)
2. Setting the value to the within-respondent mean (rounding to nearest integer)

Reporting of results should state which method is used to ensure accurate comparability of results across studies.

The total score should only be calculated if responses are provided for 15 of the 22 items (including N/A).

4 Other measurement properties

Psychometric testing of the total SMAIS score, including reliability validity, ability to detect change and meaningful change thresholds, is currently being assessed and will be included in subsequent versions of the user manual.

5 References

Bérard C, Payan C, Hodgkinson I, Fermanian J. The MFM Collaborative Study Group. A motor function measure scale for neuromuscular diseases. Construction and validation study. *Neuromuscular Disorders*. 2005;15:463-70.

Mazzone ES, Mayhew A, Montes J, Ramsey D, Fanelli L, Young SD, Salazar R, De Sanctis R, Pasternak A, Glanzman A, Coratti G. Revised upper limb module for spinal muscular atrophy: Development of a new module. *Muscle & nerve*. 2017;55(6):869-74.

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<Roche>

Approval Form

Document Title: Spinal Muscular Atrophy Independence Scale (SMAIS) User Manual

Document Version: Version 1.0

Document Date: 2nd October, 2019

Approver's Name: ███████████

Approver's Title: ███████████

Approver's Role: ███████████

Approver's Signature: ███████████

Date of Approval: October 2nd 2019

Appendix 8   Schedule of Assessment for Natural History Study BP29540

Figure 1   Study design

V2 – Follow-up
- Clinical exam
- SMA natural history /disease progression questionnaire

- Pulmonary function test if applicable,
- Timed Test if applicable
- Muscle strength if applicable
- Motor function (Moviplate if applicable + MFM+ ACTIVE-seated)
- Activity assessment[1]
- EMG
- PedsQL + HUI2
- Blood sample for biomarker

- Concomitant treatments
- AE/SAE

V4 – Follow-up or End of Study
- Clinical exam
- SMA natural history /disease progression questionnaire

- Pulmonary function test if applicable,
- Timed Test if applicable
- Muscle strength if applicable
- Motor function (Moviplate if applicable + MFM+ ACTIVE-seated)
- Activity assessment[1]
- EMG
- PedsQL + HUI2
- Blood sample for biomarker

- Concomitant treatments
- AE/SAE

T0   T6   T12   T18   T24   Months

V1 – Inclusion
- Verification of selection criteria
- Informed consent
- Demographic data

- Clinical exam
- SMA natural history /disease progression questionnaire

- Pulmonary function test if applicable,
- Timed Test if applicable
- Muscle strength if applicable
- Motor function (Moviplate if applicable + MFM + ACTIVE-seated)
- Activity assessment[1]
- MRI[2]
- EMG
- PedsQL + HUI2
- Blood sample for clinical genotyping
- Blood sample for biomarker

- Concomitant treatments
- AE/SAE

V3 – Follow-up or End of Study
- Clinical exam
- SMA natural history /disease progression questionnaire

- Pulmonary function test if applicable,
- Timed Test if applicable
- Muscle strength if applicable
- Motor function (Moviplate if applicable + MFM+ ACTIVE-seated)
- Activity assessment[1]
- MRI[2]
- EMG
- PedsQL + HUI2
- Blood sample for biomarker

- Concomitant treatments
- AE/SAE

V5 – End of study
- Clinical exam
- SMA natural history /disease progression questionnaire

- Pulmonary function test if applicable,
- Timed Test if applicable
- Muscle strength if applicable
- Motor function (Moviplate if applicable + MFM+ ACTIVE-seated)
- Activity assessment[1]
- MRI[2]
- EMG
- PedsQL + HUI2
- Blood sample for biomarker

- Concomitant treatments
- AE/SAE

1: Only on patients older than 6 years old (forecasted: 30)
2: Only on a subgroup of 20 patients older than 4 years old. MRI will be performed in 2 sites: Paris and Strasbourg

SMA=Spinal Muscular Atrohpy, MFM=Motor Function Measures, EMG=Electromyography, PedsQL=Pediatric Quality of Life Inventory , HUI2=Health utility Index 2, AE/SAE=Adverse Event/Serious Adverse Event, MRI=Magnetic Resonance Imaging

SCHEDULE OF ASSESSMENTS

	2 – 5 years old		≥ 6 – 30 years old	
	Inclusion	Follow up visit	Inclusion	Follow up visit
	M0	Every 6 months ± 28 days	M0	Every 6 months ± 28 days
Verification of selection criteria	X		X	
Informed consent	X		X	
Demographic data	X		X	
Physical examination and vital signs[1]	X	X	X	X
SMA natural history/disease progression questionnaire: - Achieved Milestone - Respiratory function - Number of school and/or work days and family or social event missing due to SMA - Other assessments from the medical file (feeding status, orthopedic status)	X	X	X	X
Pulmonary function Tests: - FVC - PCF - MEP - MIP and/or SNIP[2]			X	X
Timed Test[3]: - Time to rise from floor - Time to walk/run 10 meters - Time to climb and descend stairs - Distance walked in 6MWT			X	X
Moviplate			X	X
Muscle strength: - Myogrip - Myopinch			X	X
Activity assessment[4]			X	X
MFM[7]	MFM20[5]	MFM20[5]	MFM32	MFM32
ACTIVE-seated			X	X
PedsQL	X	X	X	X
HUI2	X	X	X	X
MRI[6]	X	X	X	X
EMG - CMAP - Decrement search	X	X	X	X
Blood Sample for clinical genotyping	X		X	
Blood Sample for biomarker	X	X	X	X
Concomitant Treatments	X	X	X	X
AE/SAE		X		X

[1] Weight, height, body temperature, heart rate, respiratory rate, systolic and diastolic blood pressure
[2] MIP and SNIP when possible. If not possible to perform both because of fatigue, MIP will be chosen
[3] Only for ambulant patients defined as patient being able to walk 10 meters without human or technical help
[4] Only on a subgroup of 30 patients
[5] MFM32 can be chosen for patients older than 4Y, depending on patient's abilities
[6] Only for 20 patients older than 4Y; only in 2 sites in Paris and Strasbourg – every 12 months
[7] Combined with Kinect-MFM only in Paris, Liège and Lyon sites
Table 1 : Study schedule description

F. Hoffmann-La Roche Ltd.
34/Statistical Analysis Plan SG41616

Clinical Study Report: RO7034067 - F. Hoffmann-La Roche Ltd
Protocol SG41616   Report Number 1101867   196

Risdiplam—F. Hoffmann-La Roche Ltd
119/Statistical Analysis Plan BP39055

Appendix 9   Schedule of Assessment for Olesoxime Study WN29836

Appendix 2
Schedule of Assessments

Table 1   Schedule of Assessments

	Selection	Treatment Period										
		Baseline Day 0	Week 4	Week 9	Week 13	Week 26	Week 39	Week 52	Week 65	Week 78	Week 91	Week 104
Visits	1-4 Weeks (V-1)	V0	V1	T1	V2	V3	V4	V5	V6	V7	V8	V9
Clinical Assessments												
Informed Consent	X											
Medical and Surgical History	X											
Genotyping if not documented	X											
Genotyping SMN2 Copy Number	X											
Physical Examination	X	X	X		X	X	X	X	X	X	X	x
Vital Signs	X	X	X		X	X	X	X	X	X	X	X
ECG	X	X	X		X	X	X	X	X	X	X	X
Hammersmith HFMS	X				X		X		X		X	
Motor Function Measure		X				X		X		X		X
CMAP/MUNE		X				X		X		X		X
Forced Vital Capacity		X			X	X	X	X		X		X
CGI (patients/parents)		X		X	X	X	X	X	X	X	X	X

Visits	Selection	Treatment Period										
		Baseline Day 0	Week 4	Week 9	Week 13	Week 26	Week 39	Week 52	Week 65	Week 78	Week 91	Week 104
	1-4 Weeks (V-1)	V0	V1	T1	V2	V3	V4	V5	V6	V7	V8	V9
Clinical Assessments												
CGI (physician)		X			X	X	X	X	X	X	X	X
PedsQL		X						X				X
Inclusion/Exclusion Criteria	X	X										
IMP Dispensation		X	X		X	X	X	X	X	X	X	
IMP Return			X		X	X	X	X	X	X	X	X
Biological Assessments												
Laboratory Tests	X		X		X	X	X	X	X	X	X	X
Biobank Blood & Urine Sample	X							X				X
Pregnancy Test	X							X				X
AEs and Concomitant Treatments	←---→											
Pharmacokinetic Sampling												
Olesoxime Plasma Trough Levels			X		X	X		X		X		X
IMP Administration												
Olesoxime		←---→										
DMC Meeting			X		X	X	X	X	X	X	X	X

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		Treatment Period										
	Selection	**Baseline Day 0**	**Week 4**	**Week 9**	**Week 13**	**Week 26**	**Week 39**	**Week 52**	**Week 65**	**Week 78**	**Week 91**	**Week 104**
Visits	**1-4 Weeks (V-1)**	**V0**	**V1**	**T1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**
Clinical Assessments												
Futility and Interim Efficacy Analysis								X				

AE = adverse event; CGI = Clinical Global Impression of Change; CMAP = Compound Muscle Action Potential;
DMC = Data Monitoring Committee; ECG = electrocardiogram; HFMS = Hammersmith Functional Motor Scale; IMP
= investigated medicinal product; MFM = motor function measure; MUNE = Motor Unit Number Estimation; PedsQL
= Pediatric Quality of Life Inventory; SMN2 = survival motor neuron 2; V = visit.

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Appendix 10 Statistical Analysis System (SAS) Code for the MMRM Analysis for the Comparison with External Comparator

Data

```
PROC MIXED DATA=data1;
CLASS patient trt visit SMATYPE SCOLIO M5DS SMN2 copy number; MODEL
change = BASE trt visit age SMATYPE M5DS SCOLIO SMN2
copy number trt*visit BASE*visit/DDFM=KR;
REPEATED visit /SUBJECT=patient TYPE=UN;
LSMEANS trt*visit / DIFFS cl;
WEIGHT attwgt;
RUN;
where
```
data1: dataset which contain data from studies of SUNFISH Part 2 (either the SUNFISH Part 2 risdiplam patients' data only or the SUNFISH Part 2 placebo patients data on risdiplam treatment only), Natural
History study and from study WN29836
patient: subject ID
visit: ID of the visit (Week 17, Week 26, Week 35, Week 52, Week 78 and Week 104 or Week 17, Week 26, Week 35 and Week 52)
BASE: baseline MFM total score
age: age at enrolment/ age at adjusted baseline (1 year after enrolment for SUNFISH Part 2 placebo patients)
trt: treatment (risdiplam treated SUNFISH Part 2 or from external comparator data)
SMATYPE: SMA Type (Type 2 or Type 3)
M5DS: MFM scale used (MFM32 or MFM20)
SCOLIO: presence of scoliosis at (original) baseline (Yes or No)
change: change from baseline in the MFM total score
attwgt: the weights derived from the propensity scores. (for weighted analyses)
agecat: age categories (2 to 5years, 6 to 11 years, 12 to 17 years and 18 to 25 years)
TYPE=UN means the unstructed variance-covariance matrix applied to model the within-patient variability.
If model does not converge, please remove 'SMATYPE', 'M5DS', 'SCOLIO', 'SMN2 copy number' in the
'MODEL' statement for the analysis. If the model still does not converge, a heterogeneous autoregressive variance-covariance structure will be used (TYPE=ARH(1)) instead. The subgroup analysis by age categories will be done by replace the 'age' variable in the 'MODEL' statement with 'agecat' and also adding in "agecat*trt" and "agecat*trt*visit" in the 'MODEL statement.