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)

NCT Number: NCT02908685

Document Date: Protocol Version 6: 22-June-2020

PROTOCOL

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
NCT NUMBER:	*NCT02908685*
MEDICAL MONITOR:	[redacted], *MD, PhD*
TEST PRODUCT:	Risdiplam (RO7034067)
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	03 May 2016
DATES AMENDED:	Version 2: 05 Oct 2016 Version 3: 07 Mar 2017 Version 3 (ROW): 13 October 2017 Version 3 (US-1): 24 October 2017 Version 3 (Canada): 30 January 2018 Version 4: 01 March 2019 Version 5: 18 May 2020 Version 6: See electronic date stamp below.

FINAL PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
22-Jun-2020 07:59:09	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 6
RATIONALE

Protocol BP39055 Version 5 was released but is not effective; this Version 6 represents changes made to Version 4 of the protocol.

Protocol BP39055 V5 has been amended to correct errors in the Appendix 1 and 3.

- In Appendix 1, footnote z has been corrected to footnote y.
- Appendix 3 has been replaced with the correct Schedule of Activities for Part 2.

Protocol BP39055 V4 was primarily amended to reduce the number of ophthalmological assessments required during the open-label extension period. Changes to the protocol, along with a rationale for each change, are summarized below:

- The study drug name has been changed from RO7034067 to risdiplam throughout the protocol.
- Background information on completed and ongoing studies of risdiplam has been updated (Section 1.2.2).
- Cautionary language on the concomitant use of CYP3A4 substrates has been removed, based on the recent results of the clinical drug-drug interaction Study BP41361 and subsequent physiologically-based pharmacokinetic modeling for extrapolation to children and infants. The study showed that coadministration with risdiplam led to only a small increase in exposure of the sensitive CYP3A substrate midazolam, which is not considered to be clinically relevant (Sections 1.2.1.2, 1.2.2, and 4.5).
- Given the absence of any risdiplam-induced ophthalmological findings to date in 471 patients exposed to risdiplam for up to 3 years, the frequency of ophthalmology assessments after completion of the study visit Week 104 has been reduced to every 6 months and intra ocular pressure assessment and fundus photography have been removed from the schedule of assessments after completion of Week 104 (Sections 1.3.2, 4.6.1.11, and Appendices 1, 3, 5, and 6).
- The follow-up visits after study completion/early withdrawal visit have been replaced with a phone call 30 days after this visit (i.e. at least 30 days after last dose of study medication) to capture adverse events. The half-life of risdiplam is short and will be completely eliminated from the patient's body within 30 days, so risdiplam-related adverse events are not expected beyond this adverse event reporting period. (Sections 3.1.1, 4.6.1, 4.7.1.1, 5.3.1, and 5.6)
- The Safety Outcome Measures text has been edited for clarity and to remove extraneous detail (Section 3.3.1).
- It has been clarified that niacin is permitted if used as a nutritional supplement (Section 4.5.2).
- The frequency of the Tanner Staging has been clarified (Section 4.6.1.6, Appendices 1 and 3).

- Some aspects of safety monitoring and stopping rules have been removed to reflect the revised potential risks of risdiplam based on the current data, as described in the Risdiplam (RO7034067) Investigator's Brochure, Version 7 (March 2020) (Sections 5.2 and 5.3.3).

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

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PROTOCOL ACCEPTANCE FORM

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
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IND NUMBER:	128972
NCT NUMBER	*NCT02908685*
TEST PRODUCT:	Risdiplam (RO7034067)
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please keep the signed original form in your study files, and return a copy to your local study monitor.

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 $AUC_{0\text{-}24h,ss}$ 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; $AUC_{0\text{-}24h,ss}$ 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) ≥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) For women 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) 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 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.*
- 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.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Events
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
AUC_{0-24}	Area under the concentration–time curve from 0 to 24 hours
BCVA	Best corrected visual acuity
CGI-C	Clinical Global Impression of Change
C_{max}	Maximum concentration
CNS	Central nervous system
CRO	Contract research organization
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTRS	Early diabetic treatment retinopathy study
ePRO	Electronic patient-reported outcome
ERG	Electroretinogram
FAF	Fundus auto-fluorescence
FDA	Food and Drug Administration
FEV	Forced expiratory volume
FMO	Flavin monooxygenase
FoxM1	Forkhead box protein M1
FVC	Forced vital capacity
HFMSE	Hammersmith Functional Motor Scale Expanded
ICH	International Conference on Harmonisation
iDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMC	Internal Monitoring Committee
IMP	Investigational medicinal product
IND	Investigational new drug (application)
IOP	Intraocular pressure
IRB	Institutional Review Board
IxRS	Interactive (voice/web) response system

LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LPLV	Last patient, last visit
MADD	MAP-kinase activating death domain
MATE	Multidrug and toxin extrusion
MEP	Maximal expiratory pressure
MFM	Motor function measure
MIP	Maximal inspiratory pressure
MMRM	Mixed model repeated measures
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
OAT	Organic anion transporter
OCT	Organic cation transporter or optical coherence tomography (in Ophthalmology sections)
OLE	*Open-Label Extension*
OTC	Over-the-counter
PBPK	Physiologically based pharmacokinetics
PCF	Peak cough flow
PD	Pharmacodynamic
PedsQL	Pediatric Quality of Life Inventory
PK	Pharmacokinetic
PRO	Patient-reported outcome
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate using the Bazett's correction factor
QTcF	QT corrected for heart rate using the Fridericia's correction factor
RBC	Red blood cell
RBR	Research biosample repository
RR	RR interval
RULM	Revised Upper Limb Module
SAD	Single-Ascending Dose
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SD-OCT	Spectral domain optical coherence tomography
SMA	Spinal muscular atrophy

SMAIS	SMA Independence Scale
SMN	Survival of motor neuron
SNIP	Sniff nasal inspiratory pressure
SoA	Schedule of assessments
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
WBC	White blood cell
WGS	Whole genome sequencing

1. BACKGROUND AND RATIONALE

1.1 BACKGROUND ON DISEASE

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

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

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

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

clearance, reduced vital capacity, gastroesophageal dysmotility, urinary incontinence, hip dislocation, and joint and muscle pain.

The medical need in SMA is very high, and several drug candidates are currently under investigation in the nonclinical and clinical setting (Lewelt et al 2012; d'Ydewalle et al 2015). The *SMN2*-targeting antisense oligonucleotide, nusinersen (SPINRAZA®), has been approved by health authorities in the US, European Union, Canada, and other jurisdictions, for the treatment of SMA in pediatric and adult patients, and marketing applications have been submitted to other regulatory authorities for approval.

Alternative management strategies focus on prevention and treatment of comorbidities, such as failure to thrive, surgical and non-surgical treatment of scoliosis and contractures, pulmonary hygiene, non-invasive ventilation, mobility and seating support, and physical and occupational therapy.

1.2 BACKGROUND ON RISDIPLAM

One of the promising strategies currently being pursued is to restore SMN protein levels in SMA patients by modulating *SMN2* splicing to favor the inclusion of exon 7 into the mRNA transcript, thereby increasing expression of stable full-length protein from the *SMN2* gene (Kolb et al 2011; Nurputra et al 2013). One such compound currently being developed is risdiplam *(previously referred to as R07034067),* which directly targets the underlying molecular deficiency of the disease and promotes the inclusion of exon 7 to generate full-length *SMN2* mRNA, which therefore increases the production of functional SMN protein. SMN protein increase after treatment with risdiplam has been shown in fibroblasts and motor neurons derived from patients with SMA.

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

See the Risdiplam (R07034067) Investigator's Brochure for details on non-clinical and clinical studies.

1.2.1 Previous Non-Clinical Studies

1.2.1.1 Pharmacology

Risdiplam effectively corrects the dysfunctional splicing of human *SMN2* pre-mRNA in cultured cells by shifting the balance of the alternative splicing reaction completely towards the inclusion of *SMN2* exon 7 and the production of full-length mRNA and functional SMN protein. In vivo, risdiplam effectively corrects the dysfunctional splicing of

the human *SMN2* pre-mRNA in SMA mouse models (the severe SMNΔ 7 model and the milder C/C-allele model) carrying human *SMN2* transgenes. This correction results in a significant increase in SMN protein levels and a profound prolongation of animal survival, protection of the neuromuscular circuit, and improvement of motor function in the SMNΔ 7 mouse model of severe SMA.

1.2.1.2 Pharmacokinetics

Risdiplam is well-absorbed in rats and monkeys following oral administration. The compound has very low intrinsic clearance in vitro and in vivo, and has free-fraction values of 11, 15, 16, and 10% in human, monkey, rat and mouse plasma, respectively. In human plasma, risdiplam is predominantly bound to serum albumin, with no binding to alpha-1 acid glycoprotein. Risdiplam is highly bound to melanin in vitro and accumulates into melanin-containing structures of the eye in pigmented rats and monkeys.

Risdiplam is cleared in animals primarily through metabolism with minor contribution from renal clearance. The enzymes involved in human metabolism of risdiplam are flavin monooxygenase (FMO) 1 and 3 and multiple members of the cytochrome P450 superfamily (CYP), especially CYP3A isoenzymes. Risdiplam is not a substrate for human P-glycoprotein (P-gp). The potential for interaction with other drugs that inhibit or induce metabolizing enzymes or active transport proteins cannot be ruled out at this stage of development.

Risdiplam is not an inhibitor of human multidrug resistance protein 1 (MDR1), organic anion-transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1 or OAT3. It is therefore unlikely that co-administration with risdiplam will alter the pharmacokinetics (PK) of other drugs whose disposition is influenced by these transporters. However, risdiplam is an inhibitor of organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE)1 and MATE2-K and the potential for interaction with other drugs that are substrates of those transport proteins cannot be ruled out at this stage. Such drugs are therefore prohibited for patients participating in this study (Section 4.5.2).

1.2.1.3 Toxicology and Safety Pharmacology

A toxicology and safety pharmacology program using risdiplam has been conducted according to the ICH guidelines, with all pivotal studies conducted in compliance with GLP regulations. Pivotal toxicity studies with once daily oral gavage administration of risdiplam of up to 26 weeks in duration were conducted in the juvenile and adult rat and up to 39 weeks in young cynomolgus monkey. In addition, various genotoxicity and safety pharmacology studies have been conducted and, because of the absorption of risdiplam in the UV range, the potential for phototoxicity was also studied in vitro. Mechanistic investigations in vitro and in vivo to elucidate mechanisms of toxicity based on physicochemical properties and secondary splice target identification were conducted. As risdiplam is being developed to chronically treat SMA, which in its most severe form manifests itself soon after birth, the toxicity testing strategy includes a 39-

week toxicity study that was started with young, 2-year old monkeys (with animals still being pre or peripubertal at the end of 39 weeks of treatment and after the 22-week recovery phase), and two repeat-dose GLP juvenile toxicity studies in rats: i) a 13-week rat juvenile study with treatment immediately post-weaning (PND 23-24), and ii) a 4-week rat juvenile study with animals dosed from PND 4 until PND 32. These studies included dedicated assessments of critical developing organ systems according to the available guidelines issued by FDA and CHMP. In addition, a 13/26-week toxicity study in pigmented rats has been conducted to study the onset, if any, and progression of changes in the retina using light/electron microscopy, sdOCT and ERG assessments. In this study, histopathological evaluation of other organs of interest (brain, pancreas and adrenals) was included to compare results of the 26-week chronic toxicity study in albino rats across rat strains.

Safety pharmacology studies in vitro and in vivo conducted with risdiplam did not demonstrate any noteworthy effects.

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

- Micronucleus induction in vitro in mouse cell lines and in rat bone marrow erythroblasts.
- Findings in GI epithelia (increased apoptosis/single cell necrosis) and lamina propria (vacuolation) in mouse, rat and/or monkey
- Parakeratosis/hyperplasia/degeneration of the skin, tongue and larynx epithelia with associated inflammation in monkey.
- Degeneration of germ cells in monkey and rat testes
- Further test item-related findings were observed in hematology (red and white cells), with correlates in small thymus and thymus atrophy in monkeys but without histopathological changes in bone marrow.

Risdiplam-related findings were associated with a clear no-observed-adverse-effect level (NOAEL) and/or a clear statistical threshold using a benchmark dose approach (for micronucleus induction in rat bone marrow).

Evidence suggests that these effects of risdiplam on proliferating cells and tissue is related to alternative splicing effects on secondary targets such as the Forkhead box protein M1 (FoxM1), a major cell cycle regulating factor, and MAPkinase activating death domain (MADD), a gene with various splice variants involved in apoptosis. Further secondary splice targets have been identified but insufficient data are published on the biological impact of changes in splice variant expression.

In rats, risdiplam resulted in embryo–fetal toxicity with retarded fetal development, evidenced by lower fetal weights and minor differences in skeletal ossification. There was no evidence of embryo lethality (embryo–fetal death) or fetal dysmorphology

(teratogenicity) in rats. The NOAEL for embryo–fetal toxicity was 3 mg/kg/day, corresponding to maximum concentration observed (C_{max}) 319 ng/mL and area under the concentration–time curve from 0 to 24 hours ($AUC_{0–24}$) 4630 ng•h/mL on gestational Day 15. In rabbits, risdiplam administered from Days 6 to 19 of gestation resulted in maternal toxicity and embryo–fetal lethality and malformations (hydrocephaly). The NOAEL for maternal toxicity and embryo–fetal development was 4 mg/kg/day for risdiplam (C_{max}1500 ng/mL, $AUC_{0–24}$ 7990 ng•h/mL on gestational Day 15).

A further finding of toxicological significance for risdiplam was noted in the retina from the chronic 39-week toxicity study in monkeys. Multifocal peripheral retina degeneration in the photoreceptor layer and microcystic spaces in the inner retinal layers in monkeys as detected by spectral domain-optical coherence tomography (sdOCT). This was associated with depressed scotopic (rod) B-wave and somewhat less affected photopic (cone) B-wave in the electroretinogram (ERG). These findings were confirmed by histopathology. The effect on the retina is thought to be connected with evidence of high melanin binding and tissue retention in the retina and impairment of lysosomal function/autophagosomal accumulation in retinal pigmented epithelial cells.

Further noteworthy observations were major differences in tolerability with repeated oral dosing in young (pre- and post-weaning) and adult rats with much higher susceptibility of younger rats to toxic effects of risdiplam than older rats at comparable doses. However, when free exposure to risdiplam is compared between species and ages, no major differences in exposure associated with subacute dose-limiting toxicity are recorded.

In terms of chronic treatment of SMA patients, it is proposed to evaluate doses not exceeding the exposure at the NOAEL/NOEL of the 39-week toxicity study in monkeys with an AUC_{0-24h} of 1870/2060 ng.h/mL in males and females, respectively. Young/ ~~V~~very young rats displayed a higher dose-based susceptibility to the subacute, life-threatening toxicity of risdiplam than older rats likely based on a higher free fraction and longer half-life. Thus, in the upcoming clinical studies, careful evaluation of free fraction in plasma of infants and children (up to the age of 12 years) is warranted with specific adaptation of the doses to be tested if differences in plasma protein binding similar to those seen in rats of different ages should be found.

See the Risdiplam Investigator's Brochure for details on non-clinical studies.

1.2.2 Previous and Ongoing Clinical Studies

As of March 2020, risdiplam has been investigated in five clinical pharmacology studies: Study BP29840 (SAD, entry-into-human study in healthy male adults); Study NP39625 (a PK study in healthy Japanese adults); Study BP39122 (a mass balance study in healthy male adults); Study BP41361 (a drug-drug interaction [DDI] study with the CYP3A substrate midazolam), and Study BP40995 (hepatic impairment study). All four studies (BP29840, NP39625, BP39122 and BP41361) have been completed;

Study BP40995 is clinically complete but the Clinical Study Report is pending (see the Rrisdiplam Investigator's Brochure for available data).

In Study BP41361, it was observed that administration of risdiplam once daily for 2 weeks in healthy adult subjects slightly increased the exposure of midazolam, a sensitive CYP3A substrate, by 11% for area under curve from time 0 to last measurable concentration (AUC0-last) and 16% for peak plasma concentration (Cmax). However, the observed magnitude of this effect is not considered clinically relevant. Based on physiologically based pharmacokinetic (PBPK) modeling, a similar magnitude of the effect is expected in children and infants as young as 2 months old.

Additionally, there are *four* ongoing studies in SMA patients: BP39054, an open-label safety and PK/PD study in non-naive SMA Type 2 or 3 patients; BP39056, a seamless open-label study to evaluate safety, PK/PD and efficacy in infants with Type 1 SMA*; BN40703, an open-label study in infants with genetically diagnosed and presymptomatic SMA* and the present study BP39055.

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

1.2.2.1 Clinical Summary Study BP29840

Study BP29840 consisted of a single ascending dose (SAD) part, including an exploratory investigation of the effect of food, in 25 healthy male subjects of whom 18 received risdiplam at doses ranging from 0.6 mg to 18 mg, and an itraconazole interaction part in 8 subjects.

Risdiplam was rapidly absorbed with a median t_{max} between 2 and 3 hours under fasted conditions. Peak plasma concentration (C_{max}) and total plasma exposure (AUC) increased in a dose-proportional manner. The elimination half-life was approximately 40-50 hours. On average, a small fraction (<10%) of the administered dose was excreted unchanged into urine. Food had no relevant effect on the pharmacokinetics of risdiplam; only the median t_{max} was delayed to 5 hours.

The co-administration of risdiplam with itraconazole resulted in a slight increase (11%) in $AUC_{0\text{-}120h}$ and a small decrease (9%) in C_{max}.

Risdiplam had a dose-dependent effect on *SMN2* splicing, as shown by a change in the ratio of full-length SMN2 mRNA to SMNΔ7 mRNA which is interpreted as proof of mechanism in terms of the expected pharmacodynamic (PD) effect.

Risdiplam was well-tolerated in this study at all dose levels. There were no deaths, serious adverse events (SAEs) or withdrawals due to adverse events (AEs). No clinically relevant changes in laboratory safety parameters, vital signs, AEs, electrocardiogram (ECG) parameters or ophthalmological assessments were observed.

A total of 27 AEs were reported in the SAD and itraconazole interaction parts. All AEs were of mild intensity and resolved within a short period of time without sequelae. All AEs were considered to be not related to risdiplam by the Investigator with the exception of pollakiuria (placebo) and headache (risdiplam 18 mg).

The most frequently affected System Organ Class was GI disorders (9 AEs) followed by nervous system disorders (4 AEs). The most frequently reported AEs were headache (4 subjects) and diarrhea, abdominal pain and nasopharyngitis (3 subjects each).

There was no dose-related increase in the incidence or severity of reported AEs and no cluster of AEs indicative of a toxic effect of the compound on a given organ system.

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

1.2.2.2 Clinical Summary Study BP39055 (Part 1)

Fifty-one patients *were* enrolled in Part 1 of study BP39055, evaluating the safety, tolerability, PK and PD of *risdiplam* in patients with Type 2 and Type 3 (ambulant or non-ambulant) SMA, with the objective to select the dose for Part 2 of the study. As described in Section 3.1.2.1, data were reviewed on an ongoing basis by an Internal Monitoring Committee (IMC) as part of the dose selection process for Part 2. Continuation of the study into Part 2 at the dose selected by the IMC was endorsed by an external independent Data Monitoring Committee (iDMC), following review of the same data package.

A total of 51 patients were enrolled in five cohorts and randomized in a 2:1 ratio to active treatment or placebo. Patients were initially assigned to the following dose levels: 3 mg and 5 mg o.d. in patients aged 12–25 years-old (Group A Cohort 1 and Cohort 2, respectively), and 0.02 mg/kg, 0.05 mg/kg and 0.25 mg/kg in patients aged 2–11 years (Group B Cohort 1, Cohort 2 and Cohort 3, respectively). As recommended by the IMC, the dose given to Group B Cohort 1 and Cohort 2 was then increased to 0.15 mg/kg (in 2 steps for Group B Cohort 1, in 1 step for Group B Cohort 2).

Across these dose levels, risdiplam PK was linear, i.e., there was a corresponding increase in risdiplam plasma concentrations with increase in dose. Steady state was attained after 7 to 14 days of treatment with risdiplam once daily.

A dose-related increase in SMN protein was observed across all dose levels and age groups upon treatment with risdiplam, with a median SMN protein increase of 151% (range 49%–251%) versus baseline at 5 mg in the age group of 12–25 years, and a 96% (range 17%–150%) increase at 0.25 mg/kg in the age group of 2–11 years.

A review of all available safety laboratory results, vital signs, ECGs and ophthalmological assessments did not show any clinically significant adverse findings as compared to baseline or the placebo group.

Risdiplam was well tolerated across all dose levels tested in both age categories and no stopping rules were met (see the Risdiplam Investigator's Brochure). There have been no deaths and no discontinuations from the study for any reason.

Based on these data, a dosing regimen of 5 mg for patients with a BW ≥20 kg and 0.25 mg/kg for patients with a BW <20 kg was selected for Part 2 of this study. *An overview of more recent data* is provided in the Risdiplam Investigator's Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

SMA is the leading genetic cause of death in infants and young children. In milder forms, it results in profound motor and respiratory disabilities and major orthopedic deformities. One drug was recently approved in the US, European Union, Canada and other jurisdictions for the treatment of SMA in pediatric and adult patients (the antisense oligonucleotide nusinersen [SPINRAZA®]) but the medical need in SMA is still very high. There is currently no oral treatment for SMA that provides stabilization or improvement of motor function, which would be of immense value for patients and parents/caregivers.

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

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

This study is designed to assess the safety, tolerability, PK and PD of risdiplam in patients with Type 2 and Type 3 SMA aged 2–25 years, across the exposure range that is expected to provide therapeutic benefit: Part 1, testing two dose-levels of risdiplam, and in Part 2, to assess the efficacy and safety of treatment with risdiplam at the dose level selected from Part 1. The dose-selection approach for Part 2 aims at maximizing efficacy and therapeutic benefit by targeting the maximum SMN protein blood level that can be achieved within the safety margins in patients with SMA, as determined in Part 1. Part 1 will include non-ambulant and ambulant SMA patients whilst Part 2 will only include non-ambulant SMA patients (Sections 2 and 3.2.2).

As this is the first study of risdiplam in SMA patients, the PK of risdiplam will be assessed in detail in Part 1, to enable the dose-selection for Part 2 for all age groups (2-25 years). Pharmacodynamic effects of risdiplam will be measured in terms of SMN protein and SMN mRNA splice forms. Efficacy will be assessed in terms of motor function, with the motor function measure (MFM), the revised upper limb module (RULM) and the Hammersmith functional motor scale expanded (HFSME). Efficacy on respiratory function will be measured with SNIP in all patients and MIP, MEP, FVC, FEV1 and peak cough flow (PCF) in patients older than 6 years.

1.3.2 Benefit-Risk Assessment

In the SAD study (BP29840; Section 1.2.2), risdiplam was shown to be safe and well-tolerated up to a single-dose of 18 mg. This study established proof-of-mechanism in healthy subjects that, at safe and tolerable doses, risdiplam is able to modulate the splicing of *SMN2* mRNA, leading to an exposure-dependent increase in the amount of full-length *SMN2* (FL-*SMN2*) mRNA and a corresponding decrease in the amount of *SMN2* mRNA lacking exon 7. In Part 1 of study BP39055 (see interim data summarized in Section 1.2.2.), treatment with risdiplam was considered to be safe and well tolerated, and an exposure-dependent increase in SMN protein levels has been observed confirming proof-of-mechanism in patients with SMA. Accordingly, available data to date suggest that risdiplam may provide significant benefit for patients with SMA.

In view of the adverse findings in the animal toxicology studies, the maximum exposure in the first clinical trial in healthy volunteers (HV) was limited to an individual plasma exposure ($AUC_{0\text{-}24h}$) of 1500 h • ng/mL, to ensure the safety of the participating subjects while assessing safety and tolerability up to a therapeutically relevant exposure level, and to determine essential PK and PD information to support modeling activities and selection of the starting-dose for therapeutic trials in children and adult patients with SMA.

In this study, a slightly higher exposure cap of 2000 h • ng/mL (mean $AUC_{0\text{-}24h,SS}$) corresponding to the overall NOAEL of the 39 week toxicology study in cynomolgus monkey, along with a thorough clinical safety monitoring plan is justified, considering the study design and the potential benefit for patients enrolled. At the dosing regimen selected for Part 2 of the study (i.e., 5 mg for patients with a BW ≥20 kg and 0.25 mg/kg

for patients with a BW <20 kg), the mean predicted exposure at the selected Part 2 dose is 1690 [95%CI: 1600–1780] ng•h/mL across the whole age group of children and adults between 2–25 years of age (see Table 1). Each dose level to be tested in this study has the potential to provide benefit to SMA patients. Available data suggest that a 100% increase in SMN protein levels (the target for the lower dose level tested in Part 1) is expected to turn more severe SMA phenotypes into milder forms, while further increase is likely to provide even greater benefit (Section 3.2.1). In Part 1 of the study, a median SMN protein increase of 151% versus baseline was observed for 5 mg in the age group of 12–25 years and a 96% increase was noted for the 0.25 mg/kg dose in the age group of 2–11 years. Safety precautions are provided and a thorough safety-monitoring plan focusing on liabilities identified in the non-clinical toxicology studies will be implemented to address potential safety concerns for the patients enrolled in the trial (Section 5.2). Toxicological findings observed in the non-clinical studies include toxicity involving skin, pharynx/larynx, fertility, potential for genotoxicity based on micronucleus induction and potential irreversible retinal toxicity which could translate into some visual impairment.

With this regard, it is essential to note that the changes found by OCT scanning (and on histopathology) in the peripheral retina in the 39-week monkey study may produce peripheral visual field defects that are usually asymptomatic and would normally not impact visually oriented behavior and quality of life. These defects would be similar to those found in early stage peripheral retinal degeneration, and pan-retinal photocoagulation for diabetic retinopathy; initially central visual function is spared in these conditions.

With the extensive ophthalmological monitoring that is included in this *study (and across the risdiplam clinical trial program),* including OCT, *initially* every 2 months throughout the *treatment phase and thereafter every 6 months,* possible retinal toxicity in patients should be detected early in a sensitive and timely fashion, conceivably before irreversible functional retinal damage. In case of clinically relevant peripheral retinal toxicity, stopping rules will apply (Section 5.2.4), since progression of toxicity and involvement of the macula cannot be ruled out. Based on these elements, the ophthalmological monitoring strategy and stopping rules included in this study appear appropriate to i) minimize the risk of irreversible symptomatic retinal injury, and ii) detect peripheral retinal abnormalities early when peripheral visual field defects would likely be asymptomatic. Implemented ocular monitoring is also addressing functional and structural integrity of central retina and general eye examination.

The key elements of risk management in this study considering non-clinical findings and clinical experience from the SAD study in healthy volunteers are summarized below:

- Frequent PK assessments (especially in Part 1, Section 1.2.1.3), and a precaution to take into account possible differences in plasma protein binding in children compared to adults, to ensure that exposure remains below the exposure cap.

- Safety monitoring throughout the treatment period*, open-label extension, the study completion/withdrawal visit and follow up* (Section 5.2.2), including ophthalmology, dermatology and clinical laboratory measures.
- Clear definition of dose-escalation criteria and cohort stopping rules in Part 1 (Section 5.2.4).
- Stopping rules at the individual patient level in Part 1 and Part 2 (Section 5.2.4).
- Inclusion of a guideline for managing specific adverse events (Section 5.2.3).
- Implementation of an IMC (Part 1) and an external iDMC (Part 2), who will review safety, PK and PD data on a regular and ad-hoc basis throughout the study (Section 3.1.2).
- Appropriate inclusion/exclusion criteria and guidance regarding prohibited therapy (including OCT-2, MATE substrates, and medications with potential retinal toxicity; Section 4.5).

The strategy and rationale for dose-selection is described in Section 3.2.1. Table 1 gives an overview of the margins versus key toxicities of risdiplam at the starting exposure of this study, at the predicted exposure at the selected Part 2 dose, and at the exposure cap.

Table 1 Overview of the Margins versus Key Toxicities of Risdiplam

Type of Toxicity	Margin at NOAEL vs Starting Exposure of 700 ng • h/mL (AUC_{0-24h})	Margin at NOAEL versus predicted exposure of 1690 ng • h/mL [mean $AUC_{0-24h,ss}$ 95% CI: 1600–1780 ng·h/mL] at selected Part 2 dose*	Margin at NOAEL vs Cap Exposure of 2000 ng • h/mL (AUC_{0-24h})
Micronucleus induction in rat bone marrow	~5	~2	~1.5
Testis toxicity in rats and monkeys	~1	No margin	No
Epithelial findings (skin, eyelid, larynx) in monkeys (with chronic dosing)	>10	>3	>2.5
Hematology changes (RBC and lymphocytes) in monkeys, rats and mice	>10	>3	>4
Retina changes in monkeys	~3	~1	~1
Overall NOAEL (13 weeks of treatment: juvenile rat)	~10	~4	>3
Overall NOAEL (39 weeks of treatment: monkey)	~3	~1	~1
Overall NOAEL (26 weeks of treatment: adult albino rat)		~1,5	

NOAEL: no-observed-adverse-event level; RBC: red blood cell.

*The predicted exposure of 1690 ng•h/mL (95% CI: 1600-1780 ng·h/mL) is the mean predicted exposure across all SMA patients (2-25 years of age) to be enrolled in Part 2 at the selected dose of 5 mg for patients with a BW ≥20 kg and 0.25 mg/kg for patients with a BW <20 kg. Margins are based on the mean exposures in animal studies in the more sensitive species/sex.

As mentioned above, for patients enrolled in this study, the aim is to maximize possible therapeutic benefit whilst maintaining appropriate safeguards. Accordingly, all patients enrolled in this study will ultimately receive active treatment. Patients initially receiving placebo will be switched to active treatment as early as possible according to the design and the respective objectives of both parts of the study, i.e., after 12 weeks of treatment in Part 1 and after 12 months in Part 2. From an efficacy perspective, 12 months of

placebo-controlled treatment is considered sufficient to show clinical benefit in terms of motor function based on natural history of disease progression (Mercuri et al 2016) and appears appropriate to make a robust assessment of the efficacy of risdiplam.

Overall, considering the severity of SMA and the potential for patients to benefit from treatment with risdiplam, Roche considers the safety margins in this study appropriate, and data from Part 1 of the study continue to justify the benefit-risk of treatment with risdiplam for 2-25 year old patients with Type 2 and 3 SMA.

2. OBJECTIVES

2.1 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) 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 MFM at 12 months.

2.2 SECONDARY OBJECTIVES

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

Secondary objectives for Part 2 are as follows (see secondary endpoints Section 3.3):

- To investigate the PK/PD relationship of risdiplam by PK/PD modeling (PD to include *SMN2* mRNA and SMN protein).
- To investigate the efficacy of 12-month treatment with risdiplam in terms of motor function as assessed by the HFMSE and the 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 SNIP and, in patients aged 6 years and older, by MIP, MEP, FVC, FEV1 and 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.

2.3 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.

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design

This is a seamless, multi-center, randomized, double-blind, placebo-controlled, Phase II 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 will not roll over into Part 2.

All patients enrolled in this study, who initially receive placebo, will be switched to active treatment, as described below for Parts 1 and 2 respectively.

Part 1 - Exploratory Dose-Finding

Part 1 is a double-blinded, placebo-controlled, randomized (2:1 risdiplam: placebo), exploratory dose-finding study in Type 2 and Type 3 (ambulant and non-ambulant) SMA patients. This will be followed by an open-label extension.

Part 1 of the study will enroll at least 36 patients in two age groups, and two cohorts per age group. Two dose-levels will be investigated in a staggered, dose-escalation manner in both age groups (Figure 1):

- Group A: adolescent and adult patients aged 12-25 years (n = 18, in two cohorts of n = 9 pts).
- Group B: children aged 2-11 years (n = 18, in two cohorts of n = 9 pts).

The approach for dose-selection is described in Section 3.2.1 of this protocol. The initial dose administered to SMA patients in Group A (age 12-25 years) will be 3 mg once daily, which is predicted to result in an $AUC_{0\text{-}24h,ss}$ of 700 ng • h/mL and a 2-fold increase (i.e., 100% increase) from baseline in SMN protein. The same exposure level of an $AUC_{0\text{-}24h,ss}$ of 700 ng • h/mL will be targeted in the first cohort of Group B (age 2-11 years); the dose will be selected once the PK data of the first 3 adolescent patients from Group A has been assessed.

In both groups, the dose that will be administered to the second cohort of patients will target a higher exposure level, predicted to result in maximum SMN protein increase, without exceeding the exposure cap specified for this study.

Throughout this part of the study, all decisions (including enrollment, dose-escalation and switch of placebo patients to active treatment) will be taken by an Internal Monitoring Committee (IMC), as described in Section 3.1.2.1.

Part 1 will proceed as follows (Figure 1):

- Enrollment will start with the first cohort of Group A, (i.e., adult and adolescent patients [age 12-25 years, n = 9]). In order to ensure enough data in adolescent (i.e., younger) patients are available for selection of the dose for Group B (age 2-11 years), 6 of the 9 patients of this cohort will be 12-17 years old.
- 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 this age group will also target an $AUC_{0\text{-}24h,ss}$ of 700 ng • h/mL. This dose will be based on the multiple-dose PK data obtained from Group A and PBPK modeling and is currently predicted to be based on body-weight and/ or age.

  In case the exposure observed in the first adolescent patients on active treatment significantly deviates from the target exposure of $AUC_{0\text{-}24h,ss}$ 700 ng • h/mL, the dose administered to Group A may also be adjusted.
- Enrollment and treatment of patients in Groups A and B will be conducted in parallel and dose-escalations into a second cohort of patients in each age group will be taken independently (i.e., not waiting for each other to proceed).

  Safety and tolerability at the first dose-level will be confirmed for the respective age group based on at least 4-week treatment duration in all patients of the cohort (by implication, patients enrolled first will have longer treatment durations). 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 the higher dose level.

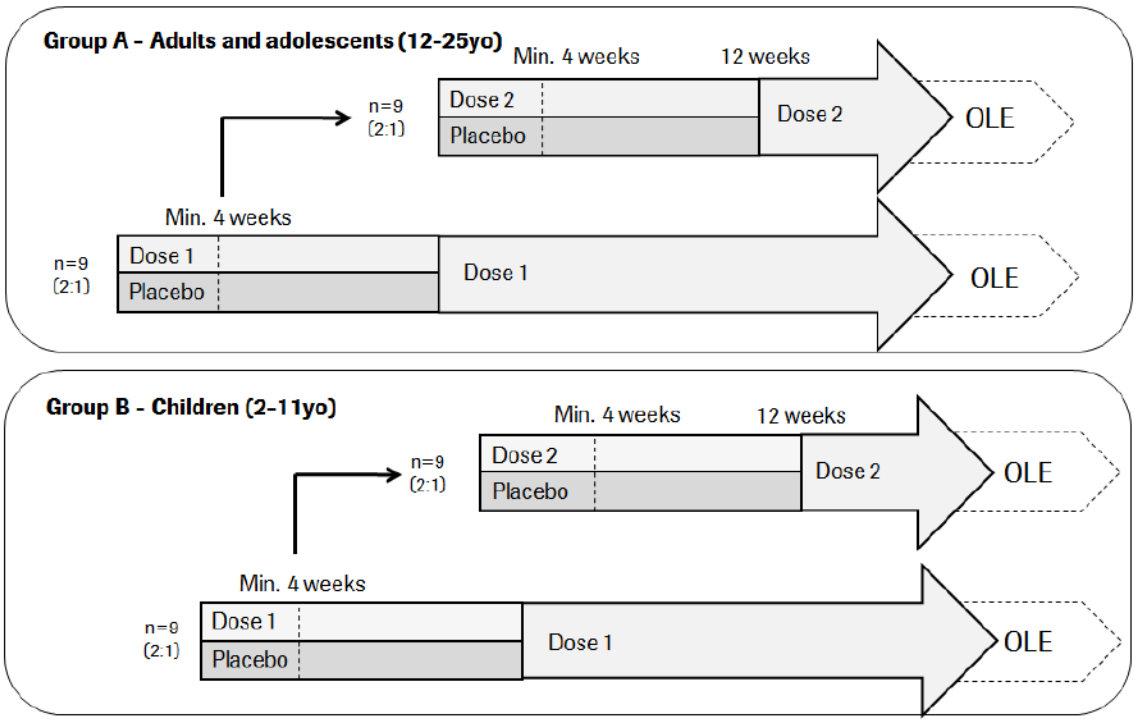
  This higher dose-level will be determined such as to achieve maximum SMN protein increase, with a corresponding target exposure not exceeding the exposure cap specified for this study, i.e., a total C_{max} of 400 ng/mL and a mean $AUC_{0\text{-}24h,ss}$ of 2000 ng • h/mL (NOAEL in the 39-week study in cynomolgus monkey; Section 1.2.1.1).
- 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, the IMC will review all available safety, tolerability, PK and PD data and the dose will be selected for Part 2. The external independent Data Monitoring Committee (iDMC; Section 3.1.2.2) will be asked to confirm that the study can continue as planned into Part 2 at the dose recommended by the IMC. The final decision will be taken by the Sponsor. Enrollment in Part 2 will begin after the dose-selection decision.
- In parallel, once the last patient of each cohort has completed 12 weeks of treatment, the IMC will review all available data from the cohort. Assuming data are in favor of risdiplam, the IMC will decide to switch placebo patients to active

risdiplam treatment, at the dose tested in their respective cohort (or at a lower dose-level if decided by the IMC). If the patients switched to risdiplam have completed the scheduled Week 17 visit, they will repeat all assessments from Day 1 onwards as planned in the Schedule of Assessments (SoA). If they have not reached Week 17, they will perform the Week 17 scheduled assessments prior to starting at Day 1. This is to ensure that all patients newly placed on active treatment have the same safety monitoring as the patients initially randomized to risdiplam treatment.

- Once Part 1 patients have completed the 12-week double-blinded treatment period and the dose has been selected for Part 2, all Part 1 patients will 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 this study (see below). Patients from the last cohort of Part 1 will need to complete treatment out to the end of the 12-week treatment period before entering the OLE.

Given the exploratory nature of this part of the study, up to 36 additional patients may be enrolled in Part 1, if required, to select the most appropriate dose for Part 2. Pre-existing cohorts may be expanded with additional patients, or new cohorts and dose-levels (always adhering to the specified exposure cap of $AUC_{0\text{-}24h,ss}$ of 2000 ng • h/mL) may be introduced, up to the maximum of a total of 36 additional patients for a total of maximum 72 patients in Part 1.

Figure 1 Study Design of Part 1 Exploratory Dose-Finding



Minimum of 4-week data from all patients in the cohort is required before selecting the next dose.
OLE = open-label extension

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

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

The OLE phase, which will include regular monitoring of safety, tolerability and efficacy, is planned to run as detailed in Section 3.1.3. If a patient *completes or withdraws early* from study treatment, the patient will be requested to attend *a study completion/early withdrawal visit and followed with a phone call from the site 30 days after the study completion/early withdrawal visit,* as described in the SoA Table (Appendix 1).

Part 2 - Confirmatory

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 o.d. for patients with a BW ≥20kg or 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 (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 where 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 of first dose.
- Treatment period: double-blinded treatment for 12 months, followed by 12-month active treatment period.

As in Part 1, the OLE phase is planned to run as detailed in Section 3.1.3. If a patient *completes or withdraws early from study treatment, the patient will be requested to*

attend a study completion/early withdrawal visit and followed with a phone call from the site 30 days after the study completion/early withdrawal visit, as described in the SoA Table (Appendix 1).

3.1.2 Committees

3.1.2.1 Internal Monitoring Committee (IMC)

The internal monitoring committee (IMC) will consist of selected Roche representatives: Clinical Pharmacologist, Translational Medicine Leader, Safety Science Leader, Statistician, and Statistical Programmer. The IMC will be 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 enrollment 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 will have longer treatment duration), and all available data from the previous cohort(s). At this point, if safety and tolerability are considered acceptable by the IMC, patients originally randomized to placebo will be switched to active treatment with risdiplam at the dose-level of their original cohort (or at a lower dose-level as decided by the IMC); see Section 4.3.

For stopping criteria, see Section 5.2.4.

Based on the review of all available PK, PD, safety and tolerability data at the point where the last patient of the last cohort in Part 1 will reach 4 weeks of treatment (a number of patients will have much longer treatment duration), the IMC will select the dose to be administered in Part 2 of the study.

Upon review of all available Part 1 data by the iDMC (Section 3.1.2.2) and confirmation of the IMC dose-selection decision, Part 2 will start and all patients from Part 1 will be switched to the dose selected for Part 2 as part of the OLE phase of this study. Patients from the last cohort of Part 1 will need to complete treatment out to the end of the 12-week treatment period of their cohort before entering the OLE.

In addition to reviewing the data at these pre-defined time-points, the IMC may, if required, meet and review the data on an ad-hoc basis throughout Part 1 of the study, as detailed in the Charter. The IMC can recommend termination of a certain cohort at any time and can also decide to enroll additional patients or additional cohorts in Part 1, if required to be able to select the most appropriate dose for Part 2. Pre-existing cohorts may accordingly be expanded with additional patients, or new cohorts and dose-levels may be introduced, up to a maximum of a total of 36 additional patients in Part 1 (i.e., a total of 72 patients in Part 1), as described above.

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

3.1.2.2 Independent Data Monitoring Committee

An external independent data monitoring committee (iDMC) will be established to monitor patient safety during the blinded placebo-controlled Part 2 of the study. The iDMC will meet to review data from Part 1 and confirm the dose-selection decision of the IMC. The iDMC will provide a recommendation to the Sponsor whether the study can continue as planned, i.e., that the study can move into Part 2 with the selected dose from Part 1 as recommended by the IMC. The final decision based on the iDMC recommendation will be made by the Sponsor. The iDMC will meet on a regular basis over the course of Part 2 of the study and may also meet on an ad-hoc basis as required, e.g., if any unexpected safety concerns arise. After meeting the iDMC will make a recommendation to the Sponsor for study conduct including (but not limited to) continuation, halting or amending the protocol.

The roles, responsibilities, membership, scope of activities, time of meetings and communication plan for the iDMC will be documented in the Charter prior to the initiation of the study. The iDMC will be chaired by a medically qualified individual with experience with SMA and will include at least one other Physician experienced in Neurology, a Clinical Pharmacologist, an Ophthalmologic Expert and a Biostatistician. No member of the iDMC will participate in the study as an investigator or sub-investigator.

3.1.3 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.

See Section 4.4.4 for conditions regarding post-trial access to risdiplam.

3.2 RATIONALE FOR STUDY DESIGN

3.2.1 Rationale for Dosage Selection

Given the severity and the high mortality and morbidity associated with SMA, all dose-levels tested in this study are aiming to provide therapeutic benefit to patients upon chronic dosing. As described in Section 3.1.1, two dose-levels will be tested in Part 1 of the study and evaluated to select the most appropriate dose for Part 2 of the study.

For Part 1, the approach for dose-selection for the respective cohorts is to target:

- Dose Level 1, target $AUC_{0\text{-}24h,ss}$ 700 ng • h/mL: an exposure predicted to result in a doubling of SMN protein levels (i.e., a 100% increase versus the patient's baseline) which is expected to lead to a substantial clinical benefit in SMA patients, turning more severe phenotypes into milder forms. This is based on SMN protein levels in SMA patients (Sumner et al 2006; Nguyen et al 2008) and on data obtained in animal SMA models regarding efficacy and the associated SMN protein increase (Risdiplam Investigator's Brochure). An $AUC_{0\text{-}24h}$ exposure of up to 1470 ng • h/mL was well-tolerated in the SAD study in healthy subjects, without any safety findings. This exposure of $AUC_{0\text{-}24h,ss}$ 700 ng • h/mL is a factor of approximately 3 (2.8) below the NOAEL level in the 39-week monkey study (i.e., 2.8-fold below the exposure level at which no adverse findings were observed). Only effects on the testes were observed at those exposure levels in the cynomolgus monkey. Reversibility of effects on testes could not be assessed in cynomolgus monkey due to sexual immaturity of the animals (see Risdiplam Investigator's Brochure); male subjects will be informed accordingly.
- Dose Level 2: a higher exposure, leading to the maximum possible SMN protein increase (provided all clinical and non-clinical safety data support this), which is predicted to provide greater benefit based on preclinical data as well as published clinical data with the antisense oligonucleotide nusinersen (Chiriboga et al 2016). The highest possible increase is currently assumed to be at maximum a 200% SMN

protein increase, based on animal and in vitro cell culture data with SMA patient fibroblasts and motor neurons (see Risdiplam Investigator's Brochure). Based on current predictions, this target may be reached at an exposure not exceeding the exposure cap of 2000 ng • h/mL $AUC_{0\text{-}24h,ss}$. Under no circumstances a dose will be selected that leads to an exposure above a mean $AUC_{0\text{-}24h,ss}$ of 2000 ng • h/mL or a mean C_{max} of 400 ng/mL.

Based on PBPK modelling using available data in healthy subjects and taking into account the tissue distribution and different body weight and body composition in SMA patients compared to healthy subjects, an oral dose of 3 mg once daily was selected for Dose Level 1 and will be administered to Group A (patients aged 12-25 years at age of randomization) who will be initially enrolled into this study. The dose of 3 mg is predicted to result in an $AUC_{0\text{-}24h,ss}$ of 700 ng • h/mL in SMA patients aged 12-25 years, which is approximately 3-fold (2.8) below the specified exposure cap and is anticipated to result in the targeted 2-fold SMN protein increase. This dose and exposure is anticipated to be safe and well-tolerated based on the SAD data obtained in healthy subjects (single-dose administration of up to 18 mg) and the animal toxicology studies.

As described in Section 3.1.1, once 3 adolescent patients (aged 12-17 years at age of randomization) complete 4 weeks of treatment with 3 mg risdiplam, all safety, PK and PD data will be assessed. If safety and tolerability, PK and PD, are judged to be acceptable, Group B (children aged 2-11 years at age of randomization) will be enrolled. The PK data obtained from Group A will be used to update the PBPK model to select a dose for the younger children in Group B. This dose for the Group B will likely be a body weight-based dosing regimen, and the aim is to achieve the same exposure as observed for Group A with the 3 mg dose.

In line with this dose-selection approach primarily based on SMN protein increase and pharmacokinetic steady state achievement, and based on preclinical data not showing new toxicities (beside retinal findings) beyond a few weeks of treatment (see Section 1.2.1.3), 4-weeks of treatment appears sufficient to assess acute safety and tolerability of the respective dose levels and make dose decisions (dose escalation in Part 1 and selection of Part 2 dose based on Part 1 data). Considering the study design and pace of enrollment, at these decision points patients enrolled first will have longer treatment durations. All information (including ophthalmological examination and OCT retinal monitoring) available at cut-off time, and not limited to 4 weeks after first dose, will be included for the dose escalation review meeting.

Patients in the age-range included in this study are expected to have a similar free-fraction of the study drug as adult individuals. However, to ensure patients' safety, for all patients in Part 1, a blood sample will be taken at screening to assess in vitro the plasma protein binding and free-fraction of the study drug to confirm this assumption. The obtained measured free-fraction will be taken into account for the dose-selection in the individual patients, i.e., in case it deviates from the values in adult patients, the dose

may be adjusted to target the selected exposure in terms of the free-fraction exposure of older patients.

As described in Section 3.1.1, the second dose-level and corresponding oral daily dose for Group A (12-25 years old at age of randomization) and Group B (2-11 years old at age of randomization) will be determined by the IMC after review of data from patients enrolled in the first dose-level cohort, respectively and independently for Group A and Group B patients.

The dose for Part 2 will be selected by the IMC based on the results obtained from Part 1, and will be a dose that:

- Is judged to be safe and well-tolerated, based on all available safety data from Part 1 and as confirmed by the iDMC.
- Results in an exposure at steady-state below the exposure cap (mean value) of $AUC_{0\text{-}24h,ss}$ 2000 ng • h/mL (adjusted for free-fraction, if required). To account for changes in PK in different age-groups, a different dose is likely to be selected for the various age-groups. The dose will be likely a body weight-adjusted dose, but other criteria, e.g., BSA or age, may be used, depending on the results of the analysis of the PK data obtained in Part 1.
- Results in an SMN protein increase that is expected to be clinically relevant.

  Overall the approach is to target the highest SMN protein increase that can be achieved with risdiplam; however, the shape of the PK/PD curve will be taken into account to determine the most appropriate target exposure (and therefore, dose), considering safety and tolerability data across exposure levels in Part 1 and the above-mentioned exposure cap threshold. Clinical judgment will prevail.

Based on the criteria listed above, a dosing regimen of 5 mg for patients with a BW ≥20 kg and 0.25 mg/kg for patients with a BW <20 kg was selected for Part 2 of this study. This dose is expected to lead to a mean exposure ($AUC_{0\text{-}24h,ss}$) of 1690 ng•h/mL [95% CI 1600–1780 ng•h/mL] across all patients 2–25 years of age, and is not expected to exceed the exposure cap for any age or body weight category.

The data summary from Part 1 supporting the dose selection for Part 2 can be found in Section 1.2.2.

3.2.2 Rationale for Study Population

This study has been designed to assess the safety, tolerability, PK, PD and efficacy of risdiplam in patients with SMA and will include patients with Type 2 and Type 3 SMA, aged 2-25 years. A separate study in infants with Type 1 SMA (BP39056) is being conducted in parallel.

The patient population to be included in Parts 1 and 2 of the study was determined in line with the respective objectives of these two parts:

- In Part 1 (first in patient evaluation of risdiplam), the objective is to study safety and tolerability across the Type 2 and Type 3 SMA patient population, which is also expected to be associated with various co-morbidities. Beside safety and tolerability, part of the primary objective of this dose-finding part is to study the multiple-dose PK and PD effects of risdiplam in terms of increase in full-length SMN2 mRNA and SMN protein in order to select a dose for the confirmatory Part 2 of this study. Accordingly, Part 1 of the study will include Type 2 and 3 (ambulant and non-ambulant) SMA patients aged 2–25 years.
- In Part 2, the objective is to investigate clinical efficacy of risdiplam in a more homogeneous patient population, which is expected to minimize variability in expected changes in motor function over time and thereby, increase the chance to be able to detect a treatment effect, enabling a conclusion to be made of the putative efficacy of risdiplam. Accordingly, Part 2 of the study will only include Type 2 and non-ambulant Type 3 SMA patients aged 2-25 years.

3.2.3 Rationale for Control Group

One drug was recently approved in the US, European Union, Canada and other jurisdictions for the treatment of SMA in pediatric and adult patients (the antisense oligonucleotide nusinersen [SPINRAZA®]) but the medical need in SMA is still very high. There is currently no oral treatment for SMA that provides stabilization or improvement of motor function.

Use of a placebo control is necessary for a robust assessment of the safety, tolerability, and efficacy of risdiplam, especially given the variability of disease status and disease progression across patients.

In order to limit the length of time that patients will possibly receive placebo, all patients enrolled in this study will be switched to active treatment as soon as possible according to the design of each part of the study i.e., i) once safety, tolerability, PK and PD are available for each dose-level and age-group in Part 1, and ii) after 12 months of treatment in Part 2.

Most symptomatic medications (e.g., salbutamol) that may be part of the standard of care treatment of patients with SMA are allowed as concomitant medications in this study (Section 4.2.3 and 4.5).

3.2.4 Rationale for Biomarker Assessments

SMA is a heterogeneous disease presenting a spectrum of motor dysfunction (from not being able to sit up to not being able to walk) and variability in disease onset (from birth to the third decade of life). Due to the variability in SMA phenotypes, careful

consideration is required when enrolling patients, when following the progression of the disease and measuring the response to study drug treatment.

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

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

The following blood samples will be collected according to the SoA and Detailed tables (see Appendix 2 and Appendix 4) for biomarker analyses:

- Clinical genotyping (Section 4.6.1.16).
- Blood samples for mandatory exploratory biomarker analyses (e.g., related to SMA disease and/or to treatment response).
- Upon optional consent, samples for Research Biosample Repository (RBR) as described in Section 4.6.1.24.

In addition, and as described in Section 4.6.1.15, the following blood samples will be collected according to the SoA, in order to assess the PD effects of risdiplam as an SMN2 splicing modifier:

- In vivo splicing modification of SMN2 mRNA in blood.
- SMN protein levels in blood.

3.3 OUTCOME MEASURES

3.3.1 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Incidence and severity of adverse events.
- 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
- 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 assessments as appropriate for age (Appendix 5 and Appendix 6). See section 4.6.1.11 for details.*
- Tanner staging for pubertal status *as appropriate for age* (see Section 4.6.1.6 for details).

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

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

3.3.2.1 Pharmacokinetic Outcome Measures

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

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

3.3.2.2 Pharmacodynamic Outcome Measures

The PD outcome measures for this study are as follows:

- *SMN2* mRNA in blood: Blood samples will be collected at the times specified in the SoA and detailed tables (see Appendix 2 and Appendix 4), to isolate mRNA and measure the relative amount of *SMN* mRNA and its splice forms. Housekeeping genes for the quantitative analysis of RNA will also be measured.
- SMN protein levels in blood.

3.3.3 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 4.0 Generic Core scale (Part 1 only)
- PedsQL 3.0 Neuromuscular module (Part 1 only)

3.3.4 Outcome Measures for Economic Analyses

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

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

3.3.5 Other Outcome Measures

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]; Section 4.6.1.20).

4. MATERIALS AND METHODS

4.1 CENTER

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

Administrative and Contact Information, and List of Investigators are provided separately.

4.2 STUDY POPULATION

This study will include both male and female patients with Type 2 and Type 3 SMA. Part 1 will include ambulant and non-ambulant patients aged 2 to 25 years. Part 2 will enroll non-ambulant patients aged 2 to 25 years.

Patients must meet all of the inclusion criteria and none of the exclusion criteria in order to qualify for the study. Unless otherwise stated, inclusion and exclusion criteria refer to screening.

4.2.1 Recruitment Procedures

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

4.2.2 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:
   a. Genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the *SMN1* gene.
   b. Clinical symptoms attributable to Type 2 or Type 3 SMA.
4. For non-ambulant patients in Part 2 (at screening):
   a. Revised upper limb module (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").
   b. Ability to sit independently (i.e., scores ≥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:

   For women 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.

– 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.

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

  With 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.

  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 post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.2.3 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 (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.

4.3 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be performed using an Interactive (voice/web) Response System (IxRS). Separate randomization lists will be generated for the exploratory dose-finding Part 1 and the confirmatory Part 2 of the study. In the exploratory Part 1 of the study, patients will be randomized to risdiplam or placebo in a 2:1 ratio for each cohort. In the confirmatory Part 2 of the study, patients will be randomized to the selected dose of

risdiplam from Part 1 or placebo in a 2:1 ratio. The randomization in Part 2 will be stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years at randomization) as further described below.

The patient number will be allocated by IxRS and will be used in the clinical database and to record data in the electronic case report form (eCRF). Sites should call the IxRS to enter the subject 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.

Part 1 – Exploratory Dose-Finding

In Part 1 of the study the patients and the investigators will be blinded to the treatment assignment within each cohort until the IMC decides to close the placebo controlled period of that cohort and begin the risdiplam open-label treatment. All individuals in direct contact with the patient at the investigative site will be blinded until this point, except for the Pharmacist handling the study drug.

For the exploratory Part 1 of this study, the Sponsor will be unblinded (in a restricted manner as described below) to the treatment assignment of the patients to enable the Internal Monitoring Committee to review the data in order to make dose-escalation decisions and to determine the dose for Part 2 of the study. With the exceptions described below and in the IMC Charter, the Part 1 randomization list for each cohort of patients in the exploratory Part 1 will not be available to other members of the project team or the study management team at Roche until the IMC decides to close the placebo controlled period of that cohort and begin the risdiplam open-label treatment. Access to potentially unblinding data (i.e., PK and PD data) generated during Part 1 will be restricted as described below.

The Part 1 randomization list will be made available to the individuals responsible for PK sample bioanalysis and the IMC analysis. The IMC members (Statistician, Statistical Programmer, Translational Medicine Leader, Clinical Pharmacologist, and Safety Science Leader) at Roche will review unblinded aggregated data displays (and also unblinded individual patient listings if needed). Unblinded Part 1 data (individual as well as at group level) will be shared between the IMC and the iDMC and with other experts or decision-making bodies of the Sponsor if deemed necessary by the IMC chair.

PK/PD and safety data during Part 1 and its OLE can be received and cleaned on an ongoing basis by the Data Acquisition Specialist. In addition, the Pharmacometrician / Clinical Pharmacology Scientist who assesses the PK data and works on the PBPK model will be unblinded to the treatment assignment of the Part 1 patients in order to analyze the PK data and refine the PBPK model (on an ongoing basis by integrating emerging data generated during the exploratory Part 1) and thereby, make recommendations on the appropriate dose(s) to use throughout the study. If presentation

of analyses generated by the Pharmacometrician / Clinical Pharmacology Scientist to the project team is warranted for decision making during the study, data will only be presented cumulatively and without any patient identifiers, to prevent unblinding of any given individual treatment assignment.

Part 2 - Confirmatory

Part 1 patients will not be included in the confirmatory analysis and new patients will be randomized into Part 2 of this study.

In Part 2 of the study the study patients and the investigators will be blinded to the initial treatment assignment until the last patient in Part 2 has completed the 24-month assessments. All individuals in direct contact with the patient at the investigative site will be blinded until this point, except for the unblinded- Pharmacist handling the study drug.

In Part 2, the 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.

For this part of the study, the Sponsor will remain blinded to the treatment assignment information of the patients randomized until the last patient randomized into Part 2 has completed their 12-month assessment (or has been withdrawn early) and the database has been locked for the purpose of the primary and secondary efficacy analyses. During Part 2, the randomization list will be transferred directly from the IxRS vendor to the independent Data Co-ordinating Centre (iDCC) in order to allow the generation of unblinded outputs for review by the iDMC. Sponsor personnel responsible for performing PK assays will be unblinded to patients' treatment assignments in Part 2 of this study to identify the appropriate PK samples to be analyzed. Prior to unblinding, the PK concentration data will not be made available to the study team (but will be reviewed by the iDMC), and *SMN2* mRNA and SMN protein level results will be blinded.

If unblinding is necessary for patient management (e.g., in the case of a serious adverse event), the Investigator will be able to break the treatment code by contacting the Interactive (voice/web) Response System (IxRS). Treatment codes should not be broken except in emergency situations. If the Investigator wishes to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The Investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event), and the patient will be discontinued from the study.

As per Health Authority reporting requirements, the Sponsor will break the treatment code for all unexpected serious adverse events (SAE; see Section 5.1) that are considered by the Investigator to be related to study drug.

Whenever disclosure of the identity of the test medication is necessary, adequate procedures will be in place to ensure integrity of the data. Any unblinding at the investigating site will be documented in the study report with date, reason for identifying the drug, and the name of all the person(s) who had to be unblinded.

4.4 STUDY TREATMENT

4.4.1 Formulation, Packaging, and Handling

4.4.1.1 Part 1 Formulation – Risdiplam and Placebo (Powder and solvent for oral solution, 20 mg and 120 mg)

Risdiplam clinical formulation for Part 1 is a powder and solvent for constitution to an oral solution. Risdiplam drug product is composed of two bottles; one containing 20 mg or 120 mg of risdiplam substance (no excipients) and another with excipients blend (powder for solvent for reconstitution). The excipient blend bottle is constituted with water for injection and entirely transferred to the drug substance bottle to yield an oral solution containing of 0.25 mg/mL and 1.5 mg/mL of risdiplam.

[redacted]. All excipients selected for the powder for oral solution formulation comply with pharmacopeia requirements (United States Pharmacopeia–National Formulary [USP/NF] and/or the European Pharmacopoeia [Ph. Eur] and EU Food regulation). Matching-placebo oral solutions for the 0.25 mg and 1.5 mg/mL risdiplam drug products will be prepared [redacted] (to match the color of the drug substance), and the same excipients as for the study drug [redacted] but containing no active drug substance.

4.4.1.2 Part 2 Formulation – Risdiplam and Placebo (Powder for oral solution, 20 mg and 60 mg)

Risdiplam clinical formulation for Part 2 is a powder for constitution to an oral solution. Each bottle contains 20 mg or 60 mg of risdiplam substance with excipients. 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.

The excipients used in the Part 2 clinical formulation are the same as for Part 1 formulation (powder and solvent for oral solution), [redacted] added as diluent.

Matching placebo oral solutions for the 0.25 mg and 0.75 mg/mL Part 2 risdiplam drug products will be prepared using [redacted] (to match the color of the drug substance), and the same excipients as for the study drug [redacted] but containing no active drug substance.

Patients from Part 1 transferred to OLE shall continue to use the Part 1 risdiplam clinical formulation until switch to the Part 2 risdiplam clinical formulation upon availability of the

new formulation. Patients in Part 2 of the study will receive the Part 2 formulation throughout their participation in the study.

4.4.1.3 Packaging and Handling

The constitution of the study medication will be carried out at the clinical study site authorized pharmacy by unblinded qualified pharmaceutical personnel. Further detailed instructions for the constitution procedure will be provided in a separate pharmacy manual. After constitution, the pharmaceutical personnel will insert a press-in-bottle-adapter into the bottle neck and close with a child-resistant closure. The bottle adapter allows insertion of oral/enteral dispensers into the bottle for withdrawal of the constituted solution. The bottle that contains the oral solution will be inserted into a labeled carton provided by Roche Clinical Trials Supplies department. The clinical study site will provide oral/enteral dispensers to the patient/caregiver to administer the solution. A manual will be provided to the patient/caregiver with instructions on study drug administration at home.

For each patient and for all occasions of dispensation of study drug, it shall be recorded by the Pharmacist or personnel under their supervision which formulation strength a patient received.

Study drug packaging will be overseen by the Roche Clinical Trial Supplies department and will bear a label with the identification required by local law, the protocol number, drug identification and dosage. The packaging and labelling of the study medication will be in accordance with Roche standard and local regulations. The qualified individual responsible for dispensing the study drug will prepare the correct drug product according to the randomization schedule and to the individual specific dose allocated to an individual patient.

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

For further details, see the Risdiplam Investigator's Brochure and BP39055 Pharmacy Manual.

4.4.2 Dosage, Administration, and Compliance

4.4.2.1 Risdiplam and Placebo

The qualified individual responsible for dispensing the study drug will prepare the correct dose according to the randomization schedule. This individual will write the date dispensed and patient number and initials on the study drug vial label and on the Drug Accountability Record. This individual will also record the MEDNO/ study drug batch

number received by each patient during the study. Throughout the study, 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 (see Appendix 1). On these days, patients should have their regular morning meal at home before coming to the site; should there be a long time between this meal and arrival at the site, a snack will be given by the site to the patient prior to study medication administration. The first dose of study medication will be administered at the clinical site on Day 1 after all pre-dose assessments have been conducted. Study participants receiving the study medication orally should always follow this by rinsing their mouth with water and swallowing. Study participants unable to swallow the study medication and who have a naso-gastric or gastrostomy tube in situ should receive the study medication by bolus via the tube. This should always be followed by a bolus flush of water through the tube. The study medication should be administered only with the supplied colored dispensers. A patient diary will be required that will capture information related to drug administration for all doses throughout the study.

If a patient, or parent/caregiver, does not administer the dose at the regular time, but realizes prior to 12:00 (noon) local time, they will be instructed to administer the regular dose at that time. If a parent or caregiver realizes a missed administration only after 12:00 (noon) local time, this will be considered a missed dose and they will be instructed to not administer study drug for that day. They should give the regular amount at the next scheduled time on the subsequent day, but not double-up the dose, and report the event in the medication diary.

Guidelines for dosage modification and treatment interruption or discontinuation are provided in Section 4.7.1.1.

4.4.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study, i.e., risdiplam or placebo, will be provided by the Sponsor. The investigational site will acknowledge receipt of IMPs, to confirm the shipment condition and content. Any damaged shipments will be replaced.

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

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

- The date(s) and quantity of the study drug returned by the patient.
- All records and drug supplies must be available for inspection by the Monitor at every monitoring visit.

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

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

Written documentation of destruction must contain the following:

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

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

4.4.4 Post-Trial Access to Risdiplam

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

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

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

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

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

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

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

4.5 CONCOMITANT THERAPY AND FOOD

4.5.1 Permitted Therapy

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

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

All concomitant therapy should be reported to the Investigator and recorded in the eCRF. Concomitant medication should be recorded on the “previous and concomitant treatment” form while physical therapy and exercise should be recorded on the “exercise or physical therapies Programs” form; if there are changes made to the type of exercise therapy during the study, these changes should be recorded on this form. Other types of non-medication interventions should be recorded on the “additional observations” eCRF form.

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

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

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

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

Examples of allowed medications include the following unless prohibited in Section 4.5.2:

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

4.5.2 Prohibited Therapy

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

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.

The following medications are explicitly prohibited for 2 weeks prior to dosing and throughout the study:

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

Any inhibitor or inducer of FMO1 or FMO3.

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

Medications intended for the treatment of SMA

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

Medications with known retinal toxicity liabilities

- Amiodarone, phenothiazines, and chronic use of minocycline.

Patients should not have received the following drugs previously and are prohibited during the study:

- Quinolines (chloroquine and hydroxychloroquine), thioridazine, retigabin and vigabatrin.

Use of the following therapies is prohibited during the study and for at least 1 year prior to randomization:

- 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.

4.6 STUDY ASSESSMENTS

4.6.1 Description of Study Assessments

All examinations listed below will be performed according to the Schedule of Assessments outlined in Appendix 1 to Appendix 4.

Prioritization of blood samples is described in Section 4.6.2.

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

Monthly pregnancy tests are planned in this study for women of childbearing potential. On months without a site visit, the pregnancy test may be conducted at home either by the patient or by a health care provider (see SoA, Appendix 1 and Appendix 3). Drug dispensation, return of *used and* unused *study* drug *bottles* and supplies will occur at scheduled site visits, ad hoc re-supply site visits, or delivery to the patient's home if necessary. If considered necessary by the Investigator *and delegated by him/her*, a qualified health care provider may also visit the patient's home to obtain a blood sample, (e.g., if a safety laboratory sample is required), *to collect vital signs, any new concomitant medication and any new AE or other information as appropriate.*

The exact timing of all study assessments (e.g., PK or PD blood sampling) may be shifted depending on emergent data, but the total number of assessments will not change.

4.6.1.1 Medical History and Demographic Data

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

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

4.6.1.2 Spinal Muscular Atrophy History

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

- SMA type
- Age of onset
- *SMN2* copy number (if available; it will be measured in any case during this study by clinical genotyping).

- Previous score on functional motor scale (e.g.,MFM, ULM/RULM, HFMSE), and/or disability scale (e.g., Brooke, Vignos).
- Current level of function and highest motor function achieved (i.e., sitting without support, rolling, crawling, standing, walking).
- Previous hospitalizations related to SMA.
- History of pulmonary infections/events (if applicable).
- History of scoliosis or hip surgery (if applicable).

4.6.1.3 Weight, Height and Head Circumference

Body weight (using calibrated scales), height and head circumference (in children below 5 years) will be measured at the time-points specified in the SoA as described below:

In patients aged 2-11 years, body weight will be measured to the nearest 100 g. In patients aged 12-25 years, body weight will be measured to the nearest kilogram.

- For wheelchair-bound patients, weight of the patient and the wheelchair will be obtained with a wheelchair balance scale with the patient in the wheelchair. Then, the wheelchair will be weighed by itself and subtracted from the total weight. For lighter patients, the caregiver may carry the patient and their combined weight measured, followed by the caregiver being weighed and subtracted from the total weight.
- Patients able to stand will be weighed directly on a standard scale.

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

- For all patients who are able to stand, height will be measured while standing using a stadiometer, with at least 3 independent measurements which will be averaged.
- For patients unable to stand for the duration of the measurement or, e.g., have too many contractures, height will be derived from the measurement of ulnar length.
- Ulnar length (from the tip of the olecranon process to that of the styloid process) will be measured using an anthropometer with the patient in sitting position, the left forearm resting comfortably on a table, elbow bent 90° to 110°, palm facing downwards and fingers extended but together.

For very young children, height will be measured with the child in lying position using an inflexible length board with fixed headboard and moveable footboard.

BMI will be derived. See the SoA tables for time-points (see Appendix 1 and Appendix 3).

Head circumference will be measured in children below the age of 5 years to the nearest 0.1 cm using a flexible, non-stretchable tape. The head circumference (or occipital-frontal circumference, OFC) is measured around the widest part of the head from the most prominent point on the back of the head (occiput) to the most prominent part of the forehead between the eyebrows. The measuring tape should remain above

the ears and fully compress any hair (hair ornaments should be removed and large plaits or braids loosened). The measurement should be taken to the nearest millimeter and repeated three times with the largest measurement being recorded.

4.6.1.4 Physical Examinations

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

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

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

4.6.1.5 Neurological Examination

A detailed neurological examination focusing on mental status, behavioral and cognitive assessments will be performed in all patients at the time points specified in the SoA.

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.

4.6.1.6 Tanner Staging

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 (see Appendix 1 and Appendix 3). Once a patient reaches stage 5, Tanner staging no longer needs to be performed.

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

4.6.1.7 Menstrual Status

For female patients, menstrual status during the study will be collected as appropriate. Once menstruation is confirmed, the patient must undergo pregnancy testing as outlined in the SoA tables (Appendix 1 and Appendix 3).

4.6.1.8 Vital Signs

Blood pressure (BP), pulse rate, respiratory rate and body temperature (oral or tympanic) will be recorded at the time-points specified in the SoA tables.

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

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

In pediatric patients (aged 17 years and below), at screening and at every blood pressure assessment throughout the study, SBP and DBP percentiles for age should be determined using the Centers for Disease Control and Prevention (CDC) tables, which require to first determine patient’s percentile for stature using the CDC growth charts.

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

4.6.1.9 Electrocardiograms

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

To minimize variability, it is important that patients be in a resting position for ≥10 minutes prior to each ECG evaluation. Body position should be consistently maintained for each ECG evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording. ECGs should be performed prior to any scheduled vital sign measurements and blood draws. If ECGs are performed after vital sign measurements and blood draws, the patient should be provided with enough time to rest in order to minimize variability. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.

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

ECG characteristics, including heart rate, QRS duration, and PR, and QT intervals, will be recorded on the eCRF. QTcB (Bazett's correction; Phan et al 2015), QTcF (Fridericia's correction) and RR will be calculated by the Sponsor/recorded on the eCRF. Both corrections of QTc will be tabulated and analyzed; although, in children, Bazett's formula appears to provide a better correction of the QT interval. Changes in T-wave and U-wave morphology and overall ECG interpretation will be documented on the eCRF, additionally as an AE as appropriate. T-wave information will be captured as normal or abnormal, U-wave information will be captured in two categories: absent/normal or abnormal. A subset of patients at selected sites may undergo more extensive ECG recordings as per the SoA. Selected sites will be those that are capable and willing to participate.

4.6.1.10 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to the Sponsor before the study starts. Laboratory safety tests shall be collected at time-points specified in the SoA tables (Appendix 1 and Appendix 3).

At any time and as described in Section 4.6.2, safety laboratory samples will be given priority over any other sample, such that the volume of blood taken at any single time-point will not exceed 1 mL/kg, and the volume collected over any 8-week period throughout the study will not exceed 4 mL/kg.

Additional blood or urine samples may be taken at the discretion of the Investigator if the results of any test fall outside the reference ranges, or clinical symptoms necessitate additional testing to monitor patient's safety. Where the clinical significance of abnormal laboratory results is considered uncertain, screening laboratory tests may be repeated before randomization to confirm eligibility. If there is an alternative explanation for a positive urine test for drugs of abuse, e.g., previous occasional intake of a medication or food containing for example codeine, benzodiazepines or opiates, the test could be repeated to confirm washout.

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

Samples for the following blood and urine laboratory tests will be collected as specified in the SoA tables and sent to the laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

- Hematology: Hemoglobin, hematocrit, erythrocytes (RBC), platelets, leukocytes (WBC), differentials (counts): neutrophils, eosinophils, lymphocytes, monocytes, basophils, reticulocyte count.
- Coagulation: prothrombin time (INR) and activated thromboplastin time (aPTT).
- Blood chemistry: Aspartate aminotransferase (AST), alanine aminotransferase (ALT), total and conjugated bilirubin, alkaline phosphatase (ALP), gamma-glutamyl-transferase (γ-GT), creatine phosphokinase (CPK), albumin, creatinine, urea nitrogen, total protein, sodium, chloride, calcium, bicarbonate, phosphate, potassium, triglycerides, total cholesterol, glucose, C-reactive protein (CRP).
- Thyroid hormones (free T4 and TSH; at the time of blood chemistry sampling at selected time-points, Appendix 1 and Appendix 3).
- Hormone: estradiol, follicle-stimulating hormone, luteinizing hormone in female patients 12−25 years or younger subjects who have menses.
- Pregnancy test

  All women of childbearing potential (including those who have had a tubal ligation) will have blood or urine pregnancy tests at the timepoints specified in the SoA tables. If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination, if clinically significant positive results from the dipstick (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).
- Drugs of abuse will be measured in urine (patients aged 12 to 25 years): cannabinoids, amphetamines, methamphetamines, opiates, methadone, cocaine, benzodiazepines, phencyclidine, tricyclic antidepressants, and barbiturates.
- Alcohol will be measured in urine (patients aged 12 to 25 years).

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

4.6.1.11 Ophthalmological Assessments and Examination

Ophthalmological examination will be performed at time-points specified in the SoA (Appendix 5 and Appendix 6). The details of the visual tests will be included in a separate technical operating manual. An ophthalmologist or other similarly trained person will perform the ophthalmological examination in all patients.

Central Reading

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

For Adults and Children Age ≥10 Years of Age at Screening

Ophthalmological examination(s) include slit lamp examination for assessment of the anterior and posterior segment including the cornea, anterior chamber, lens and the fundus (indirect ophthalmoscopy with e.g., 60 and 90 diopter lenses to examine the macula, optic nerve, mid- and peripheral areas). During selected visits (Appendix 5 and Appendix 6), the intraocular pressure will be measured using standard techniques such as Goldmann tonometry or non-contact tonometry. The method of assessment must remain constant for each patient throughout the study.

Fundus Photography

Seven-field or wide-field FP will be performed at the study sites by trained and Central Reading Center-certified personnel. Where both 7-field and wide-field devices are available, wide-field FP should be performed. It is mandatory that the same device is used for the entire duration of the study. In Part 2, after a first unsuccessful attempt, an image of the fundus may be captured during funduscopy.

Visual Acuity Tests

- Best corrected visual acuity (BCVA)

Best corrected visual acuity (BCVA) will be measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) or equivalent charts at a distance of 4 meters. The eye chart has a series of letters, with the largest at the top. As the person being tested reads down the chart, the letters gradually become smaller. The chart will be standing, at 4 meters from the patient's eyes. These sheets will be considered source data and scores from these sheets will be transcribed on the eCRF.

- Low contrast visual acuity (Sloan; Part 1 only excluding open-label extension).

Low contrast visual acuity assessment will be performed with the Sloan Letters Low Contrast Chart, which measures both low contrast and visual acuity.

Visual Field Test - Automated Static Threshold Perimetry

Visual fields will be measured using automated perimetry (e.g., Humphrey Field Test Analyzer) with the 24-2 SITA fast program. Each visual field will be assessed centrally. In case of any clinically relevant abnormality, the patient should be further examined by an ophthalmological specialist. Visual field data will be printed out and stored. In Part 2,

after a first unsuccessful attempt, threshold perimetry may be replaced by simple visual field testing such as easier perimetry protocols or as last resort confrontation visual field testing if perimetry is not possible.

Imaging of the Retina (SD-OCT and FAF)

Imaging of the retina will include Spectral Domain-Optical Coherence Tomography (SD-OCT) and Fundus Auto-Fluorescence (FAF; Part 1 only).

SD-OCT: Spectral Domain Optical coherence tomography provides both qualitative (morphology and reflectivity) and quantitative (thickness, mapping and volume) analyses of the examined tissues in real time. Each SD-OCT will be graded as normal, or abnormal. If abnormal, the character of the abnormality will be noted (e.g., changes in retinal thickness, edema, cystoid or atrophic changes, detection of fluid within the retinal layers, macular holes, vitreo-macular traction) and the degree of abnormality. In Part 2, every attempt should be made to capture additional images after up, down, left, and right gaze.

FAF (Part 1 only excluding open-label extension): Fundus Auto fluorescence is a technique that has been shown to be rather sensitive for pigmentary retinopathies and other conditions of the outer retina plus some forms of macular degeneration.

Additional ophthalmic assessments of the retina might be carried out in case of abnormalities or upon recommendation from the site or central Ophthalmologist, including e.g., MultiColor Imaging (MultiColor provides topographic maps of the outer, mid and inner retinal layers plus a composite image), dark adaptation, electro-retinography (measures electrical activity generated by the photoreceptor cells in the retina; ERG will use ISCEV standard) or other specific assessments.

Dark Adaptation (exploratory): based on preclinical toxicology findings including ERG results and effects on rods cells, dark adaptation difficulties might occur early in case of retinal abnormalities and be more sensitive than a global visual acuity test. Recently, dark adaptation testing has improved using a fast protocol and user-friendly device (e.g., AdaptDX;Maculogix) providing standardized methodology.

For Children Age <10 Years of Age

Examinations will be carried out by an experienced pediatric ophthalmology specialist, a pediatric ophthalmologist or neuro-ophthalmologist. Ophthalmic examinations are: Bruckner Test, red reflex, fix and follow test, cover-uncover test, simple visual field test, intra ocular pressure (tonometry or digital palpation of globes), visual acuity (adapted based on age and neurological development), retinal examination (dilated or not) including slit lamp examination/ophthalmoscopy (including anterior and posterior segment, fundus, optic nerve), imaging (SD-OCT; including up, down, left, and right gaze images whenever possible in Part 2 and in open-label extension in Part 1), fundus photography (in Part 2 *and Part 1 according to the SoA*, after a first unsuccessful

attempt, an image of the fundus may be captured during funduscopy) and whenever feasible, FAF (Part 1 only excluding open-label extension). Additional ophthalmic assessments such as dark adaptation threshold testing, electro-retinography might be carried out as needed in case of abnormalities or upon recommendation from the site or central Ophthalmologist.

4.6.1.12 Nutritional Check

Nutritional assessment will be performed for all patients at the time points indicated in the SoA (Appendix 1 and Appendix 3) and will include:

- Determination of BMI, from body weight and height (Section 4.6.1.3).
- Nutritional status interview of the patient or caregiver (as appropriate), including questions about ability to swallow and level of solid food intake.

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

4.6.1.13 Plasma Protein Binding

A blood sample will be collected at screening from all patients in Part 1 in order to measure plasma protein binding, and to measure the free-fraction of the study drug (Section 3.2.1). Results for a patient must be available and checked by the Sponsor before any study drug is administered to this specific patient.

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

4.6.1.14 Pharmacokinetic Assessments

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

Plasma concentrations of risdiplam will be measured by a specific validated LC-MS/MS assay. Metabolites may be measured by a specific validated LC-MS/MS assay, or other methods as appropriate, and PK samples may also be used for exploratory metabolite identification.

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

4.6.1.15 Fluid Pharmacodynamic Assessments

The following fluid PD assessments will be performed as detailed in the SoA and Detailed tables (see Appendix 2 and Appendix 4).

However, should the total blood volume to be collected at any time-point according to this Schedule of Assessments exceed 1 mL/kg, or the volume collected over any 8-week

period throughout the study exceeds 4 mL/kg, the blood sample prioritization described in Section 4.6.2 should be followed.

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

Whole blood samples will be taken from every patient at the timepoints specified in the SoA (Appendix 2 and Appendix 4) to measure in vivo splicing modification of *SMN1*, *SMN2* FL, and SMNΔ7 mRNA during the course of the study. In addition, housekeeping genes for the quantitative analysis of RNA will be measured. Additional mRNA may be used for exploratory analysis/assay development related to SMA, including, but not limited to, pathways related to SMN function and treatment response.

- SMN protein levels

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

- Mandatory exploratory biomarkers assessing treatment response (adults and adolescents only)

Serum for the analysis of exploratory biomarkers related to SMA or to the response from treatment (e.g., muscle damage or IGF system) will be collected from every adult and adolescent patient.

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

These samples will be destroyed no later than 5 years after the date of the final clinical study report and may be used for additional exploratory analysis/assay development related to SMA including, but not limited to, pathways related to SMN function or treatment response. For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.6.1.16 Clinical Genotyping Sample

A single mandatory whole blood sample will be taken for DNA extraction from every patient, at the timepoint indicated in the SoA (Appendix 1 and Appendix 3). The DNA will be used to determine the copy number of *SMN2* and to confirm the *SMN1* mutation or deletion. The clinical genotyping samples may be used for additional exploratory analysis/assay development related to SMA including, but not limited to, mitochondrial DNA and genes related to SMN function, severity of the disease or treatment response. These samples will be destroyed no later than 5 years after the date of the final clinical study report. Data arising from clinical genotyping will be subject to the confidentiality standards described in Section 8.4. For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.6.1.17 Functional Motor Assessments

Functional motor assessments will be performed as detailed in the SoA (Appendix 1 and Appendix 3). The MFM, RULM, and Hammersmith will be video recorded for quality control purposes as indicated in the Training and Quality assurance methodology manual. The videos may also be used for training purposes, if consent is provided in the Informed Consent Form. These recordings will not be part of the clinical database. *These videos may be anonymized and* accessible by the Sponsor *and health authorities.*

Motor Function Measure

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

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

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

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

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

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

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

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

The full MFM-32 will be administered to all patients (across age groups). The scale will be administered by a trained Physiotherapist or other suitably qualified professional who

has received training on the administration of the MFM, following the instructions in the MFM users' manual. If possible, the same assessor should follow the patient throughout the study. Scores will be recorded on the scoring sheet and on the eCRF and maximal score will be derived.

Revised Upper Limb Module

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

The first entry item, used to determine study eligibility (Section 4.2.2) is scored from 0 (no useful function of hands) to 6 (can adduct both arms simultaneously in a full circle until they touch above the head). This item serves as a functional class identification but does not contribute to the total score.

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

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

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

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

The Hammersmith Functional Motor Scale Expanded

The Hammersmith Functional Motor Scale Expanded (HFMSE) was developed to assess the motor function ability of individuals aged two years or older, with Type 2 and 3 SMA (O'Hagen et al 2007). The scale contains 33 items, which are scored on a 3-point Likert scale (0–2) and summed to derive the total score, with lower scores indicating greater impairment. Similar to the MFM, the HFMSE contains a series of assessments designed to assess important functional abilities, including standing, transfers, ambulation, and proximal and axial function. The original Hammersmith Functional Motor Scale (HFMS) contained 20 items and was developed primarily to assess a SMA Type 2 population. Thirteen items, adapted from the Gross Motor Function Measure (GMFM), were added to improve the sensitivity of the scale,

particularly for measuring motor function ability in Type 3 SMA patients. The HFMS and HFMSE have been used in previous and ongoing clinical trials for SMA, including as a primary endpoint (ClinicalTrials.gov Identifiers NCT02292537, NCT01302600; Chiriboga et al 2016).

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

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

4.6.1.18 Pulmonary Function Testing

Pulmonary testing will be performed as detailed in the SoA (Appendix 1 and Appendix 3).

Spirometry

Patients aged 6-25 years, hand-held spirometry will be performed using the TransAir-M ([redacted]) according to the manual of operations. The test will be performed a minimum of three times while the patient is in a sitting position.

The age at randomization will determine if spirometry is to be completed by the patient during the study. If the patient will become 6 years of age during the 30 day screening period, i.e., will turn 6 years of age within 30 days of screening, the patient should have spirometry performed during the screening visit.

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

- FVC
- FEV1
- PCF

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

Sniff Nasal Inspiratory Pressure, Maximal Inspiratory Pressure and Maximal Expiratory Pressure

The Sniff Nasal Inspiratory Pressure (SNIP) is a volitional, non-invasive test of inspiratory muscle strength that has been successfully applied to children >2 years of age. Advantages include the simplicity of the maneuver and the absence of a mouthpiece, which is particularly helpful for patients with SMA, who may have bulbar weakness. SNIP also has the advantage of measuring inspiratory pressure during a natural maneuver that is easily performed even by young children with neuromuscular disorders. Based on the shape of the normal pressure-volume curve, a loss of respiratory muscle strength is expected before a fall in volume capacity and other lung volumes. SNIP has been shown to decline in both SMA Type 2 and 3 patients, with an annual decline of 5.4 ± 6.3% and 6.4 ± 8.0%, respectively (Khirani et al 2013). It is therefore plausible that SNIP measurement may detect the respiratory muscle strength decrease earlier in the disease or in younger children than would other respiratory function tests. SNIP will be performed in all patients in the study.

Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP) are other non-invasive tests of muscle strength which are measuring the strength of the diaphragm and other inspiratory muscles and the strength of the abdominal muscles and other expiratory muscles, respectively. Both of these tests measure the maximum strength of these muscles and have been found to be reduced in patients with neuromuscular disease, including SMA. MIP and MEP will be performed in *Part 2* patients 6–25 years of age. If the patient will become 6 years of age during the 30 day screening period i.e. will turn 6 years of age within 30 days of screening, the patient should have MIP and MEP performed during the screening visit.

The SNIP, MIP and MEP tests are performed using the TransAir-M ([redacted]) according to the manual of operations.

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

4.6.1.19 Columbia-Suicide Severity Rating Scale (Adults, Adolescents, and Children Aged 6−11 Years)

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 structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior, and attempts with actual/potential lethality. A modified and reduced version exists for children that has been successfully applied in children with various psychiatric disorders that do not involve cognitive impairment (FDA Guidance for industry “Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials”, 2012). The

suggested age range for this pediatric version is from middle childhood (typically, around Age 7) through onset of adolescence (typically, through Age 11).

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

4.6.1.20 Taste Assessment

Taste of the study drug solution will be assessed in patients aged 6 years and older (except patients to whom study drug is administered through G-tube) after administration of the study drug on Day 7:

- In adults and adolescents, taste will be assessed by a taste questionnaire that each patient should complete; entries will be reviewed for completeness by the site staff and the patient will be asked to complete any blank items. Changes to the form should not be made once the patient has completed the assessment.
- In children aged 6−11 years, taste will be assessed using a five−point facial visual hedonic scale; children will be encouraged to select the visual face that best reflects how much they liked the taste of the ingested study drug solution.

Study staff and patient's caregiver, possibly present during the assessment, should remain neutral and if necessary to interrogate the patient as the patient completes the assessment. A consistent methodology of non-directive questioning should be adopted, such as not to influence the patient. For example, non-directive questions such as "How was the taste of the study drug?" should be preferred over questions such as "was it good?" that may influence the response of the patient.

Both the taste questionnaire for adults and adolescents and the taste facial visual hedonic scale for children aged 6-11 years will be provided to the sites prior to study start.

4.6.1.21 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", "Very much worse". It is a widely used endpoint in clinical trials across a variety of disease areas. Clinicians will score patients using this scale at Month 12 based on their impression of change in the patient's global health since baseline. To enhance inter-rater consistency, an instructions document (developed with input from clinical experts) will be provided, which includes examples for each of the response options.

4.6.1.22 Patient-Reported Outcomes

Part 1

The 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. Both scales have previously been used in pediatric patients with SMA (Iannaccone et al 2009), including in a clinical trial setting (Chiriboga et al 2016). For both scales, the domain and total raw scores are converted to a 0-100 scale where higher scores indicate better health-related quality of life).

The PedsQL 4.0 Generic Core Scale will be completed by patients aged 8 years or older. The PedsQL 3.0 Neuromuscular module will be completed by patients aged 8-18 years. The PedsQL 4.0 Generic Core Scale and the PedsQL 3.0 Neuromuscular module will be performed by the appropriate patients in Part 1 until the week 52 visit.

Part 2

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

The EQ-5D-5L is a generic self-report health status questionnaire that is used to calculate a health utility score for use in health economic analysis (Oppe et al 2014; van Hout et al 2012). There are two components to the EuroQol EQ-5D: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and a visual analogue scale (VAS) that measures overall health status. Published weighting systems allow for creation of a single summary score (also known as a utility value). Overall scores range from 0 (death) to 1 (full/perfect health), with low scores representing a higher level of dysfunction; for some countries (e.g., UK), scores below zero are possible. The EQ-5D-5L will be completed by patients aged≥12 years.

Part 1 and Part 2

The age at randomization will determine which PRO, if any, is completed by the patient throughout the study (i.e., a 12 year old patient will not be administered the SMAIS or EQ-5D-5L if they were 11 years old at randomization).

4.6.1.23 Caregiver-Reported Outcomes

A parent, or caregiver, if no parent is available, can complete the following:

A caregiver-reported version of the SMAIS will be completed about the patient's level of independence, where possible, by a caregiver of each patient. This questionnaire assesses the same content as the patient-reported version described above.

A proxy-reported version of the EQ-5D-5L (Proxy Version 1) will be completed about the patient's HRQoL, where possible, by a caregiver of each patient.

The WPAI:CG-SMA assesses occupational work productivity and activity impairment of parents of individuals with SMA, a minor adaptation from the original, disease-generic WPAI (Reilly et al 1993). The WPAI:CG-SMA contains six questions about the effects of SMA on the following: employment status; hours missed due to patient caregiving; hours missed due to other reasons; hours actually worked; work productivity due to caregiving (presenteeism) and regular daily activities. The WPAI:CG-SMA will be completed, where possible, by a caregiver of each patient.

In Part 1: A caregiver-reported version of the PedsQL 4.0 Generic Core scale and PedsQL 3.0 Neuromuscular module will be completed about the patient, where possible, by a caregiver of each patient. This questionnaire assesses the same content as the patient-reported version described above until the Week 52 visit.

For all caregiver-completed assessments, the same caregiver should complete the measure throughout the study.

4.6.1.24 Samples for Research Biosample Repository

Overview of the Research Biosample Repository

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

Specimens will be collected from patients ≥12 years of age 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.

Approval by the Institutional Review Board or Ethics Committee

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

Sample Collection

The following samples will be collected at the timepoints specified in the SoA tables 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 and may be sent to one or more laboratories for analysis.

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

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

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

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

Confidentiality

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

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

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

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

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

Consent to Participate in the Research Biosample Repository

The Informed Consent and Assent Form will contain a separate section that addresses participation in the RBR. The Investigator or authorized designee will explain to each patient, and their parent/caregiver if applicable, the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's

agreement to provide optional RBR specimens. Patients who decline to participate will not provide a separate signature.

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

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

Withdrawal from the Research Biosample Repository

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

global_rcr-withdrawal@roche.com

A patient's withdrawal from Study BP39055 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a patient's withdrawal from the RBR does not constitute withdrawal from Study BP39055. Timing of Study Assessments

4.6.1.25 Screening and Pretreatment Assessments

For Part 1 only: Prior to obtaining patient informed consent for participation into the study, investigational sites will be required to complete and submit to the Sponsor a Screening Notification Form. Based on the availability of screening/enrollment allocations, the Sponsor will notify the site as to whether the patient screening can or cannot proceed at that current time. This will ensure that the recruitment targets are adhered to as per this protocol.

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

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

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

Screening and pre-treatment assessments will be performed within 2 to 30 days prior to Day 1. An abbreviated rescreening, medical history, physical examination, RULM, HFMSE, body weight, safety laboratory tests, pregnancy test [females of childbearing potential only], urine analysis and inclusion/exclusion criteria) may be allowed under circumstances where the patient has passed screening but could not be randomized within the 30-day screening window due to a study halt, logistical, personal, or technical reasons. At no time should the duration between the original screening visit and the abbreviated rescreening visit exceed 3 months. An abbreviated rescreening will only be permitted in cases where this poses no safety risk to the patient. Abbreviated rescreening will NOT require a new screening number in IxRS – the same screening number can be used and IxRS will ONLY provide a soft warning that Day –1 is out of window. Drug allocation for enrollment can still be obtained.

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

4.6.1.26 Assessments during Treatment

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

The patient study visits when efficacy assessments are performed (see SoA for time-points; Appendix 1 and Appendix 3) will be the most extensive visits, including all efficacy assessments in addition to pharmacokinetics, pharmacodynamics, full physical examination, and safety assessments. Accordingly, these visits will be conducted over two days but can also be conducted over three days if preferred by the patient, e.g., the ophthalmological examination may be conducted on the morning of the day preceding Block 1 or the day after Block 4. For these visits, four blocks of assessments have been identified that must be conducted in the order described in Table 2, with Blocks 1 and 2 to be performed on Day 1 and Blocks 3 and 4 on Day 2. Flexibility is given to the site for the order of tests within each of these blocks. It is critical that in Block 1, the MFM is always preceded by a break of at least 15 min. In Block 4 the HFMSE and RULM must be preceded by a 15 minute break. Additional breaks are recommended at any other

time as appropriate for each patient. It is also recommended that for a single patient, assessments are conducted in the same order throughout the trial.

Table 2 Order and Blocks of Assessments at Visits When Measurements Are Performed

Day 1	
Block 1	• Collection of AEs and concomitant therapies • Patients and parents/caregivers: EQ-5D-5L **BREAK** • MFM 32 **BREAK** • Pulmonary testing including SNIP and, in Part 2 only, additionally MIP and MEP ⊥ **BREAK**
Block 2	• ECGs, vital signs • Physical examination • Neurological examination • C-SSRS • Ophthalmological exam
Day 2	
Block 3	• Blood samples or insertion of catheter for blood sampling **BREAK** <u>Patients</u> • SMAIS (12+ years only)/PedsQL (Neuromuscular and Core) † <u>Parent/caregivers</u>* • SMAIS/PedsQL (Neuromuscular and Core)† • WPAI:CG <u>Clinician</u> • CGI-C ‡
Block 4	**BREAK** • HFMSE **BREAK** • RULM

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

⊥ If required for the respiratory assessments, the weight and height can be obtained prior to the respiratory assessments instead of during the physical examination.

† SMAIS administered in Part 2, only. PedsQL administered in Part 1, only.

‡ CGI-C completed after patient and parent/caregiver assessments in Block 3 in Part 2 only.

* If possible, the parent/caregivers reported outcomes can be administered while the patient is completing their assessments.

4.6.1.27 Assessments at Study Completion/Early *Withdrawal* Visit

Patients who complete the study or discontinue *study drug* early will be asked to return to the clinic for a *study completion/early withdrawal visit* as shown in the SoA (Appendix 1 and Appendix 3).

4.6.1.28 Follow-Up Assessments

A follow-up phone call should occur 30 days after the study completion/ early withdrawal visit to collect information on adverse events as outlined in the SoA (Appendix 1 and Appendix 3).

4.6.1.29 Assessments at Unscheduled Visits

Assessments that are deemed necessary, by the Investigator and/or Sponsor and/or iDMC, in particular for safety, will be performed at unscheduled visits.

4.6.2 Prioritization Order for Blood Samples

Time-points for blood samples are indicated in the SoA and Detailed tables (see Appendices). However, should the total blood volume to be collected at any timepoint according to this SoA exceed 1 mL/kg or the volume collected over any 8-week period throughout the study exceed 4 mL/kg, the prioritization order indicated in Table 3 should be followed.

Table 3 Prioritization Order for Blood Samples

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

4.7 PATIENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

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

- Patient withdrawal of consent at any time.

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

4.7.1.1 Discontinuation from Study Drug

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

- Pregnancy
- Ophthalmological or other events, as described in Section 5.2.4.1
- Unable to continue to comply with study requirements.

Patients discontinuing study drug prematurely will be asked to return to the clinic for a study completion/early *withdrawal* visit (Section 4.6.1.27) and *will be followed with a phone call from the site 30 days after this last visit* (Section 4.6.1.28). The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced in Part 2 but may be replaced in Part 1 (only if the discontinuation was for reasons other than safety reasons).

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

4.7.1.2 Withdrawal from Study

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

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

Patients withdrawing from the study for safety reasons will not be replaced. Patients withdrawing from the study for other reasons will not be replaced in Part 2 but may be replaced in Part 1.

When a patient voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the patient specifically requests for these to be discarded or local laws require their immediate destruction. A patient's withdrawal from Study BP39055 does not, by itself, constitute withdrawal of specimens donated to the RBR.

4.7.2 Study and Site Discontinuation

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

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

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

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

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

5. ASSESSMENT OF SAFETY

5.1 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.1.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.9.

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug.
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies).

5.1.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

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

This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.10).
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions).
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug.
- Significant medical event in the Investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above).

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

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

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

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

Non-serious adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

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

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

5.2 SAFETY PLAN

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

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

5.2.1 Safety Precautions

Staggered enrollment, i.e., adolescent and adult patients 12-25 years cohort prior to the initiation of the children aged 2-11 years in Part 1, as well as safety precautions and monitoring measures have been implemented to maximize the safeguards for the participants enrolled in this study. The stopping rules for individuals and the dose-escalation are detailed in Section 5.2.4 will be applied in case of specific adverse events.

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

- Male fertility:
  - Inform male patients about the risk to fertility and the uncertainty about reversibility (see Section 6.5.1.3 of the Risdiplam Investigator's Brochure).
  - In circumstances where male patients exposed to study drug desire future conception, they will be informed about the time required to recover from potential changes in semen parameters based on the duration of a spermatogenic cycle.
- Possible chromosome damage:
  - Strict contraception for female patients and male patients with female partners of childbearing potential (Section 4.2.2).
  - Male patients will also be reminded of the necessity to respect a minimum period of 4 months before trying to conceive or before donating sperm (see also contraception requirements in Section 4.2.2).
- Possible retinal effects:
  - Patients should be informed of the need to seek immediate medical attention in the following situations, e.g., sudden vision loss, distorted or blurred vision, difficulties in dark adaptation after stepping into a dark room, knocking into things at the periphery of vision. Parents or caregiver will be informed that in case of visual impairments, young children could present with e.g., strabismus, behavioral changes (e.g., fixation losses, not reaching/grabbing objects, rubbing of the eyes).
  - Patients will be instructed by the investigators to comply with concomitant medications restriction, i.e., use of drugs with known retinal toxicity within 12 months before randomization is not permitted and prior use of chloroquine, hydroxychloroquine, thioridazine, retigabin or vigabatrin is an exclusion criterion.
  - Similarly drugs with known phototoxicity liabilities are prohibited as they may cause retinal toxicity, thus confounding the interpretation of treatment-emergent retinal changes during the clinical trials (Section 4.5.2).
- Effects on bone marrow/hematology: assessment of hematological parameters is part of the routine monitoring and will be performed throughout the study.
- Effects on the developing embryo:
- Studies in animals have shown that risdiplam is teratogenic and fetotoxic (see the Risdiplam Investigator's Brochure for details). Hence, strict contraception is required (Section 4.2.2; see Section 5.4.3 for pregnancy reporting requirements).

5.2.2 Safety Monitoring

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

- Ophthalmological assessments (Table 4, Table 5), *and section 4.6.1.11 for details.*
- The study will include frequent triplicate ECGs. In Part 1 in adult and adolescent patients (>12 years of age), triplicate 12-lead ECGs will be time-matched with PK samples, on selected PK days to allow PK/QTc analyses and modelling.
- Follow-up phone calls (as per the timepoints in the SoA tables, Appendix 1 and Appendix 3):
  - Patients (or caregivers of patients, as appropriate) will be called by the Investigator or designee to monitor safety and tolerability when not attending the clinic during the first 12 weeks after enrollment. Additional calls may be made at the discretion of the Investigator. Assessments will include adverse events, concomitant medication review and significant life events.

Table 4 Ophthalmological Examination in Adults and Co-operative Children *up to and including Week 104*

Ophthalmological Tests*	Modality (As Appropriate According to the Age of the Patient)	Assessment Visits
Block 1	Best Corrected Visual acuity Sloan low contrast (Part 1 only excluding open-label extension) Slit lamp examination and funduscopy SD-OCT	screening every 2 months (±1 week)
Block 2	Visual Field Perimetry testing (in children >10 years)† Intra ocular pressure **Fundus Auto-Fluorescence** (Part 1 only excluding open-label extension)	screening every 4 months (±1 week)
Block 3	Fundus color photography (7-fields or wide-field)	screening every 6 months (±1 week)
Block 4 (in selected sites; Part 1 only excluding open-label extension)	Dark adaptation	screening every 4 months (±1 week)

SD-OCT = spectral domain optical coherence tomography.

* *Blocks will be maintained in the Open-label extension; refer to Appendix 5 and Appendix 6 for assessment frequency.*

† Every 6 months for Part 2 .

When two or more ophthalmological tests coincide on an assessment visit, it is important that the following tests be performed first before eye dilation, should this be necessary:

- Best corrected visual acuity
- Sloan low contrast
- Visual Field Perimetry testing
- Dark adaptation (selected sites only)

Table 5 Ophthalmological Examination in Young and Non Co-operative Children *up to and including Week 104*

Ophthalmological Examination*	Modality	Assessment Visits
Block 1	Visual testing (Bruckner, fix and follow, cover-uncover, visual fields, visual acuity tests) Slit lamp examination and funduscopy SD-OCT **Fundus Auto-Fluorescence** (Part 1 only excluding open-label extension)	screening every 2 months (±1 week)
Block 2	Fundus color photography Intra-ocular pressure	screening every 6 months (± 1 week) *Yearly*

SD-OCT = spectral domain optical coherence tomography.

* *Blocks will be maintained in the Open-label extension; refer to Appendix 5 and Appendix 6 for assessment frequency.*

When two or more ophthalmological tests coincide on an assessment visit, it is important that the following tests be performed first before eye dilation, should this procedure be required:

- Best corrected visual acuity
- Sloan low contrast
- Visual field perimetry testing
- Dark adaptation (selected sites only)

Threshold perimetry

In Part 2 and open-label extension in Part 1, visual field testing by threshold perimetry may be replaced by simpler visual field tests such as easier perimetry protocols or as last resort confrontation visual field testing, in patients >10 years who have unsuccessfully attempted threshold perimetry. The assessment should be attempted at each ophthalmological visit where it is scheduled.

In Part 2 and open-label extension in Part 1, fundus photography may be replaced by an image captured during funduscopy in patients who have unsuccessfully attempted the assessment. The assessment should be attempted at each ophthalmological visit where it is scheduled.

Specialty physicians (dermatologist and otolaryngology specialist) will be identified and will be trained on risdiplam non-clinical toxicological findings prior to study start to enable prompt follow-up in case of any suspicious or actual AE.

5.2.3 Management of Specific Adverse Events

Specific adverse events related to ophthalmological adverse events should be managed as described in Table 6.

Table 6 Guidelines for Managing Specific Adverse Events

Event	Action to Take
Ophthalmological event	Consult study trained ophthalmologist.

5.2.4 Stopping Rules

5.2.4.1 Part 1 and Part 2: Individual Patient Stopping Rules

While the investigators, the Roche *Clinical Science Leader,* the Roche Safety Science Leader, and the IMC in Part 1 and the iDMC in Part 2 (and any other professional considered necessary to consult) will review available data for the individual patients on an ongoing basis, the following specific stopping rules for an individual patient are defined a priori:

- Functional or structural eye abnormalities:
  - Clinically relevant abnormalities on SD-OCT/FAF/fundus photography considered to be related to study drug as assessed by an ophthalmologist, i.e., changes in retinal thickness, presence of edema, cystoid or atrophic changes, hyper/hypopigmentation – in case of equivocal observations or imprecise measurements (e.g., abnormalities detected at the edge of the captured image requiring enlarged visualizations, change from baseline in retinal layer thickness at the limit of test–retest variability), retinal imaging (OCT/FAF) can be repeated to confirm or refute the initial results. In case of retinal findings, each individual case will be discussed between the investigator, the ophthalmologist examining the patient and the sponsor to decide discontinuation of study drug administration.
  - Clinically relevant impairment in visual acuity (VA)/visual field (VF) restrictions confirmed by a repeat VA/VF assessment.
- Patients with any elevated alanine transaminase (ALT) or aspartate aminotransferase (AST) of $>3\times$ upper limit of normal (ULN), alkaline phosphatase (ALP) $<2\times$ ULN, and associated with an increase in bilirubin ($\geq 2\times$ ULN) (i.e., a suspected "Hy's law" which indicates risk of severe/serious liver impairment) in the absence of a different explanation.
- Significant and clinically relevant changes in laboratory parameters, ECG or vital signs which pose an unacceptable risk for the patient.

  NB: Although no cardiovascular signal emerged from safety pharmacology studies in animals, or the clinical study in healthy subjects, a prolongation of the QTcF

exceeding 500 ms (or QTcB in children with age less than 10 years) with a repeat-ECG within 2 hours confirming the QTc abnormality should be promptly reviewed by a cardiologist on the same day and before subsequent dosing to evaluate if treatment discontinuation is warranted.

- Other findings such as a SAE or any other severe AE that indicate that dosing should be halted.

5.2.4.2 Part 1: Cohort Stopping Rules

Stopping a Cohort

The IMC will review all safety data of all patients of a cohort (i.e., same target exposure, same age group) at pre-defined time-points (and additionally on an ad-hoc basis as required; as detailed in the Charter) and can recommend termination of a certain cohort at any time. As a general rule, the cohort should be terminated if 50% or more patients (i.e.; ≥3 out of 6) treated with risdiplam in a cohort present with severe AE of the same type. If 50% or more patients (i.e.; ≥3 out of 6) treated with risdiplam experience at least one severe AE (of any type), the decision as to whether to terminate the cohort or continue dosing, and possibly to enroll additional patients in order to generate more data at the tested dose level, will be made by the iDMC based on the recommendation of the IMC. The decision to continue should be based on documented tangible evidence supporting an acceptable safety profile of the drug.

Stopping Dose-Escalation into Next Cohort

The dose will not be escalated in Part 1 if one of the following circumstances occurs in a cohort of patients treated with risdiplam (i.e., 6 patients in the same age group on active treatment at the same target exposure) unless clearly not related to the administration of the study drug:

- Grade ≥2 skin or subcutaneous reactions of the same type in ≥33% of patients (i.e., ≥2 out of 6).
- Grade ≥2 pharyngeal/laryngeal or mucosal reactions of the same type in ≥33% of patients (i.e., ≥2 out of 6).
- Grade ≥3 adverse events of the same type (other than those described above) in ≥33% of patients (i.e., ≥2 out of 6). In case ≥33% of patients (i.e., ≥2 out of 6) experience at least one Grade≥3 adverse event (of any type), the decision as to whether to proceed with dose escalation will be made by the iDMC based on the IMC recommendation. The decision should be based on documented tangible evidence supporting an acceptable safety profile of the drug for dose escalation.
- Clinically significant retinal abnormalities on SD-OCT/FAF/fundus photography in conjunction with functional changes in ≥33% of patients as assessed by an ophthalmologist (i.e., ≥2 out of 6).
- Clinically significant laboratory abnormalities of the same type in ≥33% of patients (i.e., ≥2 out of 6).

- Clinically significant changes in vital signs of the same type in ≥33% of patients (i.e., ≥2 out of 6).
- Clinically significant changes in ECGs of the same type in ≥33% of patients.
- Other findings that indicate dose-escalation should not proceed as per judgment of the IMC (e.g., occurrence of severe AEs of the same type which cumulatively in two different cohorts would raise concern).

5.2.4.3 Part 2 Stopping Rules

Clinical safety data will be reviewed on an ongoing basis by the Sponsor (blinded) and by the external iDMC at pre-defined time-points (and on an ad-hoc basis as detailed in the Charter) and the iDMC can make a recommendation to the Sponsor regarding the termination of the study.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The Investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4-5.6.

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported *for 30 days after the study completion or early withdrawal visit (i.e., at least 30 days after last dose of study drug).*

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

5.3.2 Eliciting Adverse Event Information

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

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

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

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v4.03) will be used to assess adverse event severity. Table 7 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 7 Adverse Event Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated.
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to adverse event[d]

Note:
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the NCI CTCAE (v4.03), which can be found at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

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

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

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

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or

not an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration:

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Diagnosis versus Signs and Symptoms

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

5.3.5.2 Adverse Events Occurring Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the eCRF.

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

5.3.5.3 Persistent or Recurrent Adverse Events

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

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

5.3.5.4 Abnormal Laboratory Values

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

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

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

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

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

be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia”.

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

5.3.5.5 Abnormal Vital Sign Values

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

- Accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Clinically significant in the investigator’s judgment

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

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

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

5.3.5.6 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (Section 5.3.5.1) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the

event), either as a serious adverse event or a non-serious adverse event of special interest (Section 5.4.2).

5.3.5.7 Deaths

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

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

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

5.3.5.8 Preexisting Medical Conditions

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

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

5.3.5.9 Lack of Efficacy or Worsening of Spinal Muscular Atrophy

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

5.3.5.10 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care.
- Planned hospitalization required by the protocol (e.g., for study drug administration).
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease. The patient has not suffered an adverse event.

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

- Hospitalization for an adverse event that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.
- Admission to emergency room that does not result in hospitalization will not constitute per se a serious adverse event.

5.3.5.11 Overdoses

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

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

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

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

All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills

serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.3.5.12 Patient-Reported Outcome Data

Adverse event reports will not be derived from patient-reported (or caregiver-reported) outcome data by the Sponsor, and safety analyses will not be performed using this data. Although sites are not expected to review this data, it is possible that an Investigator could become aware of PRO (Caregiver-reported outcome) data that may be indicative of an AE. Under these circumstances, the Investigator will determine whether the criteria for an adverse event have been met and, if so, will report the event on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, access to the Medical Monitors is available 24 hours a day 7 days a week. *Country specific toll-free numbers of the emergency medical call center are filed in the investigator site file.*

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

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

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Risdiplam has not been tested in animals for possible effects on the developing embryo. There is evidence for toxicity of risdiplam to the cell cycle in vitro and in vivo in rats and monkeys based on secondary splice target interaction. Thus, it is conceivable that risdiplam can have adverse effect on the developing embryo. For this reason, precautions must be used to not get pregnant during treatment with risdiplam. Female patients of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 28 days after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Pregnancy should not be recorded on the Adverse Event eCRF. The Investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

5.4.3.2 Pregnancies in Female Partners of Male Patient

Risdiplam is known to affect male germ cells in their development. This is likely based on an interaction with cell cycle genes. In animals, this effect with the *SMN2* splicing modifier, RO6885247, has been demonstrated to be reversible. Thus, male patients are advised to not father a child while on treatment and for up to four months after cessation of treatment. Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 4 months after the last dose of study drug. A Clinical Trial Pregnancy Reporting Form should be completed by the Investigator and submitted to the Sponsor within 24 hours after learning of the pregnancy. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the Investigator should update the Clinical Trial Pregnancy Reporting Form with additional information on the course and outcome of the pregnancy. An Investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy

and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.4.4 Reporting Requirements for Medical Device Complaints

The Investigator must report all medical device complaints to the Sponsor. The Investigator should document as much information as possible on the Medical Device Complaint including the product batch number and expiration date. If the medical device complaint results in an adverse event, the adverse event must be reported on the Adverse Event eCRF. If the event is serious, the Adverse Event eCRF must be completed and reported to the Sponsor within 24 hours after learning of the event (Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

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

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data

verification. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

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

5.5.2 Sponsor Follow-Up

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

5.6 POST-STUDY ADVERSE EVENTS

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

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

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

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

- Risdiplam Investigator's Brochure

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

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The 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 locked at intervals in order to analyze and report the safety, PK/PD and exploratory efficacy of those patients enrolled into Part 1 only.

Full details of the statistical methods for the confirmatory part will be pre-specified within a Statistical Analysis Plan (SAP) prior to database lock and the Sponsor being unblinded to the treatment assignment of patients randomized into Part 2 of the study. This will occur for the purpose of the primary analysis and analyses of the secondary endpoints once the last patient randomized into Part 2 has completed their 12-month assessment or has been withdrawn.

Whilst 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, at the time of the primary analysis all available efficacy data post Month 12 in Part 2 will also be reported for the exploratory efficacy endpoints. All available safety data in both parts of the study will also be reported.

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, including once the last patient randomized into Part 2 has completed their 24-month assessment or has been withdrawn in order to analyze the 24-month treatment data. Final database lock will occur at study end.

6.1 DETERMINATION OF SAMPLE SIZE

Exploratory 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. With 6 patients on active treatment in each dose/age group, there is a 74% chance to detect an AE in at least one patient, given that the true underlying adverse event rate is 20%. With 12 patients receiving active drug per dose /exposure level, this chance increases to 93%.

In Study BP29420 with the splicing modifier RO6885247, a standard deviation of approximately 930 pg/mL for the absolute change from baseline in SMN protein and of 33% for the relative change from baseline (in percent) was observed.

With 6 patients on active treatment in each dose/age group, the two-sided 95% confidence interval for the absolute change from baseline in SMN protein will extend no more than 1197 pg/mL from its observed mean, with a coverage probability of 80%.

Similarly for the relative change from baseline, with 6 patients on active treatment in each dose/age group, the two-sided 95% confidence interval for the relative change from baseline in SMN protein (in percent) will extend no more than 43% from its observed mean (in percent), with a coverage probability of 80%.

Confirmatory Part 2

The purpose of this part of the study is to estimate and test the treatment effect of risdiplam at the selected dose from Part 1 relative to placebo.

A target sample size of 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% drop-out 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 (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.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who were randomized, discontinued or ongoing treatment at the time of the primary analysis or have completed the study will be summarized. Reasons for premature study withdrawal will be listed and summarized. Enrollment and major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results. Data will be presented by treatment group for each part of the study separately and summaries for Part 1 will also be presented by cohort/ dose level.

6.3 ANALYSIS POPULATIONS

6.3.1 Safety Analysis Population

Safety Population

All patients who receive at least one dose of study medication (risdiplam or placebo) will be included in the safety population. Patients will be grouped according to the treatment received.

This population will be the primary safety analysis population to compare risdiplam to placebo.

All Exposure Population

All patients who receive at least one dose of risdiplam at any dose level (during either the double-blinded period or the OLE period) 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.

This population will be used to provide longer term safety data of risdiplam treatment, mainly in Part 1.

6.3.2 Pharmacokinetic Analysis Population

All patients with at least one time point with a measureable concentration will be included in the PK analysis data set. Patients will only be excluded from the pharmacokinetic analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol or if data are unavailable or incomplete which may influence the pharmacokinetic analysis. Excluded cases will be documented together with the reason for exclusion. All decisions on exclusions from the analysis will be made prior to database closure.

6.3.3 Efficacy Analysis Population

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. Patients will be grouped according to the treatment assigned at randomization.

6.4 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and other baseline characteristics will be summarized for the ITT population using descriptive statistics, means, standard deviations, medians, interquartile range and ranges for continuous variables and number and percentages for categorical variables, as appropriate. Baseline will be defined as the last measurement prior to randomization unless specified otherwise in the SAP. Data will be presented by treatment group and overall for each part of the study separately and summaries for Part 1 will also be presented by cohort/dose level.

6.5 SAFETY ANALYSES

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

- Incidence of adverse events (overall, by severity and by relationship to study medication).
- Incidence of serious adverse events.

- Incidence of treatment discontinuations due to adverse events.
- Incidence of laboratory abnormalities.
- Incidence of ECG abnormalities.
- Incidence of vital sign (SBP, DBP, heart rate, respiratory rate, body temperature) 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.

The safety population will be the primary safety analysis population to compare the safety of risdiplam to placebo. Safety data will be summarized descriptively by treatment group and by cohort/dose level for the placebo-controlled period of Part 1. For Part 2, the safety data will be summarized descriptively by treatment group for the first 12-month period (i.e., 12-month data for each individual patient). For Part 2 of the study, safety data for patients originally randomized to risdiplam will be summarized for the 24-month treatment period.

Longer term safety of risdiplam treatment, including safety data collected in the OLE period for both parts of the study, will be summarized using the risdiplam All Exposure Population.

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

6.5.1 Adverse Events

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

6.5.2 Clinical Laboratory Test Results

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

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

6.5.2.1 Definition of Laboratory Abnormalities

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

6.5.3 Vital Signs

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

6.5.4 Electrocardiogram Data Analysis

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

6.5.5 Concomitant Medications

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

6.6 PHARMACOKINETIC ANALYSES

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

Individual and mean plasma concentrations of risdiplam, and metabolites, as appropriate, versus time data will be tabulated and plotted.

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 pharmacokinetic parameters will be estimated and the influence of various covariates (such as age, gender and body weight) on these parameters will be investigated in an exploratory 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. Additionally exploratory analyses on exposure and safety / efficacy relationship may be conducted if deemed necessary. The details of the modelling and exploratory analyses may be reported in a document separate from the clinical study report.

Actual PK sampling times must be documented in the eCRF. Actual date and the time of dosing for the preceding two doses, and the dosing date and time on the day of PK sampling, must be documented in the eCRF.

Assessment of protein binding will be performed on pre-dose samples and results listed.

Additional PK analyses will be conducted as appropriate.

6.7 PHARMACODYNAMIC ANALYSES

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

6.8 EFFICACY ANALYSES

The intent-to-treat (ITT) population will be the primary analysis population for all efficacy analyses. The efficacy analyses will only include data from the patients randomized into Part 2 of the study; it will not include data from the Part 1 patients who will be analyzed to select the dose. Efficacy data of the patients randomized into Part 1 will be summarized descriptively and presented separately from the confirmatory efficacy analysis of Part 2 described below.

6.8.1 Primary Efficacy Endpoint

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

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

Ho: $\delta = 0$ (null) versus Ha: $\delta \neq 0$ (alternative).

If the two-sided p-value is $\leq$5% then the null hypothesis will be rejected.

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. The model will include 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. If an optional interim analysis is performed, the p-value will be compared to the critical level for significance determined by the Lan-DeMets (O'Brien Fleming boundary) alpha spending function to control the overall type I error rate at 5% for the primary endpoint (DeMets and Lan 1994).

The MFM total score will be calculated according to the user manual, expressed as a percentage of the maximum score possible for the scale (i.e., sum of the 32 item scores divided by 96 and multiplied by 100). If the MFM has been administered at a visit but item scores are missing, these items will be set to 0 (i.e., unable to perform the task) prior to the calculation of the total score. Missing MFM total scores will not be imputed.

As the primary model assumes MFM total scores at visits are missing at random, the number and pattern of missing data will be explored and different sensitivity analysis will be planned in the statistical analysis plan to explore the robustness of the primary results. If the estimation of the primary model does not converge due to the unstructured co-variance matrix structure, other structures will be explored.

6.8.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints in Part 2 of the study are as follows:

Motor Function

- Change from baseline in Total score of Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 12.
- Change from baseline in the Total score of the revised upper limb module (RULM) at Month 12.
- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline $\geq$0) on the total MFM score at Month 12.
- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline $\geq$0) on the total HFMSE score at Month 12.
- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline $\geq$0) on the total RULM score 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 MFM domain scores of D1, D2, D3 and the total combined score of (D1 + D2) at Month 12.

Respiratory

- Change from baseline in the best SNIP (expressed as a percentage of the predicted value) at Month 12.

In patients aged 6 to 25 years only:

- Change from baseline in the best MIP at Month 12.
- Change from baseline in the best MEP at Month 12.
- Change from baseline in FEV_1 at Month 12.
- Change from baseline in FVC at Month 12.
- Change from baseline in the peak cough flow (PCF) at Month 12.

Disease-Related Adverse Events

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

Disease-related adverse events will be collected through the adverse event reporting of the study and events will be identified by applying a basket of preferred terms to the adverse event dataset. This basket will be pre-defined in the SAP and finalized prior to unblinding.

Clinical Global Impression of Change

- Proportion of patients rated by clinicians as no change or improved in the Clinical Global Impression of Change (CGI-C) Scale at Month 12.
- Proportion of patients rated by clinicians as improved in the Clinical Global Impression of Change (CGI-C) Scale at Month 12.

Patient/Caregiver-Reported Outcomes

- Change from baseline in the Total Score of the caregiver-reported SMA independence Scale (SMAIS) at Month 12.

<u>In patients aged 12 to 25 years only:</u>

- Change from baseline in the Total score of the patient-reported SMA independence scale (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 by treatment group using the ITT population unless stated otherwise.

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, and 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% confidence intervals. For the HFMSE and RULM, missing item scores will be set to 0 (unable to perform the task) if the assessment has been administered at the visit prior to the calculation of the total score. Missing total scores will not be imputed.

The proportion of patients who have experienced at least one disease-related adverse event by the end of the first 12-month period will be summarized descriptively. As this endpoint will be a composite endpoint of different co-morbidities, the proportion of patients who experience at least one component of this endpoint (i.e., co-morbidity grouping) will be also be summarized. Percentages will be based on the number in the Safety population. The proportion of patients with at least one disease-related adverse event will be analyzed using a log binomial model including treatment and age group. The adjusted relative risk of experiencing at least one disease-related adverse event for patients treated with risdiplam compared to placebo will be presented with the 95% confidence interval.

A responder analysis of the primary efficacy measure (total MFM score) will be performed as a secondary analysis. Responder analyses of the total HFMSE score and

the total RULM score will also be performed. Cumulative distribution plots will be presented to show the proportion of responders when each possible cut-off point of the total score is used as the definition of response. In addition, the proportion of patients who achieve stabilization or improvement (i.e., a change from baseline $\geq$0) on the total MFM score at Month 12 will be analyzed using a logistic regression model, including the baseline total score, treatment and age group. The estimated odds ratio for stabilization or improvement at Month 12 for patients treated with risdiplam will be presented with 95% confidence intervals. Patients who withdraw or have missing total MFM scores at Month 12 will be classified as a non-responder in this analysis.

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 and age group. The estimated odds ratio for no change or improved at Month 12 for patients treated with risdiplam will be presented with 95% confidence intervals. 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 a missing CGI-C response at Month 12 will be classified as a non-responder in the analysis.

To control for multiplicity across the different endpoint domains (i.e., motor function, respiratory and CGI-C), 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% significant level (i.e., p-value $\leq$0.05). The secondary endpoints will be tested at a 5% significance level according to this hierarchy as long as the p-value is $\leq$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.

Further details of the statistical methods, definitions and analyses for all the secondary endpoints will be given within the SAP.

6.8.3 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:

- Change from baseline in the Total MFM score and its domain scores of D1, D2, D3 and the total combined score of (D1 + D2) at Month 18 and 24.

- Proportion of patients who achieve a change from baseline ≥0 on the Total MFM score at Month 18 and 24.
- Change from baseline in Total score of HFMSE at Month 18 and 24.
- Change from baseline in the Total score of the RULM at Month 18 and 24.
- Change from baseline in the best SNIP (expressed as % predicted) at Month 18 and 24.
- Change from baseline in the best MIP at Month 18 and 24.
- Change from baseline in the best MEP at Month 18 and 24.
- Change from baseline in FEV1 at Month 18 and 24.
- Change from baseline in FVC at Month 18 and 24.
- Change from baseline in PCF at Month 18 and 24.
- Change from baseline in the Total Score of the caregiver-reported SMA independence Scale (SMAIS) at Month 18 and 24.
- Change from baseline in the Total Score of the patient-reported SMA independence Scale (SMAIS) at Month 18 and 24.

All analyses of the exploratory efficacy endpoints will be performed on all available data in Part 2. Summaries will be presented by time up to 24 months of treatment for those patients originally randomized to risdiplam.

Statistical methods, definitions and analyses for all exploratory endpoints, including those for the OLE period, will be specified in more detail within the SAP.

6.9 PATIENT/CAREGIVER-REPORTED OUTCOME ANALYSES

For Part 2 of the study, the patient-reported and caregiver-reported SMA independence Scale (SMAIS) will be scored, and missing item data handled, as recommended in the scoring manual.

Statistical methods and analyses for all PRO endpoints including the PedsQL for Part 1 will be specified in the SAP.

6.10 OTHER EXPLORATORY ANALYSES

Subgroup Analysis

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 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).

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% confidence intervals for each subgroup category. P-values will be interpreted in an exploratory manner.

Further subgroup analysis of key secondary endpoints will be specified in the SAP.

Other analyses may be performed to explore the consistency of the treatment effect in other secondary efficacy and/or safety endpoints, and for other patient subgroups.

These exploratory subgroup analyses will be specified more fully in the SAP.

Pharmacoeconomic Analysis

Analysis of pharmacoeconomic data (EQ-5D-5L, WPAI:CG-SMA) and the production of a final pharmacoeconomic 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 pharmacoeconomic (PE) report.

6.11 INTERIM ANALYSES

To adapt to information that may emerge during the course of this study, 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.

The decision to conduct the optional interim analysis, along with the rationale, timing, and statistical details for the analysis will be documented in the SAP, and the SAP will be submitted to relevant Health Authorities at least 2 months prior to the conduct of the interim analysis. The iDMC charter will be updated to document potential recommendations the iDMC can make to the Sponsor as a result of the analysis (e.g., submit the results of this part of the study early for positive efficacy), and the iDMC charter will also be made available to relevant Health Authorities.

If there is a potential opportunity to submit the results of this part of the study early for positive efficacy as a result of the interim analysis, the type I error rate will be controlled to ensure statistical validity is maintained. Specifically, the Lan-DeMets α-spending function that approximates the O'Brien Fleming boundary will be applied to determine the critical value for the interim analysis in order to control the overall type I error rate at 5% for the primary endpoint (DeMets and Lan 1994). If the study continues beyond the interim analysis, the critical value at the primary analysis would be adjusted accordingly to maintain the protocol-specified overall type I error rate, per standard Lan-DeMets methodology.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

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

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

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

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

7.2 ELECTRONIC CASE REPORT FORMS

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

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

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

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

7.3 SOURCE DATA DOCUMENTATION

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

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

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

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

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

7.4 USE OF COMPUTERIZED SYSTEMS

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

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic Patient-Reported Outcome (ePRO) data (if applicable),

Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local Health Authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations. No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

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

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

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

8.2 INFORMED CONSENT

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

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

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

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

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

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

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

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

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

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (Section 9.6).

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

8.4 CONFIDENTIALITY

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

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

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

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

8.5 FINANCIAL DISCLOSURE

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

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

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

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

In U.S., it is the understanding of the Sponsor that this protocol (and any modifications) as well as appropriate consent procedures and advertisements, will be reviewed and approved by an Institutional Review Board (IRB). This board must operate in accordance

with the current Federal Regulations. The Sponsor will be sent a letter or certificate of approval prior to initiation of the study, and also whenever subsequent amendments /modifications are made to the protocol. Roche shall also submit an IND Annual Report to FDA according to local regulatory requirements and timelines.

9.2 PROTOCOL DEVIATIONS

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

9.3 SITE INSPECTIONS

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

9.4 ADMINISTRATIVE STRUCTURE

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

An IMC will be responsible for reviewing safety, PK and PD data and for dose-escalation decisions in Part 1 and the dose-selection for Part 2. An iDMC will review all available data from Part 1 to confirm the dose-decision taken by the IMC, and will review safety, efficacy, PK and PD data for Part 2. The scope and responsibility of these committees will be detailed in a specific Charter.

An IxRS system will be used to register the screening/screening failures, enrollment, randomization, drug allocation, withdrawal, discontinuation, and *completion* of patients.

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

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

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

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

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

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

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

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

9.6 PROTOCOL AMENDMENTS

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

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

10. REFERENCES

Bérard C, Payan C, Hodgkinson I, et al & MFM Collaborative Study Group. A motor function measure scale for neuromuscular diseases. Construction and validation study. Neuromuscul Disord. 2005;15:463-470.

Chiriboga CA, Swoboda KJ, Darras BT, et al. Results from a phase 1 study of nusinersen (ISIS-SMN_{RX}) in children with spinal muscular atrophy. Neurology. 2016;86:890-897.

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

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

DeMets DL, Lan KKG. Interim analysis: the alpha spending function approach. Statistics Med. 1994;13:1341-1352.

d'Ydewalle C, Sumner C. Spinal Muscular Atrophy Therapeutics: Where do we Stand? Neurotherapeutics. 2015; 12(2):303-316.

FDA Guidance for industry "Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials", Aug 2012.

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

Hua Y, Sahashi K, Rigo F, et al. Peripheral SMN restoration is essential for long-term rescue of a severe spinal muscular atrophy mouse model. Nature. 2011;478:123-126.

Iannaccone ST, Hynan LS, Morton A, et al. The PedsQL in pediatric patients with Spinal Muscular Atrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Generic Core Scales and Neuromuscular Module. Neuromuscul Disord. 2009;19:805-812.

Khirani S, Colella M, Caldarelli V, et al. Longitudinal course of lung function and respiratory muscle strength in spinal muscular atrophy type 2 and 3. Eur J Paediatr Neurol. 2013;17(6):552-560.

Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. Arch Neurol. 2011;68(8):979-984.

Lefebvre S, Burglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995;80:155-165.

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

Lorson CL, Hahnen E, Androphy E J, et al. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. Proc Natl Acad Sci USA. 1999;96:6307-6311.

Lunn MR, Wang CH. Spinal muscular atrophy. Lancet. 2008;371:2120-2133.

Mercuri E, Finkel R, Montes J, et al. Patterns of disease progresion in type 2 and 3 SMA: Implications for clinical trials. Neuromuscul Disord. 2016;26:126-131.

Munsat TL, Davies KE. International SMA Consortium Meeting (26-28 June 1992, Bonn, Germany). Neuromuscul Disord. 1992;2(5-6):423–428.

Nguyen TM, Humphrey E, Lam LT, et al. A two-site ELISA can quantify upregulation of SMN protein by drugs for spinal muscular atrophy. Neurology. 2008; 71:1757-1763.

Nurputra DK, Lai PS, Haraha NIF, et al. Spinal muscular atrophy: from gene discovery to clinical trials. Ann Hum Genet. 2013;77:435-463.

O'Hagen JM, Glanzman AM, McDermott MP, et al. An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. Neuromuscul Disord. 2007;17:693-697.

Oppe M, Devlin NJ, van Hout B, et al. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. Value Health. 2014;17:445-453.

Passini MA, et al. Antisense Oligonucleotides Delivered to the Mouse CNS Ameliorate Symptoms of Severe Spinal Muscular Atrophy. Sci Transl Med. 2011; 3(72):72ra18.

Phan DQ, Silka MJ, Lan YT, et al. Comparison of formulas for calculation of the corrected QT interval in infants and young children. J Pediatr. 2015;166:960-964.

Porensky PN, et al. A single administration of morpholino antisense oligomer rescues spinal muscular atrophy in mouse. HMG. 2012;21(7):1625-1638.

Reilly MC, Zbrozek AS, Dukes E. The validity and reproducibility of a work productivity and activity impairment measure. PharmacoEconomics. 1993;4(5):353-365.

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

Sumner CJ, Kolb SJ, Harmison GG, et al. SMN mRNA and protein levels in peripheral blood: biomarkers for SMA clinical trials. Neurology. 2006;66:1067-1073.

van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15:708-715.

Varni JW, Seid M, Rode CA. The PedsQL™: measurement model for the pediatric quality of life inventory. Medical Care. 1999;37(2):126-139.

Vuillerot C, Payan C, Girardot F, et al. Responsiveness of the motor function measure in neuromuscular diseases. Arch Phys Med Rehabil. 2012;93:2251–2256.

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

Week	Screening[a]		Week 1			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12[e]	Weeks 13-16	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[b]	Day 1	Day 7	Day 14	Day 28	Day 42	Day 56	Day 70	Day 84		Day 119	Day 120		Day 182		Day 245	Day 246		Day 301	
	Day 1	Day 2																				
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	
Neurological Examination	x												x					x				
SMA History	x																					
Vital Signs	x		x	4h[t]	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	
Preganancy test urine (home)[i,o]											x				x		x			x		x
Ophthalmological Exam[j]	x								x				x			x		x			x	
Tanner staging[k]			x[k]																			

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

Week	Screening[a]		Week 1			Week 2	Week 4	Week 6	Week 8	Week 10	Week 12[e]	Weeks 13-16	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[b]	Day 1	Day 7	Day 14	Day 28	Day 42	Day 56	Day 70	Day 84		Day 119	Day 120		Day 182		Day 245	Day 246		Day 301	
	Day 1	Day 2																				
Visit Window						+/-1	+/-3	+/-3	+/-3	+/-3	+/-3		+/-7			+/-7		+/-7			+/-7	
Assessments																						
Blood Sample for protein binding		X																				
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	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
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
Adverse Events	X[s]		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
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

Appendix 1 Schedule of Assessments: Part 1 Week 52 to Completion (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]				*Completion / Early Withdrawal*[a]		*Phone call*
Day	Day 364	Day 365		Day 427		Day 490		Day 546	Day 547		Day 609		Day 672		Day 728	Day 729	Every 13 wks	Every 26 weeks[a] D1	Every 26 weeks[a] D2	Resupply visit	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[v]		5				x					5					x			x			x	
ECG-12 lead[t]	x					x					x[u]				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	
Blood Chemistry[t]		x				x					x					x			x			x	
Coagulation[t]		x				x										x			x			x	
Urinalysis[t]		x														x			x			x	
Hormone Panel[h,t]																x							
Pregnancy test blood[i]		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		
Tanner staging[k]															x[k]			x[k]			x		

Appendix 1 Schedule of Assessments: Part 1 Week 52 to Completion (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]				*Completion / Early Withdrawal*[a]		*Phone call*
Day	Day 364	Day 365		Day 427		Day 490		Day 546	Day 547		Day 609		Day 672		Day 728	Day 729	Every 13 wks	Every 26 weeks[a] D1	Every 26 weeks[a] D2	Resupply visit	D1	D2	*Comp/EW +30 days*
Visit Window	+/-7			+/-7		+/-7		+/-7			+/-7		+/-7		+/-7		+/- 14 days	+/- 14 days					+/-7
Assessments																							
Blood Sample for protein binding																							
In vivo mRNA[v]		x														x						x	
SMN protein[v]		x														x		x				x	
MFM[w]	x							x							x			x			x		
Pulmonary testing[x]	x							x							x			x			x		
RULM/HMFSE[w]		x							x							x			x			x	
C-SSRS[l]	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[l]																							
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			*x*[y]		
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		
Adverse Events	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	
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	

Appendix 1 Schedule of Assessments: Part 1 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 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 *used and* unused *study* drug *bottles* 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 *used and* unused *study* drug *bottles* 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. *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 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 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 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 *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 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.

Appendix 1 Schedule of Assessments: Part 1 Footnotes

n Not required if screening sample < 30 days.

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.

y *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 2 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
Completion / Early Withdrawal		***	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 3 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[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	
	Day 1	Day 2																		
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	
Preganancy test urine (home)[i,o]										x			x		x			x		x
Ophthalmological Exam[j]	x								x		x			x		x			x	
Tanner staging[k]			x																	

Appendix 3 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[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	
	Day 1	Day 2																		
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
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 3 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	Every 26 weeks[a] D2	Resupply visit	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			x	
Blood Chemistry[t]		x					x					x					x			x			x	
Coagulation[t]		x					x					x					x			x			x	
Urinalysis[t]		x															x			x			x	
Hormone Panel[h,t]																	x							
Pregnancy test blood[i]		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		
Tanner staging[k]																x			*x*			x		

Appendix 3 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	Every 26 weeks[a] 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
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	
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	

Appendix 3 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 6) 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.

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

Appendix 3 Schedule of Assessments: Part 2 Footnotes

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 4
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 5 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[c]	*Completion* / Early withdrawal
Best corrected visual acuity	X	X	X	X	X	X	X	X	X	X	X	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	X
Slit Lamp and fundus examinatior	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
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[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 examinatior	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 6 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 examinatior	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 examinatior	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)