Official Title: A Phase I, 2-Part, Open-Label Study to Investigate the Safety, Tolerability, and Pharmacokinetics of Multiple Doses of Risdiplam and the Effect of Risdiplam on the Pharmacokinetics of Midazolam Following Oral Administration in Healthy Participants

NCT Number: NCT03988907

Document Date: Protocol Version 1: 23-April-2019

PROTOCOL

TITLE:	**A PHASE I, 2-PART, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE DOSES OF RISDIPLAM AND THE EFFECT OF RISDIPLAM ON THE PHARMACOKINETICS OF MIDAZOLAM FOLLOWING ORAL ADMINISTRATION IN HEALTHY PARTICIPANTS**
PROTOCOL NUMBER:	BP41361
VERSION:	1
IND NUMBER:	128972
TEST PRODUCT:	Risdiplam (RO7034067)
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	See electronic date stamp below

Approver's Name	**Title**	**Date and Time (UTC)**
[redacted]	Company Signatory	23-Apr-2019 14:02:50

FINAL PROTOCOL APPROVAL

PROTOCOL ACCEPTANCE FORM

TITLE:	**A PHASE I, 2-PART, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE DOSES OF RISDIPLAM AND THE EFFECT OF RISDIPLAM ON THE PHARMACOKINETICS OF MIDAZOLAM FOLLOWING ORAL ADMINISTRATION IN HEALTHY PARTICIPANTS**
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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 Site Monitor.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AR_{AUC}	Accumulation ratio for AUC
AR_{Cmax}	Accumulation ratio for C_{max}
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC_{inf}	Area under the plasma concentration-time curve extrapolated to infinity
AUC_{last}	Area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration
AUC_{tau}	Area under the plasma concentration-time curve over a dosing interval
BMI	Body mass index
CL_{ss}/F	Apparent total plasma clearance at steady state
C_{max}	Maximum observed plasma concentration
CNS	Central nervous system
CRF	Case Report Form
C_{trough}	Trough observed plasma concentration
CYP	Cytochrome P450
DDI	Drug-drug interaction
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HBcAb	Hepatitis B core antibody
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HRT	Hormonal replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form

ICH	International Conference for/Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
IND	Investigational New Drug (application)
IRB	Institutional Review Board
LPLV	Last participant, last visit
NSAESI	Non-serious adverse event of special interest
OTC	Over-the-counter
PK	Pharmacokinetic(s)
PR	Pulse rate
QD	Once daily
QRS	QRS complex
QT	QT interval
QTc	QT corrected for heart rate
QTcF	QT corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RR	RR interval
SAE	Serious adverse event
SMA	Spinal muscular atrophy
SMN	Survival motor neuron
SoA	Schedule of Activities
$t_{½}$	Apparent plasma terminal elimination half-life
$\mathbf{T_{max}}$	Time of maximum observed plasma concentration
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WOCBP	Woman of childbearing potential
WONCBP	Woman of non-childbearing potential

1. PROTOCOL SUMMARY

1.1 SYNOPSIS

PROTOCOL TITLE:	A PHASE I, 2-PART, OPEN-LABEL STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, AND PHARMACOKINETICS OF MULTIPLE DOSES OF RISDIPLAM AND THE EFFECT OF RISDIPLAM ON THE PHARMACOKINETICS OF MIDAZOLAM FOLLOWING ORAL ADMINISTRATION IN HEALTHY PARTICIPANTS
SHORT TITLE:	RISDIPLAM MULTIPLE DOSE AND MIDAZOLAM DRUG-DRUG INTERACTION STUDY
PROTOCOL NUMBER:	BP41361
VERSION:	1
TEST PRODUCT:	Risdiplam (RO7034067)
PHASE:	I

RATIONALE

Part 1 of this study will investigate the safety, tolerability, and pharmacokinetics (PK) of multiple oral doses of risdiplam administered once daily (QD) for 14 days to healthy participants. To date, risdiplam has not been investigated as a multiple-dose QD regimen in healthy participants; all previous Phase I studies have been single-dose studies. The PK and safety data collected in Part 1 will be used to define the dose and to enable the start of Part 2 of this study.

Part 2 of this study will assess the effect of multiple oral doses of risdiplam on the PK of midazolam following administration to healthy participants, to check for drug-drug interaction of risdiplam with cytochrome P450 3A substrates.

OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To investigate the effect of multiple oral doses of risdiplam on the pharmacokinetics (PK) of a single oral dose of midazolam in healthy participants.	Midazolam concentrations and thereof derived PK parameters for midazolam (and its metabolite[s] as appropriate) alone and in combination with risdiplam.
Secondary	
To assess the safety and tolerability of a single oral dose of midazolam alone and in combination with multiple oral doses of risdiplam in healthy participants.	Incidence and severity of adverse events (AEs); changes in vital signs, physical findings, electrocardiogram (ECG) parameters, and clinical laboratory test results during and after midazolam administration alone and in combination with risdiplam.

To assess the safety and tolerability of multiple oral doses of risdiplam administered once daily (QD) for 14 days.	Incidence and severity of AEs; changes in vital signs, physical findings, ECG parameters, and clinical laboratory test results during and after administration of multiple doses of risdiplam.
To assess the PK of risdiplam (and its metabolite[s] as appropriate) following multiple oral doses of risdiplam QD for 14 days.	Concentrations and thereof derived PK parameters for risdiplam and its metabolite(s) as appropriate.

OVERALL DESIGN

Study Design

This will be a Phase I, 2-part, open-label, non-randomized study to investigate the safety, tolerability, and PK of multiple doses of risdiplam (Part 1) and the effect of risdiplam on the PK of midazolam (Part 2) following oral administration in healthy adult male and female participants.

Treatment Groups and Duration

Study Treatment Name:	Risdiplam (RO7034067)	Midazolam (Part 2 only)
Dose Formulation:	Powder for constitution to an oral solution	Solution
Dose:	5 mg (6.66 mL) (Part 1)	2 mg (1 mL)
Route of Administration:	Oral	Oral

Note: The risdiplam dose for Part 2 will be defined based on Part 1 data.

Length of Study

The total duration of the study for each participant will be up to approximately 8 weeks divided as follows:

- Screening: Up to 27 days (Days -28 to -2).
- In clinic period: Day -1 to Day 16 (Part 1) or Day -1 to Day 18 (Part 2).
- Non-residential visits: Days 18 and 20 (Part 1) or Days 20 and 22 (Part 2).
- Safety Follow-up (Post-study): 10±2 days post final dose of study drug in Parts 1 and 2.

End of Study

The end of the study is defined as the date when the last participant last visit occurs.

PARTICIPANT POPULATION

The participants in this study will be healthy female and male volunteers between 18 and 55 years of age, inclusive, who fulfill all of the given eligibility criteria.

Inclusion/Exclusion Criteria

Inclusion Criteria

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

1. Willingness and ability to provide written consent to participate in the clinical trial.
2. Healthy participants.

Healthy status is defined by the Investigator based on detailed review of medical and surgical history, results of physical examination, vital signs, 12-lead ECG, and laboratory assessments (hematology, coagulation, blood chemistry, serology, and urinalysis).

3. Male and female participants aged 18 to 55 years of age, inclusive, at Screening.

a) Female participants: A female participant is eligible to participate if she is a woman of non-childbearing potential (WONCBP).

4. A body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, at Screening.

5. Use of adequate contraception methods during the treatment period and until 4 months after last study drug administration. Males must refrain from donating sperm during this same period.

a) Contraception methods for male participants considered as acceptable for the study:

- With non-pregnant female partners, use contraceptive measures such as a condom with spermicide plus an additional contraceptive method that together result in a failure rate of <1% per year, with partners who are women of childbearing potential. The additional contraceptive method must be 1 of the following: diaphragm in combination with spermicide, intrauterine device, injectable or implantable contraceptives, oral hormonal contraceptives (e.g., "progesterone only pills," tablets, patch, or vaginal ring with both estrogen and progesterone). Contraception is required during the treatment period and for at least 4 months after the last dose of risdiplam.
- With pregnant female partners, use contraceptive measures such as a condom to avoid exposing the embryo during the treatment period and for at least 28 days after the last dose of risdiplam.

Abstinence (including those who practice abstinence as part of their normal and preferred lifestyle, periodic abstinence, e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception in this study.

Note that only WONCBP and men are eligible for the study.

6. Willingness and ability to complete all aspects of the study.

Exclusion Criteria

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

1. History of any clinically significant GI, renal, hepatic, broncho-pulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological, or allergic disease, metabolic disorder, cancer, or cirrhosis.
2. 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 participant in this study, including but not limited to the following:
   - Any major illness within 1 month before Screening or any febrile illness within 1 week prior to Screening and up to first study drug administration.
3. History or evidence of any medical condition potentially altering the absorption, metabolism, or elimination of drugs.
4. Surgical history of the GI tract affecting gastric motility or altering the GI tract (with the exception of uncomplicated appendectomy and hernia repair) (a cholecystectomy is exclusionary).
5. History or presence of clinically significant ECG abnormalities (based on the average of 3 consecutive measurements [if the first measurement is out of range, complete 2 more and take the average]) (e.g., PQ/PR interval >210 ms, QT interval corrected for heart rate using Fridericia's formula [QTcF] >450 ms for males and QTcF >470 ms for females) 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).
6. History of malignancy in the past 5 years.
7. Confirmed (based on the average of 3 consecutive measurements [if the first measurement is out of range, complete 2 more and take the average]) systolic blood pressure >140 or <90 mmHg, and diastolic blood pressure >90 or <50 mmHg at Screening only.
8. Confirmed (based on the average of 3 consecutive measurements) resting pulse rate (PR) >100 or <40 bmp at Screening only.
9. Clinically significant abnormalities (as judged by the Investigator) in laboratory test results (including hematology, chemistry panel, and urinalysis). In case of uncertain or questionable results, tests performed during Screening may be repeated on Day -1 to confirm eligibility.

10. Positive result on human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B virus, or hepatitis C virus (serology) tests at Screening.
11. Any suspicion or history of alcohol abuse and/or any history or suspicion of regular consumption/addiction of drugs of abuse within 2 years prior to study drug administration or a positive drug screen test as performed at Screening.
12. Any consumption of tobacco-containing products (including but not limited to the following: smoking cigarettes, cigars, etc.) from 1 month before Screening until Follow-up.
13. Donation of blood or blood products for transfusion over 500 mL within 3 months prior to first study drug administration and for the duration of the study.
14. Participation in an investigational drug medicinal product or medical device study within 90 days prior to Screening.
15. Use of prohibited medications or herbal remedies.
16. Any clinically significant history of hypersensitivity or allergic reactions, either spontaneous or following study drug administration, or exposure to food or environmental agents.
17. History of hypersensitivity to any of the excipients in the formulation of the study drug.
18. History of hypersensitivity to midazolam or any other benzodiazepine or its formulation ingredients (this applies to participants in Part 2 only).
19. For Part 2 participants: history of acute angle glaucoma.
20. Participants who, in the Investigator's judgment, pose a suicidal risk, or any participant with a history of suicidal or homicidal attempts.
21. Participants under judicial supervision, guardianship, or curatorship.
22. Participants who, in the opinion of the Investigator, should not participate in this study.

NUMBER OF PARTICIPANTS

In total a maximum of 40 participants may be enrolled in this study as follows:

- Part 1: 8 participants will be enrolled in order to obtain 6 evaluable participants.
- Part 2: 28 participants will be enrolled in order to obtain at least 26 evaluable participants.

The additional 4 participants are in case the dropout rate in Part 2 is higher than expected in order to achieve 26 evaluable participants.

CONCOMITANT MEDICATIONS

No concomitant medication is permitted, except acetaminophen, hormone replacement therapy for post-menopausal women, and medication to treat AEs.

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) and any non-medication interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy) used by a participant from 30 days prior to Screening until the Follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates), and dosage information (including dose and frequency).

Permitted Therapy

Participants who use hormone replacement therapy should continue their use.

Acetaminophen, at doses of $\leq$ 2 g/day, is permitted for use as needed. Other concomitant medication required to treat AEs may be considered on a case-by-case basis by the Investigator.

Prohibited Therapy

All medications (prescription and OTC) taken within 30 days of Screening will be recorded on the appropriate eCRF.

As a general rule, no concomitant medication will be permitted, with the exception of acetaminophen, hormone replacement therapy for post-menopausal women, and medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor and archived in the site file.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 14 days or 5 half-lives (whichever is longer) before the start of study treatment until completion of the Follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

The following medications are explicitly prohibited:

- Any inhibitor of CYP3A4 (e.g., ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, cimetidine).
- Any inducer of CYP3A4 (e.g., rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John's wort).
- Any organic cation transporter 2 and MATE substrates (e.g., amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acycolovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine).
- Medications with known or potential retinal toxicity (e.g., chloroquine and hydroxychloroquine, thioridazine, retigabin, vigabatrin, desferoxamine, topiramate, latanoprost, niacin, rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon, chronic use of minocycline).

1.2 SCHEDULE OF ACTIVITIES

The Schedule of Activities is provided in Table 1.

Table 1 Schedule of Activities

Part 1:

	Screening (Days -28 to -2)	Day -1	Days 1 to 20	Post-study (10±2 days post final dose)/Early Termination
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Demographic data	X			
Medical history	X			
Urine drugs of abuse screen (including cotinine) and alcohol test (refer to Appendix 4)	X	X		
Confirmation of non-childbearing potential (females only) (refer to Appendix 4)	X			
Pregnancy test (females only) [a] (refer to Appendix 4)	X	X		X
Serology (refer to Appendix 4)	X			
Study residency:				
Check-in		X		
Check-out			Day 16: Following 48-hour PK sample collection	
Non-residential visit	X		Day 18 and Day 20	X
Study drug administration:			risdiplam: Days 1 to 14, once daily	
Safety and tolerability:				
Adverse event questioning		X	Ongoing	X
Vital signs (supine) [b] and 12-lead ECG	X		Day 1: Predose Day 7: Predose Day 14: Predose Day 16: 48 hours after last study drug administration	X
Clinical laboratory evaluations (refer to Appendix 4)	X	X	Day 7: Predose Day 14: Predose Day 16: 48 hours after last study drug administration	X

	Screening (Days -28 to -2)	Day -1	Days 1 to 20	Post-study (10±2 days post final dose)/Early Termination
Body weight, height, and BMI [c]	X	X		
Physical examination [d]	X	X		X
Pharmacokinetics:				
Blood sampling for risdiplam PK			Day 1: Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours postdose Day 2 to Day 13: Predose Day 14: Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 96, and 144 hours postdose	

Abbreviations: BMI = body mass index; ECG = electrocardiogram; PK = pharmacokinetic.
[a] Performed in serum.
[b] Systolic and diastolic blood pressure, pulse rate, and oral body temperature (oral body temperature at Screening and Day 1 predose only).
[c] Height and BMI at Screening only.
[d] Complete physical examination at Screening; brief physical examination thereafter.

Part 2:

	Screening (Days -28 to -2)	Day -1	Days 1 to 22	Post-study (10±2 days post final dose)/Early Termination
Informed consent	X			
Inclusion/exclusion criteria	X	X		
Demographic data	X			
Medical history	X			
Urine drugs of abuse screen (including cotinine) and alcohol test (refer to Appendix 4)	X	X		
Confirmation of non-childbearing potential (females only) (refer to Appendix 4)	X			
Pregnancy test (females only) [a] (refer to Appendix 4)	X	X		X
Serology (refer to Appendix 4)	X			
Study residency:				
Check-in		X		
Check-out			Day 18: Following 48-hour risdiplam PK collection	
Non-residential visit	X		Day 20 and Day 22	X
Study drug administration:			midazolam: Days 1 and 15 (administered 1 hour after the risdiplam dose on Day 15) risdiplam: Days 3 to 16	
Safety and tolerability:				
Adverse event questioning		X	Ongoing	X
Vital signs (supine) [b] and 12-lead ECG	X		Day 1: Predose, 1, 2, 4, and 6 hours postdose Day 3: Predose, 2, 4, 6, and 12 hours postdose Day 7: Predose Day 15: Predose, 1, 2, 4, and 6 hours postdose Day 16: Predose Day 18: 48 hours after last study drug administration Day 22	X

	Screening (Days -28 to -2)	Day -1	Days 1 to 22	Post-study (10±2 days post final dose)/Early Termination
Clinical laboratory evaluations (refer to Appendix 4)	X	X	Day 3: Predose Day 7: Predose Day 15: Predose Day 18: 48 hours after last study drug administration Day 22	X
Body weight, height, and BMI [c]	X	X		
Physical examination [d]	X	X		X
Pharmacokinetics:				
Blood sampling for midazolam PK			Day 1 and Day 15: Predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours postdose	
Blood sampling for risdiplam PK			Day 3: Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, and 12 hours postdose Day 4 to Day 15: Predose Day 16: Predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 96, and 144 hours postdose	

Abbreviations: BMI = body mass index; ECG = electrocardiogram; PK = pharmacokinetic.

Note: Nominal timepoints refer to the timepoint of risdiplam dose administration, with the exception of midazolam PK sampling and vital signs and ECG on Day 1, which refer to the timepoint of midazolam dose administration. The midazolam PK sample at 1 hour postdose corresponds to the same time of day as the risdiplam 2-hour postdose sample.

[a] Performed in serum.
[b] Systolic and diastolic blood pressure, pulse rate, and oral body temperature (oral body temperature at Screening and Day 1 predose only).
[c] Height and BMI at Screening only.
[d] Complete physical examination at Screening; brief physical examination thereafter.

2. INTRODUCTION

Refer to the Investigator's Brochure (IB)[1] for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational medicinal product (IMP).

2.1 OVERVIEW OF THE DISEASE

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness beginning in infancy.[2,3] It is the leading genetic cause of mortality in infants and young children, with an incidence of 1 in approximately 11,000 live births, and a carrier frequency estimated at between 1 in 50 and 1 in 70.[4]

SMA is pathologically characterized by the degeneration of alpha motor neurons within the anterior horn of the spinal cord, leading to skeletal muscle weakness and atrophy. Muscle weakness and atrophy are symmetrical and progressive, often impacting the legs more than the arms, eventually leading to a decline in intercostal muscle strength. Respiratory failure and complications of orthopedic deformity account for the majority of deaths in patients with SMA.[5]

SMA is caused by homozygous deletion (95% of cases) or mutation of the *survival motor neuron* (*SMN)1* gene.[6] In humans, there are 2 SMN genes (telomeric *SMN1* gene and centromeric *SMN2* gene), which originated from an intrachromosomal duplication of 5q13 and subsequent divergence due to genetic drift. Species, other than humans, have only 1 *SMN* gene, which is equivalent to the human *SMN1* gene. *SMN2* differs from *SMN1* by the presence of a translationally synonymous C→T mutation at nucleotide 6 in exon 7. As a result of this, the *SMN2* pre-mRNA undergoes alternative splicing which excludes exon 7 from 85% to 90% of *SMN2* transcripts, which produces an unstable SMNΔ7 protein that is rapidly degraded.[7] In the remaining 10% to 15% of splicing events, the full-length *SMN2* mRNA is generated, leading to the production of functional full-length SMN protein. Accordingly, patients with SMA lacking a functioning *SMN1* gene are dependent on their *SMN2* gene and SMA is the consequence of decreased, insufficient levels of full-length functional SMN protein which is produced only by the *SMN2* gene.[8]

2.2 OVERVIEW OF RISDIPLAM

There is currently no approved oral treatment that provides stabilization or improvement of motor function to patients with SMA. One of the promising strategies currently being pursued is to increase SMN protein levels in patients with SMA by modulating *SMN2* splicing to favor the inclusion of exon 7 into the mRNA transcript, thus increasing expression of stable full-length protein from the *SMN2* gene.[8,9] One such compound currently being developed is risdiplam (RO7034067), which directly targets the underlying molecular deficiency of SMA, to promote the inclusion of exon 7 to generate full-length *SMN2* mRNA, increasing the production of functional SMN protein. The

increase in SMN protein following treatment with risdiplam has been shown in fibroblasts and motor neurons derived from patients with SMA, and in clinical trials in patients with SMA.

2.2.1 Summary of Clinical Experience

The Phase I development of risdiplam comprised 3 completed studies in healthy subjects: a single-ascending dose study including an exploratory investigation of the effect of food and an itraconazole interaction part (Study BP29840), a study to investigate potential differences in the pharmacokinetic (PK) and safety and tolerability of risdiplam in healthy Japanese subjects compared with Caucasians (Study NP39625), and a mass balance study (Study BP39122).

Currently, 3 clinical studies in patients with SMA are ongoing: a study in children and young adults with Type 2 and Type 3 SMA (Study BP39055) and in infants with Type 1 SMA (Study BP39056), and an exploratory study in patients with SMA previously treated with another SMA therapy (Study BP39054). A study to assess the efficacy, safety and tolerability, and PK/pharmacodynamics of risdiplam in pre-symptomatic infants genetically diagnosed with SMA is in preparation.

2.2.1.1 Safety

In Study BP29840, single doses of risdiplam administered alone at doses of 0.6 mg, 2 mg, 6 mg, and 18 mg, or 6 mg in combination with itraconazole were well tolerated in healthy male subjects. There were no deaths, serious adverse events (SAEs), or withdrawals due to AEs. Overall, 27 AEs were reported, all of which were mild in intensity and resolved within a short period of time without sequelae. With the exception of 2 AEs (pollakiuria [placebo] and headache [18 mg risdiplam]), all events were considered by the Investigator to be unrelated to risdiplam. The most frequently affected system organ class was gastrointestinal (GI) disorders (9 AEs) and nervous system disorders (4 AEs). The most frequently reported AEs were headache (4 subjects) and diarrhea, abdominal pain, and nasopharyngitis (3 subjects each). There were no dose-related increases 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. Although there were no safety findings at any dose administered, dose escalation was stopped at 18 mg, as the protocol-specified plasma exposure cap of 1500 h.ng/mL for area under the plasma concentration-time curve (AUC) from time zero to 24 hours postdose on an individual basis for healthy subjects only was approached with this dose.

Study NP39625 in healthy Japanese subjects demonstrated that single oral doses of risdiplam at 2 mg, 6 mg, and 12 mg were well tolerated with no marked differences in the safety profile between Japanese and Caucasian subjects. There were no SAEs, AEs leading to withdrawal from the study, or severe AEs reported. Overall, 12 AEs were reported, of which 10 were visual AEs reported in 6 subjects (visual acuity reduced in 2 subjects who received placebo; bilateral cataracts and visual acuity reduced, and bilateral cataracts and vision blurred in 2 subjects who received 6 mg risdiplam; and

visual acuity reduced in 2 subjects who received 12 mg risdiplam). The events of visual acuity reduced in the placebo and 12 mg risdiplam groups and 1 of the bilateral cataract cases in the 6 mg risdiplam group were considered by the Investigator to be related to study treatment. However, the clinically trained ophthalmologist from the central reader Optic Nerve Research Center assessed that the findings were pre-existing cataracts that had worsened, which is in keeping with the natural history of the condition. No evidence was observed suggesting that the AEs of vision blurred or the worsened cataracts were related to the study medication. The Sponsor assessed the events as unrelated to study medication based on asymmetrical findings in both eyes, exposure to a single dose of study medication, no similar findings in other patients exposed to multiple doses (caveat higher age/Asian ethnicity), no findings in the previous healthy subject study with single ascending doses up to 18 mg (Study BP29840), no preclinical findings in lens, consideration that cataracts appear significantly earlier in Asians compared to Caucasians and therefore the study subject was at significant risk for cataract irrespective of study therapy.

In Study BP39122, a single oral dose of 18 mg of [^{14}C/^{12}C]-risdiplam was well tolerated in healthy male subjects. All 6 subjects reported at least 1 AE, the most frequent being dry skin (3 subjects). There were no severe AEs or AEs leading to withdrawal from study treatment. One subject reported an SAE of pneumonia, which was assessed by the Investigator as unrelated to study treatment and resolved upon supportive treatment.

In none of these studies were there any clinically significant treatment or dose-dependent changes compared with baseline in vital signs, electrocardiograms (ECGs), laboratory parameters, or ophthalmological assessments.

Risdiplam has, so far, been well tolerated in the 3 currently ongoing clinical studies in patients with SMA, with a treatment duration of up to more than 1 year (with once daily [QD] administration). For further information, refer to the IB.[1]

2.2.1.2 Pharmacokinetics

In the completed single-ascending dose study (including exploratory investigation of the effect of food and itraconazole interaction) in healthy adults (Study BP29840), risdiplam was rapidly absorbed with a median time of maximum observed plasma concentration (T_{max}) between 2 and 3 hours postdose under fasted conditions. The maximum observed plasma concentration (C_{max}) and AUC increased in a dose-proportional manner. The apparent plasma terminal elimination half-life ($t_{½}$) was approximately 41 hours to 64 hours. On average, a small fraction (<10%) of the administered dose was excreted unchanged into urine. Food had no relevant effect on the PK of risdiplam; only median T_{max} was delayed to 4.5 hours postdose. Itraconazole had a minor effect on the PK of a single oral dose of risdiplam resulting in an increase (11%) of the AUC from time zero to 120 hours postdose and a reduction (9%) of the C_{max}.

A mass balance study (Study BP39122) with single-dose administration of [^{14}C/^{12}C]-risdiplam was conducted in healthy adult subjects. The mean overall recovery of total administered [^{14}C]-radioactivity was 81.4%, ranging from 60.3% to 89.6%. The major pathway of elimination of [^{14}C]-radioactivity was fecal excretion with, on average, 53.2% of the dose administered; urinary excretion of [^{14}C]-radioactivity accounted for, on average, 28.2% of the dose administered.

Study NP39625 demonstrated no relevant differences in plasma or urine PK parameters, or the pharmacodynamic effects of risdiplam on SMN mRNA and SMN protein, between Japanese and Caucasian healthy subjects.

M1 was confirmed as the major metabolite in patients with SMA, but it is not pharmacologically active. The median M1-to-parent ratio of all trough samples was approximately 30% with no apparent dose, time, body weight, or age dependency.

2.3 STUDY RATIONALE

This study will assess the effect of risdiplam on the PK of the sensitive cytochrome P450 (CYP)3A substrate midazolam, as measured by midazolam systemic exposure.

An in vitro signal for time-dependent inhibition of CYP3A by risdiplam has been identified recently. The assessment of time-dependent inhibition in vivo requires multiple-dose administration of risdiplam for 2 weeks as QD dosing. To date, however, risdiplam has not been investigated as a multiple-dose regimen in healthy participants; all previous Phase I studies have been single-dose studies. Therefore, Part 1 of this study will investigate the safety, tolerability, and PK of multiple oral doses of risdiplam administered QD for 14 days to healthy participants. After review of Part 1 data, Part 2 of the study will begin.

Part 2 of this study will assess the effect of multiple doses of risdiplam on the PK of midazolam following oral administration to healthy participants, to check for drug-drug interaction (DDI) of risdiplam with CYP3A substrates.

The rationale for the study design is provided in Section 4.2.

2.4 BACKGROUND

2.4.1 Background on Risdiplam

Refer to Section 2.1 for an overview of the disease SMA and to Section 2.2 for an overview of risdiplam.

A detailed description of the chemistry, pharmacology, efficacy, and safety of risdiplam is provided in the IB.[1]

2.4.2 Background on Midazolam

Midazolam is a short-acting benzodiazepine. Midazolam is the paradigm marker substrate for the in vivo assessment of CYP3A activity recommended by the Food and Drug Administration (FDA) and European Medicines Agency (EMA).[10]

Midazolam is rapidly absorbed after oral administration and is subject to substantial intestinal and hepatic first-pass metabolism. Midazolam is primarily metabolized in the liver and gut by human CYP3A to its pharmacologically active metabolite 1-OH-midazolam. In the subsequent UDP-glucuronosyltransferase-mediated phase II-reaction, the main urinary metabolite 1'-OH-midazolam-glucuronide is formed; 63% to 80% of the dose is found conjugated in the urine within 24 hours, while only 1% is excreted unchanged. The mean $t_{½}$ of midazolam ranges from 2.2 to 6.8 hours following single oral dose administration.

The PK interactions with CYP3A inhibitors or inducers are of higher magnitude on oral administration of midazolam compared to intravenous administration, particularly because CYP3A is also present in the upper GI tract. The reason for this is that by the oral administration route, both systemic clearance and bioavailability are subject to change, while by the parenteral administration route, only the systemic clearance will be affected.

Pharmacodynamic properties of midazolam and its metabolites include sedative, anxiolytic, amnesic, and hypnotic activities. Benzodiazepine pharmacological effects appear to result from reversible interactions with the γ-amino butyric acid benzodiazepine receptor in the central nervous system (CNS), the major inhibitory neurotransmitter in the CNS.[11]

An oral dose of 2 mg of midazolam will be used in this study.

2.5 BENEFIT/RISK ASSESSMENT

Participants in the current study will not receive any health benefit (beyond that of an assessment of their medical status) from participating in the study. The risks of participation are primarily those associated with adverse reactions to the study treatments, although there may also be some discomfort from collection of blood samples and other study procedures. However, the potential risks for any participant due to the treatment with risdiplam, midazolam (applicable to patients enrolled in Part 2 only), or study-related procedures are considered minimal and are outweighed by the opportunity for developing a new oral treatment for SMA.

To minimize any potential risk, participants will be carefully selected in line with eligibility criteria and closely monitored for safety and will be under continuous medical observation during the course of the study.

Single doses of up to 18 mg risdiplam were well tolerated in healthy participants previously, and patients with SMA have received doses of up to 5 mg risdiplam QD for more than 1 year without any obvious drug-related safety signals.

More detailed information about the potential risks associated with administration of risdiplam is provided in the IB.[1]

3. OBJECTIVES AND ENDPOINTS

The objectives and corresponding endpoints are provided in Table 2.

Table 2 Objectives and Endpoints

Objectives	Endpoints
Primary	
To investigate the effect of multiple oral doses of risdiplam on the pharmacokinetics (PK) of a single oral dose of midazolam in healthy participants.	Midazolam concentrations and thereof derived PK parameters for midazolam (and its metabolite[s] as appropriate) alone and in combination with risdiplam.
Secondary	
To assess the safety and tolerability of a single oral dose of midazolam alone and in combination with multiple oral doses of risdiplam in healthy participants.	Incidence and severity of adverse events (AEs); changes in vital signs, physical findings, electrocardiogram (ECG) parameters, and clinical laboratory test results during and after midazolam administration alone and in combination with risdiplam.
To assess the safety and tolerability of multiple oral doses of risdiplam administered once daily (QD) for 14 days.	Incidence and severity of AEs; changes in vital signs, physical findings, ECG parameters, and clinical laboratory test results during and after administration of multiple doses of risdiplam.
To assess the PK of risdiplam (and its metabolite[s] as appropriate) following multiple oral doses of risdiplam QD for 14 days.	Concentrations and thereof derived PK parameters for risdiplam and its metabolite(s) as appropriate.

4. STUDY DESIGN

4.1 OVERALL DESIGN

This will be a Phase I, 2-part, open-label, non-randomized study to investigate the safety, tolerability, and PK of a multiple-dosing regimen of risdiplam (QD; Part 1) and the effect of risdiplam on the PK of midazolam (Part 2) following oral administration in healthy adult male and female participants.

In total a maximum of 40 participants may be enrolled in this study as follows:

- Part 1: 8 participants will be enrolled in order to obtain at least 6 evaluable participants.
- Part 2: 28 participants will be enrolled in order to obtain at least 26 evaluable participants.

The additional 4 participants are in case the dropout rate in Part 2 is higher than expected in order to achieve 26 evaluable participants. Participants enrolled in Part 1 of this study must not be enrolled in Part 2.

In Part 1, participants will receive a dose of 5 mg risdiplam QD for 14 consecutive days. The dose of 5 mg risdiplam has been shown to be safe and well tolerated for more than 1 year of treatment in patients with SMA. The decision to proceed to Part 2 of the study will be made following review of all available safety and tolerability data, including AEs, ECGs, vital signs, laboratory safety test results (i.e., hematology, clinical chemistry, and urinalysis) collected up to (and including) 48 hours after last study drug administration and available plasma PK data up to (and including) 24 hours after last study drug administration from a minimum of 4 Part 1 participants. The risdiplam dose in Part 2 will be determined based on the PK and safety data obtained in Part 1, with the aim to achieve an average exposure (mean AUC over a dosing interval [AUC_{tau}] at steady state) of 2000 ng.h/mL in Part 2 (i.e., the therapeutic exposure observed in SMA patients).

A Dose Escalation Meeting will be conducted prior to the start of Part 2 (see Section 4.1.1), in order to evaluate the Part 1 data and to select the risdiplam dose to be administered in Part 2 of this study.

In Part 2, all study participants will receive a single oral dose of 2 mg midazolam on Day 1. On Day 3, the 14-day QD treatment period with risdiplam will begin (targeting a mean AUC_{tau} at steady state of 2000 ng.h/mL; the precise dose will be based on the results of Part 1), with single dose administration of 2 mg midazolam again on Day 15 (1 hour after the thirteenth dose of risdiplam).

In both study parts, PK blood samples will be collected at timepoints specified in Table 1. Safety monitoring will be performed throughout the study as described in Section 8.2. The Schedule of Activities (SoA) for Parts 1 and 2 is provided in Table 1.

4.1.1 Dose-decision Criteria

The decision to proceed to Part 2 will be made following review of all safety and tolerability information collected up to 48 hours after last study drug administration (including AEs, ECGs, vital signs, and clinical laboratory test results), and of all PK data collected up to (and including) 24 hours after last study drug administration in Part 1 from a minimum of 4 participants. The dose of risdiplam to be administered in Part 2 will be selected to target a mean AUC_{tau} at steady state of 2000 ng.h/mL (the therapeutic

exposure observed in patients with SMA). The dose to be administered in Part 2 may only be greater than in Part 1 if the dose of 5 mg of risdiplam tested in Part 1 was safe and well tolerated and stopping rules were not met.

The decision to proceed to Part 2 will be made jointly by the Sponsor Clinical Pharmacologist and the Investigator and any other person(s) they consider necessary to assist with the decision.

The maximum possible dose for Part 2 is 18 mg of risdiplam, and this dose will not be exceeded under any circumstances.

4.1.2 Stopping Rules Criteria

The dose of risdiplam in Part 2 will not be increased beyond 5 mg, if 1 of the following circumstances occurs in participants treated with 5 mg risdiplam in Part 1, unless it is obvious that the occurrence is not related to the administration of risdiplam.

- Severe AEs of the same type in $\geq$ 50% of participants.
- Clinically significant laboratory abnormalities of the same type in $\geq$ 50% of participants.
- Clinically significant changes in ECGs of the same type in $\geq$ 50% participants.
- Other findings, which at the joint discretion of the Sponsor Clinical Pharmacologist and the Investigator, indicate that the dose in Part 2 should not be increased.

4.1.3 Individual Stopping Rules

Dosing will be stopped in a given individual participant if, compared to baseline (as applicable), 1 of the following circumstances occurs, unless it is obvious that the occurrence is not related to the administration of risdiplam:

- An SAE.
- Any elevation of alanine aminotransferase (ALT) $>$ 3 x upper limit of normal (ULN), with an associated increase in bilirubin $>$ 2 x ULN, and with aspartate aminotransferase (AST) $<$ 2 x ULN, in the absence of an alternative explanation.
- Other findings that, at the joint discretion of the Sponsor Clinical Pharmacologist and the Investigator, indicate that dosing should be stopped.

4.1.4 Communication Strategy

In Part 1, there will be an ongoing review of available data. A dose-decision meeting will be conducted between the Sponsor study team and the Investigator prior to start of Part 2.

4.1.5 Length of the Study

The total duration of the study for each participant will be up to approximately 8 weeks divided as follows:

- Screening: Up to 27 days (Days -28 to -2).
- In clinic period: Day -1 to Day 16 (Part 1) or Day -1 to Day 18 (Part 2).
- Non-residential visits: Days 18 and 20 (Part 1) or Days 20 and 22 (Part 2).
- Safety Follow-up (Post-study): 10±2 days post final dose of study drug in Parts 1 and 2.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The study rationale is provided in Section 2.3.

An in vitro signal for time-dependent inhibition of CYP3A by risdiplam has been identified recently. The assessment of time-dependent inhibition in vivo requires multiple-dose administration of risdiplam for 2 weeks QD dosing. Since risdiplam has not yet been tested as a multiple-dosing regimen in healthy participants, in Part 1 the safety, tolerability, and PK of multiple oral doses of 5 mg risdiplam QD for 14 consecutive days will be assessed. The information gained in Part 1 will inform the dose selection for Part 2, in which the effect of multiple doses of risdiplam on the PK of the sensitive CYP3A substrate midazolam will be assessed, at a risdiplam dose targeting a mean AUC_{tau} at steady state of 2000 h.ng/mL, which is the therapeutic exposure observed in SMA patients.

The seamless transition between the 2 parts and the adaptive nature of the study will allow for effective use of emerging data across the 2 parts of the study, while ensuring the safety of the participants through strict dose decision rules. In order to ensure maximum safety and tolerability, the effects of the dose in Part 1 will be reviewed carefully before starting Part 2. Part 2 will take place after the review of safety, tolerability, and PK data as described in Section 4.1.1.

In Part 2, the effect of multiple oral doses of risdiplam (QD) on the PK of midazolam, a substrate specific for the drug-metabolizing CYP isozyme CYP3A, will be explored. The dose of risdiplam in Part 2 will be selected based on all available data from a minimum of 4 participants from Part 1.

4.2.1 Rationale for Study Population

Healthy male participants and female participants of non-childbearing potential aged 18 to 55 years (inclusive) were chosen because of the absence of potentially confounding disease processes, which will lead to a clearer and more consistent assessment of drug safety, tolerability, and pharmacological activity. Healthy participants are unlikely to require concomitant medication which could have an impact on the PK of

risdiplam and/or midazolam, respectively, or on the assessment of a potential DDI between these 2 compounds, which is the primary objective of this study.

4.2.2 Rationale for Pharmacokinetic Assessments

Pharmacokinetic assessment of risdiplam and midazolam concentrations, and their metabolite(s) if appropriate, in plasma are included in the study. The times of PK sample collection are based on previous studies and are considered adequate to allow characterization of the drug's PK after oral dosing. Furthermore, sample collection up to 144 hours postdose for risdiplam and up to 24 hours postdose for midazolam is anticipated to be sufficient to allow reasonable estimation of half-life during the terminal elimination phase.

4.3 JUSTIFICATION FOR DOSE

4.3.1 Risdiplam

Safety data of risdiplam in healthy subjects from the dedicated clinical pharmacology studies (BP29840, BP39122, and NP39625) demonstrated that single oral doses of risdiplam up to 18 mg have been safe and well tolerated in healthy subjects without relevant safety concerns. Treatment with risdiplam up to 5 mg QD for more than 1 year has been safe and well tolerated in patients with SMA in the currently ongoing clinical studies. Further details are provided in the IB.[1] The dose of 5 mg risdiplam is the therapeutic dose administered to adult patients with SMA in the ongoing pivotal trials to evaluate the safety and efficacy of risdiplam. The exposure observed at this dose is a mean AUC_{tau} at steady state of 2000 ng.h/mL. In order to evaluate the potential for DDI, the dose administered in Part 2 will therefore target a mean AUC_{tau} at steady state of 2000 ng.h/mL.

The duration of risdiplam dosing of 14 days is required, and is considered to be sufficient, to evaluate the potential for time-dependent inhibition of CYP3A by risdiplam.

4.3.2 Midazolam

Midazolam is a short-acting benzodiazepine. It has been selected because it is exclusively metabolized by CYP3A, is not a substrate of P-glycoprotein, and it has been validated in a number of studies as a CYP3A substrate. It is recommended as the sensitive model substrate for CYP3A by regulatory agencies (e.g., the FDA and EMA) and is the most widely used CYP3A probe substrate.[12] As the majority of co-medication in the targeted patient population is administered by the oral route, the oral administration of midazolam has been selected, which will reveal the effect of possible inhibition of intestinal and liver CYP3A.

A midazolam dose of 2 mg has been selected for Part 2 of this study because this dose is expected to yield midazolam plasma concentrations sufficient to adequately capture midazolam PK outcomes.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if they have completed all portions of the study including the last scheduled procedure shown in the SoA (Section 1.2).

The end of the study is defined as the date when the last participant last visit (LPLV) occurs.

5. STUDY POPULATION

The study population rationale is provided in Section 4.2.1.

The participants in this study will be healthy male and female of non-childbearing potential volunteers between 18 and 55 years of age, inclusive, who fulfill all of the given eligibility criteria.

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

5.1 INCLUSION CRITERIA

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

23. Willingness and ability to provide written consent to participate in the clinical trial.
24. Healthy participants.

    Healthy status is defined by the Investigator based on detailed review of medical and surgical history, results of physical examination, vital signs, 12-lead ECG, and laboratory assessments (hematology, coagulation, blood chemistry, serology, and urinalysis).
25. Male and female participants aged 18 to 55 years of age, inclusive, at Screening.

    a) Female participants: A female participant is eligible to participate if she is a woman of non-childbearing potential (WONCBP; as defined in Section 1 of Appendix 5).
26. A body mass index (BMI) of 18.0 to 32.0 kg/m^2, inclusive, at Screening.
27. Use of adequate contraception methods during the treatment period and until 4 months after last study drug administration. Males must refrain from donating sperm during this same period.

    a) Contraception methods for male participants considered as acceptable for the study:

    - With non-pregnant female partners, use contraceptive measures such as a condom with spermicide plus an additional contraceptive method that together result in a failure rate of <1% per year, with partners who are women of childbearing potential (as defined in Section 1 of Appendix 5).

The additional contraceptive method must be 1 of the following: diaphragm in combination with spermicide, intrauterine device, injectable or implantable contraceptives, oral hormonal contraceptives (e.g., “progesterone only pills,” tablets, patch, or vaginal ring with both estrogen and progesterone). Contraception is required during the treatment period and for at least 4 months after the last dose of risdiplam.

- With pregnant female partners, use contraceptive measures such as a condom to avoid exposing the embryo during the treatment period and for at least 28 days after the last dose of risdiplam.

Abstinence (including those who practice abstinence as part of their normal and preferred lifestyle, periodic abstinence, e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception in this study.

Note that only WONCBP and men are eligible for the study (see Appendix 5).

28. Willingness and ability to complete all aspects of the study.

5.2 EXCLUSION CRITERIA

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

29. History of any clinically significant GI, renal, hepatic, broncho-pulmonary, neurological, psychiatric, cardiovascular, endocrinological, hematological, or allergic disease, metabolic disorder, cancer (refer to Exclusion Criterion 6), or cirrhosis.
30. 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 participant in this study, including but not limited to the following:
    - Any major illness within 1 month before Screening or any febrile illness within 1 week prior to Screening and up to first study drug administration.
31. History or evidence of any medical condition potentially altering the absorption, metabolism, or elimination of drugs.
32. Surgical history of the GI tract affecting gastric motility or altering the GI tract (with the exception of uncomplicated appendectomy and hernia repair) (a cholecystectomy is exclusionary).
33. History or presence of clinically significant ECG abnormalities (based on the average of 3 consecutive measurements [if the first measurement is out of range, complete 2 more and take the average]) (e.g., PQ/PR interval >210 ms, QT interval corrected for heart rate using Fridericia’s formula [QTcF] >450 ms for males and QTcF >470 ms for females) 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).
34. History of malignancy in the past 5 years.
35. Confirmed (based on the average of 3 consecutive measurements [if the first measurement is out of range, complete 2 more and take the average]) systolic blood

pressure >140 or <90 mmHg, and diastolic blood pressure >90 or <50 mmHg at Screening only.

36. Confirmed (based on the average of 3 consecutive measurements) resting pulse rate (PR) >100 or <40 bmp at Screening only.
37. Clinically significant abnormalities (as judged by the Investigator) in laboratory test results (including hematology, chemistry panel, and urinalysis). In case of uncertain or questionable results, tests performed during Screening may be repeated on Day -1 to confirm eligibility.
38. Positive result on human immunodeficiency virus (HIV)-1, HIV-2, hepatitis B virus, or hepatitis C virus (serology; see Appendix 4) tests at Screening.
39. Any suspicion or history of alcohol abuse and/or any history or suspicion of regular consumption/addiction of drugs of abuse within 2 years prior to study drug administration or a positive drug screen test as performed at Screening.
40. Any consumption of tobacco-containing products (including but not limited to the following: smoking cigarettes, cigars, etc.) from 1 month before Screening until Follow-up.
41. Donation of blood or blood products for transfusion over 500 mL within 3 months prior to first study drug administration and for the duration of the study.
42. Participation in an investigational drug medicinal product or medical device study within 90 days prior to Screening.
43. Use of prohibited medications or herbal remedies (see Section 6.5.2).
44. Any clinically significant history of hypersensitivity or allergic reactions, either spontaneous or following study drug administration, or exposure to food or environmental agents.
45. History of hypersensitivity to any of the excipients in the formulation of the study drug.
46. History of hypersensitivity to midazolam or any other benzodiazepine or its formulation ingredients (this applies to participants in Part 2 only).
47. For Part 2 participants: history of acute angle glaucoma.
48. Participants who, in the Investigator's judgment, pose a suicidal risk, or any participant with a history of suicidal or homicidal attempts.
49. Participants under judicial supervision, guardianship, or curatorship.
50. Participants who, in the opinion of the Investigator, should not participate in this study.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and Dietary Restrictions

While confined at the Clinical Research Unit, participants will receive a standardized diet at scheduled times that do not conflict with other study-related activities. Participants will be fasted overnight (at least 8 hours) before collection of blood samples for clinical laboratory evaluations.

Participants will be fasted overnight (at least 8 hours) prior to dosing on Day 1 (Part 1) and on Days 1, 3, and 15 (Part 2) and will refrain from consuming water from 1 hour predose until 2 hours postdose, excluding the amount of water consumed at dosing. Food is allowed from 4 hours postdose. At all other times during the study, participants may consume water ad libitum.

Foods and beverages containing poppy seeds will not be allowed from 7 days prior to Check-in (Day -1) and throughout the study (until after the Follow-up visit).

Foods and beverages containing grapefruit/grapefruit juice or Seville oranges will not be allowed from 14 days prior to study drug administration (Day 1) and throughout the study (until after the Follow-up visit).

Caffeine-containing foods and beverages will not be allowed from 48 hours before Check-in (Day -1) until discharge on Day 14.

Consumption of alcohol will not be permitted from 48 hours prior to Check-in (Day -1) until the Follow-up visit.

5.3.2 Exercise

Participants are required to refrain from strenuous exercise from 7 days before Check-in (Day -1) until the Follow-up visit and will otherwise maintain their normal level of physical activity during this time (i.e., will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

Participants may participate in light recreational activities during studies (e.g., watching television, reading).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but do not fulfill all of the eligibility criteria and are not subsequently progressing in the study.

The Investigator will maintain a screening log to record details of all consented/screened participants. The log will provide confirmation of eligibility or reason for failure for all participants at the site.

Individuals who do not meet the criteria for participation in this study (screen failure) will not be re-screened unless agreed with the Sponsor. A repeat of a screening laboratory test because of a borderline result is not considered a re-screening and can be done only once at Day -1.

5.5 RECRUITMENT PROCEDURES

Participants will be identified for potential recruitment using pre-screening enrollment logs, clinical database and/or Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) approved newspaper/radio/social-media advertisements prior to consenting to take place in this study.

6. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

The IMP for this study is risdiplam. Midazolam is a non-IMP for this study. Risdiplam will be provided by the Sponsor. Midazolam will be sourced locally by the trial site. All study drug administration will occur at the study center under supervision of medically qualified site staff.

6.1 TREATMENTS ADMINISTERED

Table 3 summarizes the treatments administered.

Table 3 Summary of Treatments Administered

Study Treatment Name:	Risdiplam (RO7034067)	Midazolam (Part 2 only)
Dose Formulation:	Powder for constitution to an oral solution	Solution
Unit Dose Strength:	Each bottle contains 60 mg of risdiplam substance with excipients. The powder is constituted with purified water to yield an oral solution containing 0.75 mg/mL of risdiplam.	2 mg/mL
Dose:	5 mg (6.66 mL) (Part 1) Dose for Part 2 to be determined based on Part 1 data	2 mg (1 mL)
Route of Administration:	Oral	Oral
Sourcing:	Provided centrally by the Sponsor	Provided locally by the trial site

See the local prescribing information for more details on midazolam.

See the IB and Pharmacy Manual for more details on risdiplam.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

Study drug packaging will be overseen by the Roche clinical trial supplies department and contain a label with the identification required by local law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standard and local regulations.

The investigational site will acknowledge receipt of IMP and confirm the shipment condition and content. Any damaged shipments will be replaced.

Upon arrival of the IMP at the site, site personnel will complete the following:

- Check the IMP for damage.
- Verify proper identity, quantity, integrity of seals, and temperature conditions.
- Report any deviations or product complaints to the Study Monitor upon discovery.

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the treatment assignment schedule/Pharmacy Manual.

The Investigator or delegate must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff. Any temperature excursions during storage should be reported to the Sponsor immediately. Affected IMP cannot be administered until permission is granted by the Sponsor.

The Investigator is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Investigational medicinal products will either be disposed of at the study site according to the study site’s institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. Local or institutional regulations may require immediate destruction of used IMP for safety reasons. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Further guidance and information for the final disposition of unused study treatment are provided in the Pharmacy Manual.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 Method of Treatment Assignment

This is a non-randomized study and has a fixed treatment sequence.

The study will use objective PK endpoints, and therefore no bias is anticipated.

Assignment of participant numbers will be in ascending order and no numbers will be omitted. Participants will be dosed in numerical order.

6.3.2 Blinding

This is an open-label study; blinding procedures are not applicable.

6.4 TREATMENT COMPLIANCE

The qualified individual responsible for dispensing the study treatment will prepare the correct dose according to the treatment schedule. This individual will write the date dispensed and participant number on the study treatment bottle label and on the Drug Accountability Record. This individual will also record the study treatment number received by each participant during the study. The number will be noted for the IMP; for participants in Part 2, midazolam accountability will be done separately.

The following measures will be employed to ensure treatment compliance:

- All doses will be administered under the supervision of suitably qualified study site staff.
- Immediately after dose administration, visual inspection of the mouth will be performed for each participant.
- A predose and postdose inventory of IMP will be performed.

6.5 CONCOMITANT THERAPY

No concomitant medication is permitted, except acetaminophen, hormone replacement therapy for post-menopausal women, and medication to treat AEs.

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, approved dietary and herbal supplements, nutritional supplements) and any non-medication interventions (e.g., individual psychotherapy, cognitive behavioral therapy, smoking cessation therapy, and rehabilitative therapy) used by a participant from 30 days prior to Screening until the Follow-up visit must be recorded along with reason for use, dates of administration (including start and end dates), and dosage information (including dose and frequency).

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy. Such consultation should be adequately documented and archived in the site file.

All concomitant medications should be reported to the Investigator and recorded on the Concomitant Medications electronic Case Report Form (eCRF).

All therapy and/or medication administered to manage AEs should be recorded on the Adverse Event eCRF.

6.5.1 Permitted Therapy

Participants who use hormone replacement therapy should continue their use.

Acetaminophen, at doses of ≤ 2 g/day, is permitted for use as needed. Other concomitant medication required to treat AEs may be considered on a case-by-case basis by the Investigator.

6.5.2 Prohibited Therapy

All medications (prescription and OTC) taken within 30 days of Screening will be recorded on the appropriate eCRF.

As a general rule, no concomitant medication will be permitted, with the exception of acetaminophen, hormone replacement therapy for post-menopausal women, and medications to treat AEs, unless the rationale for exception is discussed and clearly documented between the Investigator and the Sponsor and archived in the site file.

Participants must abstain from taking prescription or non-prescription drugs (including vitamins and dietary or herbal supplements) within 14 days or 5 half-lives (whichever is longer) before the start of study treatment until completion of the Follow-up visit, unless, in the opinion of the Investigator and Sponsor, the medication will not interfere with the study.

The following medications are explicitly prohibited:

- Any inhibitor of CYP3A4 (e.g., ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, cimetidine).
- Any inducer of CYP3A4 (e.g., rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John’s wort).
- Any organic cation transporter 2 and MATE substrates (e.g., amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acycolovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine).
- Medications with known or potential retinal toxicity (e.g., chloroquine and hydroxychloroquine, thioridazine, retigabin, vigabatrin, desferoxamine, topiramate, latanoprost, niacin, rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon, chronic use of minocycline).

6.6 DOSE MODIFICATION

Not applicable.

6.7 TREATMENT AFTER THE END OF THE STUDY

Not applicable.

7. DISCONTINUATION OF STUDY, STUDY TREATMENT, AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Details on study and site closures are provided in Appendix 1.

7.1 DISCONTINUATION OF STUDY TREATMENT

See the SoA (Section 1.2) for data to be collected at the time of treatment discontinuation/Early Termination and Follow-up and for any further evaluations that need to be completed.

Every effort should be made to obtain information on participants who withdraw from the study but have not withdrawn consent. Participants who discontinue study treatment prematurely will be asked to return to the clinic for a Study Completion/Early Termination visit (see Section 8.11.3) and may undergo follow-up assessments (see Section 8.11.4), unless the participant withdrew consent. The primary reason for premature study treatment discontinuation should be documented on the appropriate eCRF. Participants who discontinue study treatment prematurely may be replaced depending on the reason for discontinuation, as defined in Section 7.2 below.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants have the right to voluntarily withdraw from the study at any time for any reason.

In addition, the Investigator has the right to withdraw a participant from the study for medical conditions that the Investigator or Sponsor determines may jeopardize the participant's safety if he/she continues in the study.

If possible, information on reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Participants will not be followed for any reason after consent has been withdrawn.

When a participant voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the participant specifically requests for these to be discarded or local laws require their immediate destruction. However, if samples have been tested prior to withdrawal, results from those tests will be used as part of the overall research data.

Participants who withdraw from the study for safety reasons will not be replaced. Participants who withdraw from the study for other reasons may be replaced at the joint discretion of the Investigator and the Sponsor Clinical Pharmacologist.

See the SoA (Section 1.2) for data to be collected at the time of study discontinuation.

7.3 LOST TO FOLLOW-UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, they will be considered to have withdrawn from the study.

Discontinuation of sites or of study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timepoints are summarized in the SoA (Section 1.2). Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment. Such consultation should be adequately documented and archived in the site file.

The maximum amount of blood collected from each participant will not exceed 500 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 EFFICACY ASSESSMENTS

Not applicable.

8.2 SAFETY ASSESSMENTS

Planned timepoints for all safety assessments are provided in the SoA (Section 1.2).

Safety assessments will consist of monitoring and recording AEs, including SAEs and AEs of special interest (AESIs); measurement of protocol-specified safety laboratory assessments, vital signs, and ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, dermatological, and musculoskeletal systems in addition to the head, eyes, ears, nose, throat, neck, and lymph nodes. Height, weight, and BMI will also be calculated and recorded at specified times. Further examination of other body systems may be performed in case of evocative symptoms at the Investigator's discretion.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

The physical exam will NOT include pelvic, rectal, or breast exams.

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

As clinically indicated, limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in the participant's notes. New or worsened clinically significant abnormalities should be recorded as AEs on the Adverse Event eCRF.

8.2.2 Vital Signs

Temperature, PR, and systolic and diastolic blood pressure will be assessed as outlined in the SoA (see Section 1.2).

Blood pressure and pulse measurements will be assessed in a supine position with a completely automated device. Manual techniques will be used only if an automated device is not available. When possible, the same arm and device should be used for all blood pressure measurements.

Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).

8.2.3 Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

To minimize variability, it is important that participants be in a resting position for ≥10 minutes prior to each ECG evaluation. Supine 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. Electrocardiograms should be performed prior to any scheduled vital signs measurements and blood draws.

8.2.4 Clinical Safety Laboratory Assessments

A list of clinical laboratory tests to be performed is provided in Appendix 4 and these assessments must be conducted in accordance with the SoA (Section 1.2).

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.

- 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.
- If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified within participant's standard of care and the Sponsor notified.

Results of clinical laboratory testing will be recorded on the eCRF or be received as electronically-produced laboratory reports submitted directly from the local laboratory.

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 and deemed clinically significant by the Investigator, or clinical symptoms necessitate additional testing to monitor participant safety.

Where the clinical significance of abnormal laboratory results at Screening is considered uncertain, screening laboratory tests may be repeated to confirm eligibility once at Day -1.

8.2.5 Medical History and Demographic Data

Medical history includes clinically significant diseases and all medications (e.g., prescription drugs, OTC drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 30 days prior to the Screening visit.

Demographic data will include age, sex, and self-reported race/ethnicity.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The definitions of an AE or SAE can be found in Appendix 2. The non-serious AESIs (NSAESIs) are discussed in Section 8.3.6.

The Investigator and any qualified designees are responsible for ensuring that all AEs (including assessment of seriousness, severity, and causality; see Appendix 2) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Appendix 2.

Procedures used for recording AEs are provided in Appendix 3:

- Diagnosis versus signs and symptoms
- AEs occurring secondary to other events
- Persistent or recurrent AEs
- Abnormal laboratory values
- Abnormal vital signs values
- Abnormal liver function tests
- Deaths
- Pre-existing medical conditions
- Hospitalization or prolonged hospitalization.

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

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 2 and Appendix 3 as applicable.

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

After informed consent has been obtained **but prior to initiation of study treatment**, only SAEs caused by a protocol-mandated intervention as judged by the Investigator should be reported. Any other AE should not be reported.

After initiation of study treatment, all AEs, regardless of relationship to study treatment, will be reported until the Follow-up visit.

Post-study AEs and SAEs: The Investigator is not required to actively monitor participants for AEs after the end of the AE reporting period (after the Follow-up visit, defined as 10±2 days post final dose of study treatment; see SoA [Section 1.2]).

However, if the Investigator learns of any SAE (including a death) or other AEs of concern that are believed to be related to prior treatment with study treatment, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study

participation, the Investigator must promptly notify the Sponsor. For the procedure of reporting, see Appendix 2.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

A consistent methodology of non-directive questioning should be adopted for eliciting AE information at all participant evaluation timepoints.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

8.3.3.1 Investigator Follow-up

The Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the Investigator, the event is otherwise explained, the participant is lost to follow-up (Section 7.3), or the participant withdraws consent. Every effort should be made to follow all SAEs considered to be related to study treatment or trial-related procedures until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented on the Adverse Event eCRF and in the participant'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 8.3.5.

8.3.3.2 Sponsor Follow-up

For SAEs, NSAESIs, 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.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical

investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

For immediate and expedited reporting requirements from Investigator to Sponsor and from Sponsor to Health Authority, Investigators, and IRB/EC, see Appendix 2.

8.3.4.1 Emergency Medical Contacts

To ensure the safety of study participants, access to the Medical Monitors is available 24 hours a day 7 days a week. Medical Monitor contact details will be available on a separate list generated by the study management team.

8.3.5 Pregnancy

Male participants will be instructed through the Informed Consent Form to immediately inform the Investigator if their partner becomes pregnant during the study or within 90 days after the final dose of study drug.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the pregnancy reporting process as detailed in Appendix 5.

Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs (Appendix 5).

8.3.6 Non-serious Adverse Events of Special Interest

Non-serious AESIs 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 Appendix 2 for reporting instructions).

Non-serious AESIs for this study include the following:

- Cases of an elevated ALT or aspartate aminotransferase (AST) in combination with either an elevated bilirubin or clinical jaundice, as defined in Appendix 3.
- Suspected transmission of an infectious agent by the study treatment, as defined below:

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

8.3.7 Disease-related Events and/or Disease-related Outcomes Not Qualifying as AEs or SAEs

Not applicable for this healthy participant study.

8.3.8 Management of Specific Adverse Events

Not applicable for this healthy participant study.

8.4 TREATMENT OF OVERDOSE

Study treatment overdose is the accidental administration of a drug in a quantity that is higher than the assigned dose. An overdose or incorrect administration of study treatment is not an AE unless it results in untoward medical effects (see Section 5.2 of Appendix 2 for further details).

Decisions regarding dose-interruptions or modifications (if applicable) will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant. Such consultation should be adequately documented and archived in the site file.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor's Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities until resolved.
3. Obtain a blood sample for PK analysis if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the eCRF (recorded in the comments of the AE or as additional observations).

8.5 PHARMACOKINETICS

Mandatory blood samples to evaluate concentrations of study treatment (and its metabolite[s], if appropriate) will be collected. The date and time of each sample collection will be recorded in the eCRF. Risdiplam and midazolam (Part 2 only) levels will be analyzed by using validated assays. The PK samples will be taken as outlined in the Schedules of Activities tables (see Section 1.2). During the course of the study, PK sampling timepoints may be modified on the basis of emerging data to ensure the PK of study treatment can be adequately characterized. Metabolites may be measured by a

specific validated liquid chromatography with tandem mass spectrometry assay, or other fit for purpose methods as appropriate.

The PK blood samples will be destroyed after the date of final Clinical Study Report or after approval of sample destruction by the study management team. Details on sampling procedures, sample storage, and shipment are given in the sample documentation.

Any changes in the timing or addition of PK timepoints must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files, but this will not constitute a protocol amendment.

8.6 IMMUNOGENICITY ASSESSMENTS

Not applicable.

8.7 PHARMACODYNAMICS AND BIOMARKERS ANALYSES

Not applicable; biomarkers are not evaluated in this study.

8.8 PHARMACODYNAMICS AND BIOMARKER SAMPLES

Not applicable.

8.9 SAMPLES FOR RESEARCH BIOSAMPLE REPOSITORY

Not applicable.

8.10 HEALTH ECONOMICS OR MEDICAL RESOURCE UTILIZATION

Health Economics/Medical Resource Utilization parameters are not evaluated in this study.

8.11 TIMING OF STUDY ASSESSMENTS

8.11.1 Screening and Pre-treatment Assessments

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

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

An Eligibility Screening Form documenting the Investigator’s assessment of each screened participant 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 28 days prior to Day 1, unless otherwise specified.

8.11.2 Assessments During Treatment

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

All assessments must be performed as per SoA (see Section 1.2). Assessments scheduled on the day of study treatment administration should be performed prior to administration of study treatment, unless otherwise noted in the SoA.

8.11.3 Assessments at Study Completion/Early Termination Visit

Participants who complete the study or discontinue from the study early will be asked to return to the clinic 10±2 days after the final dose of study drug for a Follow-up visit.

8.11.4 Follow-up Assessments

After the Study Completion/Early Termination visit, AEs should be followed as outlined in Sections 8.3.1 and 8.3.3.

9. STATISTICAL CONSIDERATIONS

9.1 SAMPLE SIZE DETERMINATION

In total a maximum of 40 participants may be enrolled in this study as follows:

- Part 1: 8 participants will be enrolled in order to obtain 6 evaluable participants. The Part 1 sample size was determined by practical considerations and not based on statistical power calculations.
- Part 2: 28 participants will be enrolled in order to obtain at least 26 evaluable participants. The Part 2 sample size is based on estimates for the within-subject coefficient of variation of 26% and 35% for AUC extrapolated to infinity (AUC_{inf}) and C_{max} of midazolam, respectively, from a previous clinical study.[13] A sample size of 26 evaluable participants ensures that the two-sided 90% confidence interval for the geometric population mean of the individual exposure ratios of Day 16 to Day 1 will lie within the 0.75 to 1.33 limits of the geometric population mean with at least 80% probability (power).

The additional 4 participants are in case the dropout rate in Part 2 is higher than expected in order to achieve 26 evaluable participants.

9.2 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined in Table 4.

Table 4 Analysis Populations

Population	Description
Safety	All participants who received at least 1 dose of the study treatment, whether prematurely withdrawn from the study or not, will be included in the safety analysis.
Pharmacokinetic	All participants who have received at least 1 dose of study treatment and who have data from at least 1 postdose PK sample will be included in the PK analysis population. Participants will be excluded from the PK analysis population if they significantly violate the inclusion or exclusion criteria, deviate significantly from the protocol, or if data are unavailable or incomplete which may influence the PK 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.

9.3 STATISTICAL ANALYSES

9.3.1 Safety Analyses

All safety analyses will be based on the safety analysis population. Safety analyses are detailed in Table 5.

No formal statistical analyses of the safety data are planned.

Table 5 Safety Statistical Analysis Methods

Endpoint	Statistical Analysis Methods
Adverse events	The original terms recorded on the eCRF by the Investigator for adverse events will be coded by the Sponsor. Adverse events will be summarized by mapped term and appropriate thesaurus level.
Clinical laboratory tests	All clinical laboratory data will be stored on the database in the units in which they were reported. Laboratory test values will be presented in International System of Units (SI units; Système International d'Unités) by individual listings with flagging of abnormal results. Summaries of clinical laboratory tests will also be used, as appropriate.
Vital signs	Vital signs data will be presented by individual listings with flagging of values outside the normal ranges and flagging of abnormalities. In addition, tabular summaries will be used, as appropriate.
ECG data analysis	ECG data will be presented by individual listings. In addition, tabular summaries will be used, as appropriate.

Concomitant medications	The original terms recorded on the participants' eCRF by the Investigator for concomitant medications will be standardized by the Sponsor by utilizing a mapped term and appropriate drug dictionary level. Concomitant medications will be presented in summary tables and listings.

9.3.2 Pharmacokinetic Analyses

Analyses will be carried out on the PK analysis population. All PK parameters will be presented by listings and descriptive summary statistics (arithmetic mean, standard deviation, geometric mean, geometric coefficient of variation, median, minimum, and maximum). For T_{max}, only the median, minimum, and maximum values will be presented.

Pharmacokinetic parameters will be read directly from the plasma concentration-time profiles, or calculated using standard non-compartmental methods.

The following PK parameters will be computed for risdiplam and its metabolite(s) as appropriate and midazolam and its metabolite(s) as appropriate. Other PK parameters might be computed in addition as appropriate.

- T_{max} Time of maximum observed plasma concentration
- C_{max} Maximum observed plasma concentration
- C_{trough} Trough observed plasma concentration
- AUC_{tau} Area under the plasma concentration-time curve over a dosing interval
- AUC_{last} Area under the plasma concentration-time curve from time 0 to the time of last quantifiable concentration (t_{last})
- AUC_{inf} Area under the plasma concentration-time curve extrapolated to infinity
- λ_z Apparent terminal elimination rate constant
- $t_{½}$ Apparent plasma terminal elimination half-life
- CL_{ss}/F Apparent total plasma clearance at steady state
- AR_{AUC} Accumulation ratio for AUC
- AR_{Cmax} Accumulation ratio for C_{max}

No formal statistical analyses are planned for Part 1.

In Part 2, the effect of multiple oral doses of risdiplam on the PK of a single oral dose of midazolam (and its metabolite[s] as appropriate) will be explored using an analysis of variance applied to the log-transformed PK parameters C_{max} and AUC_{inf} (or, if AUC_{inf}

cannot be properly estimated, AUC_{last} or an alternate partial AUC from time zero to a common postdose time, AUC_{0-t}). The model will include treatment as a fixed effect and subject as a random effect. From the model estimates, the geometric mean ratios (midazolam alone versus midazolam in combination with risdiplam) will be derived together with corresponding two-sided 90% confidence intervals.

9.4 INTERIM ANALYSES

No formal interim analysis is planned. Data from Part 1 will be evaluated before the start of Part 2, and the dose selection for Part 2 will be based on Part 1 data.

9.5 SUMMARIES OF CONDUCT OF STUDY

All protocol deviations will be listed. Data for study drug administration and concomitant medication will be listed. The number of participants who were enrolled, discontinued, and completed the study will be summarized and listed.

10. REFERENCES

1. RO7034067 – Investigator's Brochure (Version 6). March 2019.
2. Crawford TO, Pardo CA. The neurobiology of childhood spinal muscular atrophy. Neurobiol Dis. 1996 Apr;3(2):97–110.
3. Lunn MR, Wang CH. Spinal muscular atrophy. Lancet. 2008 Jun 21;371(9630):2120–33.
4. Sugarman EA, Nagan N, Zhu H, Akmaev VR, Zhou Z, Rohlfs EM, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. Eur J Hum Genet EJHG. 2012 Jan;20(1):27–32.
5. Lorson CL, Rindt H, Shababi M. Spinal muscular atrophy: mechanisms and therapeutic strategies. Hum Mol Genet. 2010 Apr 15;19(R1):R111-8.
6. Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. Cell. 1995 Jan 13;80(1):155–65.
7. Lorson CL, Hahnen E, Androphy EJ, Wirth B. A single nucleotide in the SMN gene regulates splicing and is responsible for spinal muscular atrophy. Proc Natl Acad Sci USA. 1999 May 25;96(11):6307–11.
8. Kolb SJ, Kissel JT. Spinal muscular atrophy: a timely review. Arch Neurol. 2011 Aug;68(8):979–84.
9. Nurputra DK, Lai PS, Harahap NIF, Morikawa S, Yamamoto T, Nishimura N, et al. Spinal muscular atrophy: from gene discovery to clinical trials. Ann Hum Genet. 2013 Sep;77(5):435–63.

10. European Medicines Agency (EMA). Guideline on the Investigation of Drug Interactions. CPMP/EWP/560/95/Rev. 1 Corr. 2. 21 June 2012. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf.

11. Midazolam. In: DRUGDEX System (Micromedex 2.0). Greenwood Village, CO: Truven Health Analytics; c1974-2013. Available from: http://www.micromedexsolutions.com/micromedex2/librarian#.

12. Hohmann N, Kocheise F, Carls A, Burhenne J, Haefeli WE, Mikus G. Midazolam microdose to determine systemic and pre-systemic metabolic CYP3A activity in humans. Br J Clin Pharmacol. 2014 Feb. 79(2):278–85.

13. [redacted], et al. The bioavailability and pharmacodynamics of midazolam (RO 21-3981 and its 1'-hydroxymethyl midazolam metabolite (RO 21-6347) following single dose intravenous, intramuscular, oral solution, and oral tablet administration to normal subjects. Research Report N-36884, October 9, 1982.

Appendix 1
Regulatory, Ethical, and Study Oversight Considerations

1. REGULATORY AND ETHICAL CONSIDERATIONS

1.1. COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the International Conference for Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the 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 (US) or under a US Investigational New Drug (IND) application will comply with US Food and Drug Administration regulations and applicable local, state, and federal laws. Studies conducted in the European Union/European Economic Area will comply with the EU Clinical Trial Directive (2001/20/EC).

1.2. INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms (ICFs), any information to be given to the participant (e.g., advertisements, diaries etc), and relevant supporting information must be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) by the Principal Investigator and reviewed and approved by the IRB/IEC before the study is initiated. In addition, any participant recruitment materials must be approved by the IRB/IEC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC. Investigators are also responsible for promptly informing the IRB/IEC of any protocol amendments (Section 2.3.1 of this Appendix).

The Investigator should follow the requirements for reporting all adverse events (AEs) to the Sponsor. 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/IEC, and archived in the site's study file.

1.3. INFORMED CONSENT

The Sponsor's Master ICF (and ancillary sample ICFs such as a Child's Assent or Caregiver's ICF, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 Code of federal Regulations 50,

local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample ICFs or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/IEC submission. The final IRB/IEC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes according to local requirements. Participants must be re-consented to the most current version of the ICF(s) during their participation in the study. A copy of the ICF(s) signed by all parties must be provided to the participant or the participant's legally authorized representative.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant 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 participant to take part. The final revised IRB/IEC-approved Consent Forms must be provided to the Sponsor for Health Authority submission purposes if required as per local regulations.

Participants 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/IEC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant 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 participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant's study file or in the site file and must be available for verification by study monitors at any time.

1.4. CONFIDENTIALITY

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

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

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

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request.

1.5. 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 1 year after completion of the study (i.e., last participant last visit [LPLV]).

2. DATA HANDLING AND RECORD

2.1. DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

2.1.1. Data Quality Assurance

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

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

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

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

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

2.1.2. Source Data Records

Source documents (paper or electronic) are those in which participant 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, 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 electronic CRFs (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 electronic CRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described below.

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/IEC review. The investigational site must also allow inspection by applicable Health Authorities.

2.1.3. 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.

2.2. RETENTION OF RECORDS

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the Investigator for at least 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records

may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

2.3. STUDY RECORDS

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully reconstructed, including but not limited to the protocol, protocol amendments, ICFs, and documentation of IRB/IEC and governmental approval.

Roche shall also submit an Annual Safety Report once a year to the IRB/IEC according to local regulatory requirements and timelines of each country participating in the study.

2.3.1. Protocol Amendments

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

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

2.3.2. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor for approval prior to submission. 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.

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

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.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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.

2.3.3. Site Inspections

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

3. ADMINISTRATIVE STRUCTURE

The Sponsor of the trial is F. Hoffmann-La Roche Ltd.

Covance is the contract research organization.

4. STUDY AND SITE CLOSURE

The Sponsor (or designee) has the right to close the study site or 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 AEs in this or other studies indicates a potential health hazard to participants.
- Participant enrollment is unsatisfactory.

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

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local Health Authorities, the Sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the Investigator.
- Discontinuation of further study treatment development.

Appendix 2
Adverse Events: Definitions and Procedures for Evaluating, Follow-up, and Reporting

1. DEFINITION OF ADVERSE EVENTS

According to the E2A International Conference for Harmonisation guideline for Good Clinical Practice, an **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be:

- 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.

Events Meeting the AE Definition:

- Deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (e.g., electrocardiogram, X−ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment (see Appendix 3, Section 4).
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- 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).

Events NOT Meeting the AE Definition:

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

2. DEFINITION OF SERIOUS ADVERSE EVENTS

If an event is not an AE per definition above, then it cannot be a serious AE (SAE) even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that at any dose:

- **Results in death.**
- **Is life-threatening.**

  The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.
- **Requires inpatient hospitalization or prolongation of existing hospitalization** (see Appendix 3).

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

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**

  Disability means substantial disruption of the participant's ability to conduct normal life functions.

  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**.
- **Other significant events**:

  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or

convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

3. RECORDING OF ADVERSE EVENT AND/OR SERIOUS ADVERSE EVENT

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator will then record all relevant AE/SAE information in the Case Report Form (CRF).

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Medical Monitor in lieu of completion of the electronic CRF.

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

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

3.1. ASSESSMENT OF SEVERITY

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the categories provided in Table 1 below (as a guidance for assessing AE severity).

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (rated as mild, moderate, or severe, or according to a pre-defined grading criteria [e.g., National Cancer Institute Common Terminology Criteria for Adverse Events criteria]); 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 AE recorded on the electronic CRF.

Serious AEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Table 1 Adverse Event Severity Grading Scale

Severity	Description
Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating with inability to work or to perform normal daily activity

Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see above).

3.2. ASSESSMENT OF CAUSALITY

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

- Temporal relationship of event onset to the initiation of study treatment.
- Course of the event, considering especially the effects of dose-reduction, discontinuation of study treatment, or reintroduction of study treatment (where applicable).
- Known association of the event with the study treatment or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the participant 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.

For participant receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

4. FOLLOW-UP OF AES AND SAES

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

If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.

New or updated information will be recorded in the originally completed CRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

5. 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 treatment:

- Serious AEs.
- Non-serious adverse events of special interest (NSAESI).
- Pregnancies (see Section 8.3.5).

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 SAEs to the local Health Authority and Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

5.1 REPORTING REQUIREMENTS OF SERIOUS ADVERSE EVENTS AND NON-SERIOUS ADVERSE EVENTS OF SPECIAL INTEREST

Events That Occur Prior to Study Treatment Initiation

After informed consent has been obtained but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention should be reported. The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the Serious Adverse Event Responsible person immediately (i.e., no more than 24 hours after learning of the event).

Events That Occur After Study Treatment Initiation

For reports of SAEs and NSAESIs (Section 8.3.6) that occur after initiation of study treatment (Section 8.3.1), Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form and submit to the Sponsor or its designee immediately (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.

Reporting of Post-Study Adverse Events and Serious Adverse Events

If the Investigator becomes aware of any other SAEs occurring after the end of the AE reporting period, if the event is believed to be related to prior study treatment, the event should be reported directly to the Sponsor or its designee, either by faxing or by scanning and emailing the SAE Reporting Form using the fax number or email address provided to Investigators.

5.2 REPORTING REQUIREMENTS FOR CASES OF ACCIDENTAL OVERDOSE OR MEDICATION ERROR (SPECIAL SITUATIONS)

Accidental overdose and medication error (hereafter collectively referred to as "special situations") are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.

Special situations are not in themselves AEs, but may result in AEs. Each AE associated with a special situation should be recorded separately on the Adverse Event electronic CRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event). For risdiplam, AEs associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the AE term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the AE term. Check the "Accidental overdose" and "Medication error" boxes.

In addition, all special situations associated with risdiplam, regardless of whether they result in an AE, should be recorded on the Adverse Event electronic CRF. Special situations should be recorded as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

As an example, an accidental overdose that resulted in a headache would require the completion of 2 Adverse Event electronic CRF pages, 1 to report the accidental overdose and 1 to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked on both electronic CRF pages.

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

The Sponsor will promptly evaluate all SAEs and NSAESI against cumulative product experience to identify and expeditiously communicate possible new safety findings to Investigators, IRBs, IECs, and applicable Health Authorities based on applicable legislation.

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

- 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.

Appendix 3
Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events (AEs) on the Adverse Event electronic Case Report Form (eCRF). Avoid colloquialisms and abbreviations.

Only 1 AE term should be recorded in the event field on the Adverse Event eCRF.

1. DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by 1 AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

2. ADVERSE EVENTS OCCURRING SECONDARY TO OTHER EVENTS

In general, AEs 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 AEs 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 3 events should be reported separately on the eCRF.

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

3. PERSISTENT OR RECURRENT ADVERSE EVENTS

A persistent AE is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event

eCRF. The initial severity 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 AE is one that resolves between participant evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

4. ABNORMAL LABORATORY VALUES

Not every laboratory abnormality qualifies as an AE. A laboratory test result should be reported as an AE 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 AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 times the upper limit of normal [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 AE. 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. ABNORMAL VITAL SIGN VALUES

Not every vital sign abnormality qualifies as an AE. A vital sign result should be reported as an AE 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 signs findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

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.

6. ABNORMAL LIVER FUNCTION TESTS

The finding of an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (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 AE 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 8.2.4 and Appendix 2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as an SAE or a NSAESI (Appendix 2).

7. DEATHS

All deaths that occur during the protocol-specified AE reporting period (see Section 5 of Appendix 2), regardless of relationship to study treatment, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor.

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 1 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").

8. PRE-EXISTING MEDICAL CONDITIONS

A pre-existing 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 pre-existing medical condition should be recorded as an AE 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 pre-existing condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

9. HOSPITALIZATION OR PROLONGED HOSPITALIZATION

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Appendix 2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an AE or an SAE:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study treatment administration)
- Hospitalization for a pre-existing 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 participant has not suffered an AE.

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

- Hospitalization for an AE that would ordinarily have been treated in an outpatient setting had an outpatient clinic been available.

Appendix 4
Clinical Laboratory Tests

The tests detailed in Table 1 will be performed by the local laboratory in Parts 1 and 2. If the local laboratory results are used, the results must be captured in source documentation and entered into the electronic Case Report Form (CRF).

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Sections 5.1 and 5.2, respectively, of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 1 Protocol-Required Safety Laboratory Assessments

Serum biochemistry:	**Urinalysis:**
Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline phosphatase Gamma-glutamyl transferase (GGT) Sodium Potassium Chloride Calcium Inorganic phosphate Glucose Urea Bilirubin (Total and Direct) Creatinine Total protein Albumin Cholesterol Triglycerides Thyroid-stimulating hormone (TSH) [c]	Microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria), if blood or protein is abnormal. pH Protein Glucose Blood
	Urinary drug screen:
	Drugs of abuse [a]
	Hormone panel: [b, c]
	Follicle-stimulating hormone (FSH) [d] Estradiol [d] Human chorionic gonadotropin (hCG) (serum pregnancy test)
	Serology: [c]
	Hepatitis B surface antigen (HBsAg) Hepatitis C antibody Human immunodeficiency virus (HIV) antibodies
Hematology:	**Coagulation:** [c]
White blood cell count (WBC) Red blood cell count (RBC) Hemoglobin Hematocrit Platelet count Differential WBC (basophils, neutrophils, eosinophils, monocytes, and lymphocytes)	International normalized ratio (INR) Activated partial thromboplastin time (aPTT) Prothrombin time (PT)

[a] Opiates, amphetamines, cannabinoids, benzodiazepines, cocaine, barbiturates, methadone, cotinine, and alcohol.
[b] Females only.
[c] Analyzed at Screening only.
[d] Post-menopausal females only.

The results of each test must be entered into the CRF.

Investigators must document their review of each laboratory safety report.

Additional Statistical Considerations for Clinical Laboratory Data

- Standard Reference Ranges and Transformation of Data

Potential analysis considerations for analyzing laboratory data includes the use of standard reference ranges and potential transformation of data for specific lab tests.

In this scenario, Roche standard reference ranges, rather than the reference ranges of the Investigator, can be used for specific parameters. For these parameters, the measured laboratory test result will be assessed directly using the Roche standard reference range. Certain laboratory parameters will be transformed to Roche's standard reference ranges.

A transformation will be performed on certain laboratory tests that lack sufficiently common procedures and have a wide range of Investigator ranges (e.g., enzyme tests that include aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase and total bilirubin). Since the standard reference ranges for these parameters have a lower limit of zero, only the upper limits of the ranges will be used in transforming the data.

- Definition of Laboratory Abnormalities

For all laboratory parameters included in this analysis, there exists a Roche predefined standard reference range. Laboratory values falling outside this standard reference range will be labeled "H" for high or "L" for low in participant listings of laboratory data.

In addition to the standard reference range, a marked reference range has been predefined by Roche for these laboratory parameters. The marked reference range is broader than the standard reference range. Values falling outside the marked reference range that also represent a defined change from baseline will be considered marked laboratory abnormalities (i.e., potentially clinically relevant). If a baseline value is not available for a participant, the midpoint of the standard reference range will be used as the participant's baseline value for the purposes of determining marked laboratory abnormalities. Marked laboratory abnormalities will be labeled in the participant listings as "HH" for very high or "LL" for very low.

Appendix 5
Contraceptive Guidance and Collection of Pregnancy Information

1. DEFINITIONS

- **Woman of Childbearing Potential (WOCBP)**

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. The definition of childbearing potential may be adapted for alignment with local guidelines or requirements.

- **Women in the following categories are considered to be a Woman of Non-Childbearing Potential (WONCBP)**

a) Pre-menarchal

b) Pre-menopausal female with 1 of the following:

  – Documented hysterectomy.

  – Documented bilateral salpingectomy.

  – Documented tubal ligation.

  – Documented bilateral oophorectomy.

  Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

c) Post-menopausal female

– A post-menopausal state is defined as no menses for ≥ 12 months without an alternative medical cause other than menopause. A high follicle-stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

– Females on HRT and whose menopausal status is in doubt will be required to use 1 of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status before study enrollment.

2. CONTRACEPTION GUIDANCE

- **Female Participants**

Not applicable; female participants of childbearing potential (WOCBP) will not be allowed to participate in this study. Women of non-childbearing potential are eligible for the study. Both are defined in Section 1 above.

- **Male Participants**

Use of adequate contraception methods during the treatment period and until 4 months after last study drug administration. Males must refrain from donating sperm during this same period.

a) Contraception methods for male participants considered as acceptable for the study:

   - With non-pregnant female partners, use contraceptive measures such as a condom with spermicide plus an additional contraceptive method that together result in a failure rate of <1% per year, with partners who are WOCBP (as defined in Section 1 above). The additional contraceptive method must be 1 of the following: diaphragm in combination with spermicide, intrauterine device, injectable or implantable contraceptives, oral hormonal contraceptives (e.g., “progesterone only pills,” tablets, patch, or vaginal ring with both estrogen and progesterone). Contraception is required during the treatment period and for at least 4 months after the last dose of risdiplam.
   - With pregnant female partners, use contraceptive measures such as a condom to avoid exposing the embryo during the treatment period and for at least 28 days after the last dose of risdiplam.

   Abstinence (including those who practice abstinence as part of their normal and preferred lifestyle, periodic abstinence, e.g., calendar, ovulation, symptothermal, or post ovulation methods) and withdrawal are not acceptable methods of contraception in this study.

3. PREGNANCY TESTING

Female participants of childbearing potential will not be allowed to participate in this study. Blood sample and urine pregnancy tests will be performed according to Schedule of Activity tables (see Section 1.2). If a urine pregnancy test is positive, it must be confirmed by a blood pregnancy test.

4. COLLECTION OF PREGNANCY INFORMATION

- **Male participants with partners who become pregnant**

The Investigator will attempt to collect pregnancy information on any male participant’s female partner who becomes pregnant while the male participant is in this study (see Section 8.3.5 Pregnancy).

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male participant exposed to study treatment. The Investigator will record pregnancy information on the Clinical Trial Pregnancy Reporting Form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. 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 when available. An Investigator who is contacted by the male participant 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. The female partner will be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Monitoring of the participant's partner should continue until conclusion of the pregnancy. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for procedure.

5 ABORTIONS

Any spontaneous abortion should be classified as an SAE (as the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event electronic Case Report Form (eCRF), and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5 of Appendix 2).

Any induced abortion due to maternal toxicity and/or embryo-fetal toxicity should also be classified as an SAE, 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 of Appendix 2).

Elective or therapeutic abortion not associated with an underlying maternal or embryo-fetal toxicity (e.g., induced abortion for personal reasons) does not require expedited reporting but should be reported as outcome of pregnancy on the Clinical Trial Pregnancy Reporting Form.

6 CONGENITAL ANOMALIES/BIRTH DEFECTS

Any congenital anomaly/birth defect in a child born to a female partner of a male participant exposed to study treatment should be classified as an SAE, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).