

**Official Title:** An Open-label, Single-dose, Parallel-group, Two-part Study to Evaluate the Pharmacokinetics and Safety of Risdiplam in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function

**NCT Number:** NCT03920865

**Document Date:** Protocol Version 1: 08-January-2019

## Protocol

---

### **An Open-label, Single-dose, Parallel-group, Two-part Study to Evaluate the Pharmacokinetics and Safety of Risdiplam in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function**

Protocol Status: Final  
Protocol Date: 08 January 2019  
Protocol Version: 1

Investigator Product: risdiplam

Protocol Reference Number: BP40995  
Covance Study Number: 8397571  
IND Number: 128972

Sponsor:  
F. Hoffmann-La Roche Ltd.  
Grenzacherstrasse 124  
4070 Basel  
Switzerland

Sponsor Signatory:  
 Pharm.D, PhD

Information described herein is confidential and may be disclosed only with the express written permission of the Sponsor.

**SPONSOR APPROVAL**

I have read the protocol and approve it:

  
\_\_\_\_\_  
Pharm.D, PhD  
Clinical Pharmacologist

8 Jan 2019  
Date \_\_\_\_\_

---

**INVESTIGATOR AGREEMENT**

I have read the protocol and agree to conduct the study as described herein.

Printed name and qualifications: \_\_\_\_\_

Signature: \_\_\_\_\_

Date: \_\_\_\_\_

Name and address of site: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

---

**STUDY IDENTIFICATION**

---

Sponsor F. Hoffmann-La Roche Ltd.  
Grenzacherstrasse 124  
4070 Basel  
Switzerland

---

Sponsor's Study Contact [REDACTED]  
F. Hoffmann-La Roche Ltd.  
Grenzacherstrasse 124  
4070 Basel  
Switzerland

---

Sponsor's Medical Contact [REDACTED] MD  
F. Hoffmann-La Roche Ltd.  
[REDACTED]  
Grenzacherstrasse 124  
4070 Basel  
Switzerland  
Tel: [REDACTED]  
Tel (cell): [REDACTED]

---

Covance Medical Monitor [REDACTED] MD  
Covance Clinical Research Unit Inc.  
[REDACTED]  
3402 Kinsman Blvd.  
Madison, WI 53704  
United States  
Tel: [REDACTED]  
Tel (cell): [REDACTED]  
E-mail: [REDACTED]

---

Study Site(s) Obtain information from Form FDA 1572

---

Principal Investigator Obtain information from Form FDA 1572

---

Sub-investigator(s) Obtain information from Form FDA 1572

---

---

Bioanalytical Laboratory

Dr. [REDACTED]  
[REDACTED]  
SYNLAB Analytics & Services Switzerland AG  
Sternenfeldstrasse 14  
4127 Birsfelden  
Switzerland  
Central: +41 58 400 1900  
Tel: [REDACTED]  
Fax: [REDACTED]  
E-mail: [REDACTED]

---

Statistician

[REDACTED] BSc, MSc, GradStat  
Covance

---

Pharmacokineticist

[REDACTED] BSc  
Covance [REDACTED]

---

## SYNOPSIS

**Title of study:** An Open-label, Single-dose, Parallel-group, Two-part Study to Evaluate the Pharmacokinetics and Safety of Risdiplam in Subjects with Mild or Moderate Hepatic Impairment Compared to Subjects with Normal Hepatic Function

**Objectives:**

The primary objective of the study is to determine the effect of mild or moderate hepatic impairment on the plasma pharmacokinetics (PK) of a single oral dose of risdiplam compared to matched healthy subjects with normal hepatic function.

The secondary objective of the study is to determine the effect of mild or moderate hepatic impairment on the safety and tolerability of a single oral dose of risdiplam compared to matched healthy subjects with normal hepatic function.

**Study design:**

This is a Phase I, multi-center, open-label, non-randomized, parallel-group, 2-part study to evaluate the effect of hepatic impairment on the PK and safety and tolerability of a single oral dose of risdiplam compared to matched healthy subjects with normal hepatic function.

In Part 1, 8 subjects with mild hepatic impairment (per Child-Pugh Class A [score of 5 to 6] as assessed at Screening and Check-in [Day -1]) and 8 demographically matched healthy subjects with normal hepatic function will be enrolled. Preliminary PK and safety and tolerability data from a minimum of 4 subjects with mild hepatic impairment and 4 matched subjects with normal hepatic function will be reviewed prior to the start of Part 2.

In Part 2, 8 subjects with moderate hepatic impairment (per Child-Pugh Class B [score of 7 to 9] as assessed at Screening and Check-in [Day -1]) and 8 demographically matched subjects with normal hepatic function will be enrolled.

In Parts 1 and 2, each subject with normal hepatic function (ie, matched control subject) will be enrolled following the completion of a mild or moderate hepatically impaired subject. Each subject with normal hepatic function will be demographically matched (1:1) by sex, age ( $\pm 10$  years), body mass index (BMI;  $\pm 15\%$ ), and smoking status to the completed hepatic impairment subject(s). A subject with normal hepatic function may serve as a matched control across both Parts 1 and 2 but may only serve as a matched control to a maximum of 1 hepatically impaired subject within either Part 1 or Part 2.

Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to study drug administration and will be admitted to the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 14. On the morning of Day 1, following a fast of at least 8 hours, a single oral dose of 5 mg risdiplam will be administered. No food will be allowed for at least 4 hours postdose. Subjects will return to the CRU for outpatient visits on Days 15, 16, 18, 20, 22, and 24, and a Follow-up visit  $28 \pm 3$  days postdose.

**Number of subjects:**

16 evaluable subjects with hepatic impairment (8 evaluable subjects with mild impairment and 8 evaluable subjects with moderate impairment, per Child-Pugh classification) and 8 to 16 evaluable subjects with normal hepatic function will be enrolled in the study.

Subjects who withdraw or are withdrawn from the study for safety reasons, considered to be study drug related by the Investigator, will not be replaced.

Subjects who withdraw or are withdrawn from the study for other reasons may be replaced at the discretion of the Investigator (or designee) and the Sponsor's Clinical Pharmacologist.

**Diagnosis and main criteria for inclusion:**

Male and female subjects aged between 18 and 70 years (inclusive) with a BMI between 18.0 and 36.0 kg/m<sup>2</sup> (inclusive) and body weight  $\geq$ 50 kg. Subjects will be in good health except for specific inclusion criteria related to the status of hepatic impairment.

Females must not be pregnant or lactating and must be of non-childbearing potential (ie, surgically sterile or post-menopausal [amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels within the post-menopausal range designated per the laboratory (for females aged <55 years only) and estradiol test without hormone replacement therapy (HRT)]).

**Investigational product, dose, and mode of administration:**

Single dose of 5 mg risdiplam, given orally as a 1  $\times$  5-mg solution on Day 1 after an overnight fast of at least 8 hours.

**Duration of subject participation in the study:**

Planned Screening duration: up to 27 days.

Planned study duration (Screening to Follow-up): approximately 8 weeks.

**Sample size calculation:**

Up to 32 evaluable subjects will be enrolled in the study.

No formal sample size calculation has been performed. The sample size determination has been based on historical studies of a similar nature. Eight evaluable subjects per hepatic impairment function group (ie, mild and moderate) and 8 to 16 evaluable subjects with normal hepatic function are planned to complete the study. This is considered a sufficient sample size to evaluate the PK of risdiplam under various degrees of hepatic function.

**Endpoints:**

**Pharmacokinetics:**

Blood samples will be collected for the analysis of plasma concentrations of risdiplam and its metabolite M1 (as appropriate) at the timepoints indicated in the Schedule of Assessments. Blood samples will also be collected and analyzed for unbound risdiplam and unbound M1 concentrations at the timepoints listed in the Schedule of Assessments.

The PK parameters of risdiplam and M1 (as appropriate) will be calculated using standard non-compartmental methods.

Primary PK parameters:

- area under the plasma concentration-time curve from time zero to infinity ( $AUC_{inf}$ )
- area under the plasma concentration-time curve from time zero to the last measurable concentration ( $AUC_{last}$ ; will be used for PK comparison if  $AUC_{inf}$  cannot be estimated with sufficient accuracy)
- maximum observed plasma concentration ( $C_{max}$ )

Secondary PK parameters:

- time of the maximum observed plasma concentration ( $T_{max}$ )
- apparent plasma terminal elimination half-life ( $t_{1/2}$ )
- percentage of area under the plasma concentration-time curve due to extrapolation ( $\%AUC_{extrap}$ )
- terminal elimination rate constant ( $\lambda_z$ )
- adjusted coefficient for determination of exponential fit ( $R^2$ -adjusted)
- apparent total clearance (CL/F)
- fraction of drug unbound (risdiplam and metabolite, M1, as appropriate)
- molecular weight adjusted metabolite-to-parent ratio for  $AUC_{inf}$ ,  $C_{max}$ , and  $AUC_{last}$ , if appropriate

Other PK parameters may be determined, as appropriate.

**Safety:**

Safety endpoints for this study include adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, coagulation, and urinalysis), vital sign measurements, 12-lead electrocardiograms (ECG), and physical examinations.

**Statistical methods:**

**Pharmacokinetics:**

The PK population will include all subjects who received a dose of risdiplam and have evaluable PK data. A subject will be excluded from the PK descriptive statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration or if they have any major protocol deviation(s) thought to impact PK analysis.

Plasma concentrations and PK parameters of risdiplam and its metabolite M1 (as appropriate) will be summarized by hepatic function using summary statistics.

The primary analysis is the evaluation of the PK of risdiplam (and M1, as appropriate) following a single dose in subjects with mild or moderate hepatic impairment ('Test' groups), compared to subjects with normal hepatic function ('Reference' group). The primary PK parameters are  $AUC_{inf}$  and  $C_{max}$  for risdiplam (and M1, as appropriate). An analysis of variance (ANOVA) will be used to estimate the effect of hepatic impairment on the primary PK parameters ( $AUC_{inf}$  [or  $AUC_{last}$  if appropriate] and  $C_{max}$ ) including the factor 'hepatic impairment' (ie, mild, moderate, or none). The PK parameters will be log-transformed prior to analysis. The data from subjects with mild or moderate hepatic impairment and their matched control subjects will be included in the analysis.

Geometric mean ratios and the corresponding 90% confidence intervals (CIs) of  $AUC_{inf}$  (or  $AUC_{last}$ , as appropriate) and  $C_{max}$  of risdiplam between the groups of hepatically impaired subjects and healthy subjects with normal hepatic function will be calculated. Additional statistical analyses, on primary and/or on secondary PK parameters, may be conducted as appropriate.

**Safety:**

All subjects who received a dose of risdiplam will be included in the safety analyses. All safety assessments, including AEs and serious adverse events (SAEs), clinical laboratory evaluations, vital sign measurements, and 12-lead ECGs will be summarized by impaired hepatic function group. All other assessments will be listed only.

No formal statistical analyses of the safety data are planned.

## TABLE OF CONTENTS

TITLE PAGE .....	1
SPONSOR APPROVAL .....	2
INVESTIGATOR AGREEMENT.....	3
STUDY IDENTIFICATION .....	4
SYNOPSIS.....	6
TABLE OF CONTENTS.....	10
LIST OF TABLES AND FIGURES.....	12
LIST OF ABBREVIATIONS.....	13
1. INTRODUCTION .....	15
1.1. Overview of the Disease .....	15
1.2. Overview of Risdiplam .....	15
1.3. Non-clinical Data .....	16
1.3.1. Non-clinical Pharmacology .....	16
1.3.2. Non-clinical Pharmacokinetics .....	16
1.4. Summary of Clinical Experience .....	17
1.4.1. Safety .....	17
1.4.2. Pharmacokinetics .....	18
1.5. Study Rationale.....	19
1.6. Benefit-risk Assessment.....	19
2. OBJECTIVES AND ENDPOINTS .....	20
2.1. Objectives .....	20
2.2. Endpoints .....	20
2.2.1. Primary Endpoints .....	20
2.2.2. Secondary Endpoints .....	21
3. INVESTIGATIONAL PLAN.....	21
3.1. Overall Study Design and Plan .....	21
3.1.1. Child-Pugh Classification .....	23
3.2. Discussion of Study Design .....	23
3.3. Selection of Doses in the Study .....	24
4. SELECTION OF STUDY POPULATION .....	25
4.1. Inclusion Criteria .....	25
4.2. Exclusion Criteria .....	26
4.3. Subject Number and Identification .....	29
4.4. Subject Withdrawal and Replacement .....	29
4.5. Study Termination .....	30
5. STUDY TREATMENTS.....	31
5.1. Study Treatment Definition .....	31

5.2.	Description, Storage, Packaging, and Labeling	31
5.3.	Study Treatment Administration	32
5.4.	Randomization	32
5.5.	Blinding	32
5.6.	Treatment Compliance	32
5.7.	Drug Accountability	32
6.	CONCOMITANT THERAPIES AND OTHER RESTRICTIONS	33
6.1.	Concomitant Therapies	33
6.2.	Diet	33
6.3.	Smoking	34
6.4.	Exercise	34
6.5.	Blood Donation	34
7.	STUDY ASSESSMENTS AND PROCEDURES	35
7.1.	Pharmacokinetic Assessments	35
7.1.1.	Pharmacokinetic Blood Sample Collection and Processing	35
7.1.2.	Analytical Methodology	35
7.2.	Safety and Tolerability Assessments	36
7.2.1.	Adverse Events	36
7.2.2.	Clinical Laboratory Evaluations	36
7.2.3.	Vital Signs	37
7.2.4.	12-Lead Electrocardiogram	37
7.2.5.	Physical Examination	37
8.	SAMPLE SIZE AND DATA ANALYSIS	37
8.1.	Determination of Sample Size	37
8.2.	Analysis Populations	38
8.2.1.	Pharmacokinetic Population	38
8.2.2.	Safety Population	38
8.3.	Pharmacokinetic Analyses	38
8.4.	Safety Analysis	39
8.5.	Interim Analysis	39
9.	REFERENCES	39
10.	APPENDICES	41
	Appendix 1: Adverse Event Reporting	42
	Appendix 2: Clinical Laboratory Evaluations	55
	Appendix 3: Total Blood Volume	56
	Appendix 4: Contraception Guidance	57
	Appendix 5: Regulatory, Ethical, and Study Oversight Considerations	59
	Appendix 6: Schedule of Assessments	63

**LIST OF TABLES AND FIGURES**

Table 1: Child-Pugh Assessment of Hepatic Function .....23  
Table 2: Schedule of Assessments .....64  
Figure 1: Study Schematic.....22

## LIST OF ABBREVIATIONS

<b>Abbreviation</b>	<b>Definition</b>
AE	adverse event(s)
ALT	alanine aminotransferase
AST	aspartate aminotransferase
%AUC <sub>extrap</sub>	percentage of area under the plasma concentration-time curve due to extrapolation
AUC <sub>inf</sub>	area under the plasma concentration-time curve from time zero to infinity
AUC <sub>last</sub>	area under the plasma concentration-time curve from time zero to the last measurable concentration
BMI	body mass index
bpm	beats per minute
CFR	Code of Federal Regulations
C <sub>max</sub>	maximum observed plasma concentration
CRU	Clinical Research Unit
CV	coefficient of variation
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
FMO	flavin mono-oxygenase
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for/Conference on Harmonisation
IMP	investigational medicinal product
IRB	Institutional Review Board
MATE	multidrug and toxin extrusion
NSAESI	non-serious adverse events of special interest
OCT	organic cation transporter
PK	pharmacokinetic(s)
SAE	serious adverse event
SD	standard deviation
SMA	spinal muscular atrophy

SMN	survival motor neuron
<i>SMN1</i>	<i>survival motor neuron 1</i>
<i>SMN2</i>	<i>survival motor neuron 2</i>
$t_{1/2}$	apparent plasma terminal elimination half-life
$T_{max}$	time of the maximum observed plasma concentration
ULN	upper limit of normal
WBC	white blood cell

## 1. INTRODUCTION

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

### 1.1. 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.<sup>2,3</sup> 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.<sup>4</sup>

Spinal muscular atrophy 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.<sup>5</sup>

Spinal muscular atrophy is caused by homozygous deletion (95% of cases) or mutation of the *survival motor neuron 1 (SMN1)* gene.<sup>6</sup> In humans, there are 2 *survival motor neuron (SMN)* genes (telomeric *SMN1* gene and centromeric *survival motor neuron 2 [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 SMN $\Delta$ 7 protein that is rapidly degraded.<sup>7</sup> 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.<sup>8</sup>

### 1.2. 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.<sup>8,9</sup> 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.

### 1.3. Non-clinical Data

#### 1.3.1. Non-clinical Pharmacology

Risdiplam effectively corrects the dysfunctional splicing of the human *SMN2* pre-mRNA in cultured cells by shifting the balance of the alternative splicing reaction towards the inclusion of *SMN2* exon 7 and the production of the full-length mRNA and functional SMN protein. An increase in SMN protein following treatment with risdiplam has been demonstrated in fibroblasts and motor neurons derived from patients with SMA. In vivo, risdiplam effectively corrects the dysfunctional splicing of the human *SMN2* pre-mRNA in SMA mouse models (the severe *SMNΔ7* model and the milder *C/C*-allele model) carrying human *SMN2* transgenes. This correction results in a significant increase in SMN protein levels and a profound prolongation of animal survival, protection of the neuromuscular circuit, and improvement of motor function in the *SMNΔ7* mouse model of severe SMA.

#### 1.3.2. Non-clinical Pharmacokinetics

Risdiplam is well absorbed in rats and monkeys following oral administration. The compound has very low intrinsic clearance in vitro and in vivo, with respective free fraction values of 11%, 15%, 10%, and 15% in human, monkey, mouse, and rabbit plasma (all adult).

Risdiplam is cleared in animals primarily through metabolism with minor contribution from renal clearance. The N-hydroxy metabolite M1 (RO7112063) was confirmed as a major circulating metabolite in the plasma of patients (median M1-to-parent ratio approximately 30%) and was detected in mouse, rat, rabbit and monkey plasma, and accounted for 12% to 21%, 38%, 4.6%, and 12%, respectively, of the parent compound risdiplam after a single dose of risdiplam. In vitro, M1 is not pharmacologically active.

The enzymes involved in human metabolism of risdiplam are flavin mono-oxygenase (FMO) 1 and 3 and multiple members of the cytochrome P450 superfamily (CYP), especially CYP3A enzymes. Risdiplam is not a substrate for human P-glycoprotein (P-gp). At this stage in the development of risdiplam, the potential for interaction with other drugs that inhibit or induce metabolizing enzymes or active transport proteins cannot be ruled out.

In vitro studies showed that risdiplam and its major circulating metabolite M1 did not inhibit (reversible or time-dependent) any of the CYP enzymes tested with the exception of CYP3A.

Preliminary physiology-based pharmacokinetic (PBPK) modeling suggests a low-to-moderate (up to 2-fold on average) increase in plasma exposure of the sensitive CYP3A substrate midazolam in adults. The interaction is predicted to be due to CYP3A enzyme inactivation in both the gastrointestinal tract and the liver.

Based on in vitro data and in silico prediction, plasma exposure of concomitant medications predominantly metabolized by the CYP3A enzyme and with significant intestinal first-pass metabolic extraction could thus be increased after oral administration of risdiplam.

Risdiplam is not an inducer of the major human CYPs and is not an inhibitor of human multidrug resistance protein 1 (MDR1), organic anion-transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, or OAT3. Risdiplam is an inhibitor of organic cation transporter 2 (OCT-2), multidrug and toxin extrusion (MATE)1, and MATE2-K and the potential for interaction with other drugs that are substrates of those transport proteins cannot be ruled out at this stage.

The N-hydroxymetabolite, M1, does not confer any additional drug-drug interaction potential based on its inhibition and induction profiles in vitro.

#### **1.4. 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/pharmacodynamic of risdiplam in pre-symptomatic infants genetically diagnosed with SMA is planned.

##### **1.4.1. 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 (SOC) was gastrointestinal 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 from time zero to 24 hours postdose ( $AUC_{0-24h}$ ) 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 (ONRC) 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 [ $^{14}\text{C}/^{12}\text{C}$ ]-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 administration). For further information, refer to the IB.<sup>1</sup>

#### **1.4.2. 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 the maximum observed plasma concentration ( $T_{\text{max}}$ ) between 2 and 3 hours postdose under fasted conditions. The maximum observed plasma concentration ( $C_{\text{max}}$ ) and area under the plasma concentration-time curve (AUC) increased in a dose-proportional manner. The apparent plasma terminal elimination half-life ( $t_{1/2}$ ) 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  $T_{\text{max}}$  was delayed to 4.5 hours postdose. Itraconazole had a minor effect on the PK of a single oral dose of risdiplam resulting in a slight increase (11%) of the area under the plasma concentration-time curve from time zero to 120 hours postdose ( $\text{AUC}_{0-120\text{h}}$ ) and a slight reduction (9%) of the  $C_{\text{max}}$ .

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

Study NP39625 demonstrated no 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 a 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.

### 1.5. Study Rationale

Liver disease can cause alterations in drug disposition and PK, which can reduce the clearance of drugs eliminated by hepatic metabolism or biliary excretion and affect protein binding and could influence the process of distribution and elimination.

Following a single oral dose of 18 mg [<sup>14</sup>C/<sup>12</sup>C]-risdiplam in healthy male subjects (Study BP39122),<sup>1</sup> the major pathway of elimination of [<sup>14</sup>C]-radioactivity was fecal excretion with on average 53.2% of the dose administered; urinary excretion of [<sup>14</sup>C]-radioactivity accounted for on average 28.2% of the dose administered.

This study is being conducted to provide information to develop dosing recommendations for risdiplam in subjects with hepatic impairment. For this purpose, the PK parameters of risdiplam and its major metabolite M1 will be determined in a population of mild and moderate hepatically impaired subjects and will be compared with a population of matched healthy subjects with normal liver function.

There are a number of methods used to categorize the severity of hepatic impairment. The Child-Pugh classification is the most widely used and is an acceptable method supported by regulatory agencies (including the US Food and Drug Administration [FDA] and the European Medicines Agency [EMA]). The FDA and EMA Guidelines recommend ‘the number of subjects enrolled should be sufficient to detect clinically relevant PK differences’.<sup>10,11</sup> In the current study, 8 subjects with mild hepatic impairment, 8 subjects with moderate hepatic impairment, and 8 to 16 subjects with normal hepatic function will be enrolled. The PK profiles and safety and tolerability between each hepatic impairment group and their matching healthy subjects (in terms of sex, age, body mass index [BMI], and smoking status) will be compared.

### 1.6. Benefit-risk Assessment

Subjects 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 subject due to the treatment with risdiplam or study-related procedures are considered minimal and are outweighed by the opportunity for developing a new oral treatment for SMA. More information about the known and expected benefits, risks, and reasonably anticipated AEs associated with risdiplam may be found in the IB.<sup>1</sup>

To minimize any potential risk, subjects will be closely monitored for safety and will be under continuous medical observation during the course of the study. Initially, only subjects with mild hepatic impairment (Part 1) will be enrolled, and safety and PK will be assessed in these subjects and compared to matched healthy subjects before proceeding with enrollment of patients with moderate hepatic impairment (Part 2).

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

## **2. OBJECTIVES AND ENDPOINTS**

### **2.1. Objectives**

The primary objective of the study is:

- to determine the effect of mild or moderate hepatic impairment on the plasma PK of a single oral dose of risdiplam compared to matched healthy subjects with normal hepatic function.

The secondary objective of the study is:

- to determine the effect of mild or moderate hepatic impairment on the safety and tolerability of a single oral dose of risdiplam compared to matched healthy subjects with normal hepatic function.

### **2.2. Endpoints**

#### **2.2.1. Primary Endpoints**

Primary PK parameters for risdiplam and its metabolite M1 (as appropriate):

- area under the plasma concentration-time curve from time zero to infinity ( $AUC_{inf}$ )
- area under the plasma concentration-time curve from time zero to the last measurable concentration ( $AUC_{last}$ ; will be used for PK comparison if  $AUC_{inf}$  cannot be estimated with sufficient accuracy)
- maximum observed plasma concentration ( $C_{max}$ )

Secondary PK parameters for risdiplam and its metabolite M1 (as appropriate):

- time of the maximum observed plasma concentration ( $T_{max}$ )
- apparent plasma terminal elimination half-life ( $t_{1/2}$ )
- percentage of area under the plasma concentration-time curve due to extrapolation ( $\%AUC_{extrap}$ )
- terminal elimination rate constant ( $\lambda_z$ )
- adjusted coefficient for determination of exponential fit ( $R^2$ -adjusted)
- apparent total clearance (CL/F)
- fraction of drug unbound (risdiplam and metabolite [M1], as appropriate)
- molecular weight-adjusted metabolite-to-parent ratio for  $AUC_{inf}$ ,  $C_{max}$ , and  $AUC_{last}$  (if appropriate)

Other PK parameters may be determined, as appropriate.

### 2.2.2. Secondary Endpoints

The safety outcome measures for this study are as follows:

- incidence and severity of AEs
- incidence of laboratory abnormalities, based on hematology, clinical chemistry, coagulation, and urinalysis test results
- vital sign measurements
- 12-lead ECG parameters
- physical examinations.

## 3. INVESTIGATIONAL PLAN

### 3.1. Overall Study Design and Plan

This is a Phase I, multi-center, open-label, non-randomized, parallel-group, 2-part study to evaluate the effect of hepatic impairment on the PK and safety and tolerability of a single oral dose of risdiplam compared to matched healthy subjects with normal hepatic function.

In Part 1, 8 subjects with mild hepatic impairment (per Child-Pugh Class A [score of 5 to 6] as assessed at Screening and Check-in [Day -1]) and 8 demographically matched healthy subjects with normal hepatic function will be enrolled. Preliminary PK and safety and tolerability data from a minimum of 4 subjects with mild hepatic impairment and 4 matched subjects with normal hepatic function will be reviewed prior to the start of Part 2.

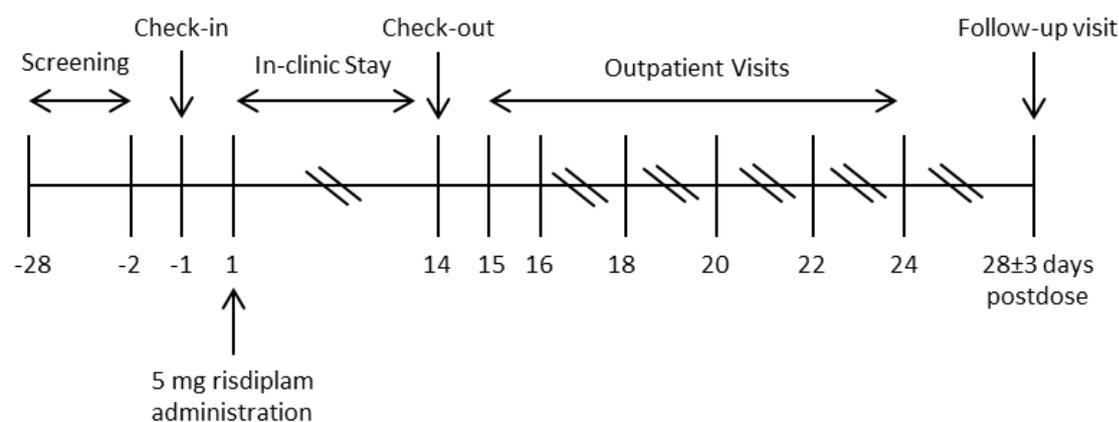
In Part 2, 8 subjects with moderate hepatic impairment (per Child-Pugh Class B [score of 7 to 9] as assessed at Screening and Check-in [Day -1]) and 8 demographically matched healthy subjects with normal hepatic function will be enrolled.

Hepatic function for all subjects will be classified according to the Child-Pugh system (Section 3.1.1).

In Parts 1 and 2, each subject with normal hepatic function (ie, matched control subject) will be enrolled following the completion of a mild or moderate hepatically impaired subject. Each subject with normal hepatic function will be demographically matched (1:1) by sex, age ( $\pm 10$  years), BMI ( $\pm 15\%$ ), and smoking status to the completed hepatic impairment subject(s). Should another subject with hepatic impairment be identified with whom an already enrolled healthy subject is demographically matched, the healthy subject may also be matched with that impaired subject as long as the impaired subject is in a different hepatic group (ie, a subject with normal hepatic function may serve as a matched control across both Part 1 and Part 2 but may only serve as a matched control to a maximum of 1 hepatically impaired subject within either Part 1 or Part 2).

An overview of the study design is shown in Figure 1.

**Figure 1: Study Schematic**



Potential subjects will be screened to assess their eligibility to enter the study within 28 days prior to study drug administration. Subjects will be admitted into the Clinical Research Unit (CRU) on Day -1 and be confined to the CRU until discharge on Day 14. Subjects will return to the CRU for outpatient visits on Days 15, 16, 18, 20, 22, and 24, and a Follow-up visit 28±3 days postdose.

On the morning of Day 1, following a fast of at least 8 hours, a single oral dose of 5 mg risdiplam will be administered. No food will be allowed for at least 4 hours postdose. Pharmacokinetic samples will be obtained from predose through 552 hours postdose (Day 24).

The total duration of study participation for each subject (from Screening through Follow-up visit) is anticipated to be approximately 8 weeks.

The start of the study is defined as the date the first subject who is subsequently enrolled signs an Informed Consent Form (ICF). The point of enrollment occurs at the time of subject number allocation. The end of the study is defined as the date of the last subject's last assessment (scheduled or unscheduled).

A Schedule of Assessments is presented in [Appendix 6](#).

### 3.1.1. Child-Pugh Classification

Per FDA and EMA guidance,<sup>10,11</sup> hepatic impairment will be classified according to the Child-Pugh system ([Table 1](#)), and the parameters to determine Child-Pugh classification for each subject will be collected at Screening and re-collected at Check-in (Day -1; [Appendix 6](#)).

**Table 1: Child-Pugh Assessment of Hepatic Function**

	Points Scored for Observed Findings		
	1	2	3
Hepatic encephalopathy grade <sup>a</sup>	0	1 or 2 <sup>b</sup>	3 or 4 <sup>b</sup>
Ascites <sup>c</sup>	Absent	Slight	Moderate
Serum bilirubin, mg/dL (μmol/L)	<2 (<34)	2 to 3 (34 to 50)	>3 (>50)
Serum albumin, g/dL (g/L)	>3.5 (>35)	2.8 to 3.5 (28 to 35)	<2.8 (<28)
International normalized ratio	<1.7	1.7 to 2.3	>2.3

Chronic hepatic impairment is classified into Child-Pugh class A to C, employing the added score of the 5 parameters described above.

Mild impairment (Child-Pugh class A) = 5 to 6 points

Moderate impairment (Child-Pugh class B) = 7 to 9 points

a. In the current study, hepatic encephalopathy will be graded according to the following criteria:

*Grade 0:* normal consciousness, personality, neurological examination, or normal electroencephalogram.

*Grade 1:* restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, or 5 cycles per second (cps) waves.

*Grade 2:* lethargic, time-disoriented, inappropriate, asterixis, ataxia, or slow triphasic waves.

*Grade 3:* somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, or slower waves.

*Grade 4:* unarousable coma, no personality/behavior, decerebrate, or slow 2 to 3 cps delta activity.

b. Subjects with hepatic encephalopathy Grade 2 or above will not be enrolled into the study.

c. Subjects with evidence of severe ascites will not be enrolled into the study. Ascites will be graded according to the following criteria:

*Absent:* no ascites is detectable by manual examination or by ultrasound investigation (if performed).

*Slight:* ascites palpitation doubtful, but ascites measurable by ultrasound investigation (if performed).

*Moderate:* ascites detectable by palpitations and by ultrasound investigation (if performed).

*Severe:* necessity of paracentesis; does not respond to treatment.

### 3.2. Discussion of Study Design

The design of this study, a single-dose, non-randomized, open-label, parallel design is based on the current understanding of the risdiplam PK and recommendations provided in the FDA and EMA guidance documents for hepatic impairment studies. The subject's degree of hepatic impairment will be assessed using the Child-Pugh score, which is the most widely used rating system in clinical practice and is recommended by both FDA and EMA guidelines. Dose administration will be limited to a single oral dose of 5 mg risdiplam, allowing for assessment of safety and tolerability, as well as to determine if adjustment of risdiplam dosage would be needed in patients with hepatic impairment.

A parallel design is required to include subjects with hepatic impairment and matched control subjects with normal hepatic function. The study will be open-label as the endpoints (PK) are not considered subjective.

Available clinical PK data (BP39055) have shown that risdiplam exhibited a similar PK profile after a single dose and at steady-state over the dose range tested; there was no

indication of non-linear PK versus dose nor a change in PK with time following multiple dose administration.<sup>1</sup> These data suggest that a single-dose study in subjects with hepatic impairment should accurately describe the PK of the drug. Extended PK samples will be collected to ensure adequate characterization of terminal phase kinetics in consideration of potential prolonged elimination of risdiplam with hepatic impairment.

Given that risdiplam and M1 are bound to plasma proteins (predominantly to serum albumin) that are synthesized in the liver, plasma unbound risdiplam and M1 concentrations will be determined in this study to estimate the fraction unbound in subjects with hepatic impairment.

Previous clinical studies have supported the administration of risdiplam with or without food; in the present study risdiplam will be administered in the fasted state to simplify study conduct.

This study will be conducted in subjects with stable hepatic impairment and matched healthy subjects with normal hepatic function. Subjects with stable hepatic impairment may have acceptable comorbid conditions in terms of safety and stability that are not anticipated to confound the study results. The safety and PK assessments are standard parameters for clinical studies in drug development.

Safety, tolerability, and PK data from a minimum of 4 subjects with mild hepatic impairment subjects and a minimum of 4 matched healthy subjects will be evaluated prior to enrollment of the moderate hepatic impairment subjects. Results from the review of safety, tolerability, and PK data from the mild hepatic impairment and matched healthy subject cohort will be utilized to support the dose selection for the moderate hepatic impairment cohort.

Plasma sampling is timed to sufficiently estimate PK parameters of risdiplam exposure.

### **3.3. Selection of Doses in the Study**

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.

To ensure sufficient safety margins, a reduced single oral dose of 5 mg risdiplam has been chosen for this study as this dose is expected to provide sufficient exposure to adequately characterize the PK of risdiplam and is expected to be well-tolerated in the healthy subject population. Administration of once daily oral doses of up to 5 mg has been tolerated well in patients with SMA, with a treatment duration of more than 1 year, without safety concerns, and 5 mg (once daily) is the anticipated therapeutic dose for adult patients with SMA.

## 4. SELECTION OF STUDY POPULATION

### 4.1. Inclusion Criteria

Subjects must satisfy all of the following criteria at the Screening visit, unless otherwise stated:

#### All Subjects

1. Males or females, of any race, between 18 and 70 years of age, inclusive.
2. BMI between 18.0 and 36.0 kg/m<sup>2</sup>, inclusive, and body weight ≥50 kg.
3. Females must not be pregnant or lactating and must be of non-childbearing potential (ie, surgically sterile or post-menopausal [amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels within the post-menopausal range designated per the laboratory (for females aged <55 years only) and estradiol test without hormone replacement therapy (HRT)]) at Check-in (Day -1).
4. Male subjects (whether surgically sterilized or not) with female partners of childbearing potential must use 2 methods of contraception from Screening until 4 months after their dose of the study drug as detailed in [Appendix 4](#).
5. Male subjects must not donate sperm from Check-in (Day -1) until 4 months after their dose of the study drug.
6. Able to comprehend and willing to sign an ICF and to abide by the study restrictions.

#### Subjects with Normal Hepatic Function Only

7. Matched to subjects with mild or moderate hepatic function in sex, age (±10 years), BMI (±15%), and smoking status.
8. In good health, as determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital sign measurements, and clinical laboratory evaluations (congenital non-hemolytic hyperbilirubinemia [eg, suspicion of Gilbert's syndrome based on total and direct bilirubin] is not acceptable) at Screening and Check-in (Day -1) as assessed by the Investigator (or designee).

#### Subjects with Hepatic Impairment Only

9. Documented chronic stable liver disease (Child-Pugh class A or B at Screening); diagnosis of cirrhosis due to parenchymal liver disease. This will exclude biliary liver cirrhosis or other causes of hepatic impairment not related to parenchymal disorder:
  - a. 'Documented' is defined by at least 1 of the following: medical history, physical examination, hepatic ultrasound, computed axial tomography scan, magnetic resonance imaging, and/or liver biopsy.
  - b. 'Chronic stable' is defined as no clinically significant change in disease status within the last 3 months, as documented by the subject's recent medical history (eg, no worsening of clinical signs of hepatic impairment, or no

worsening of total bilirubin or prothrombin time [PT] by more than 50%) and no alteration to relevant concomitant medication treatment regimen, according to the Investigator's clinical judgment, within the 3 months prior to study drug administration (Day 1). A dose change only (not addition/discontinuation of a new drug) within 3 months may be permitted if approved by the Investigator (or designee) and Sponsor.

10. Subjects with mild or moderate hepatic impairment may have medical findings consistent with their hepatic dysfunction, as determined by medical history, physical examination, 12-lead ECG, vital sign measurements, and clinical laboratory evaluations at Screening and Check-in (Day -1). Subjects with abnormal findings considered not clinically significant by the Investigator will be eligible.
11. Non-hepatic, abnormal clinical laboratory evaluations must not be clinically relevant, as judged by the Investigator (or designee) and Covance Medical Monitor.
12. Currently on a stable medication regimen, defined as not starting new drug(s) or changing drug dose(s) within 3 months of administration of study drug (Day 1). Concomitant medications administered within 30 days prior to study drug administration must be approved by the Investigator (or designee), Sponsor, and Covance Medical Monitor.
13. Anemia secondary to hepatic disease will be acceptable, if hemoglobin  $\geq 9$  g/dL and anemia symptoms are not clinically significant as judged by the Investigator (or designee) and Covance Medical Monitor. Subjects must have a platelet count  $\geq 35\ 000$  platelets.

#### **4.2. Exclusion Criteria**

Subjects will be excluded from the study if they meet any of the following criteria at the Screening visit, unless otherwise stated:

##### **All Subjects**

1. Significant history or clinical manifestation of any metabolic, allergic, dermatological, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder, as determined by the Investigator (or designee).
2. History of significant hypersensitivity, intolerance, or allergy to any drug compound, constituents or excipients of the study drug, food, or other substance, unless approved by the Investigator (or designee).
3. History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered drugs (uncomplicated appendectomy and hernia repair will be allowed; cholecystectomy will not be permitted).
4. Clinically significant eye pathology affecting best corrected visual acuity (BCVA), color vision, intraocular pressure, or field of vision, or a history of glaucoma, retinal detachment, hemorrhage, retinal surgery, intraocular trauma, retinal dystrophy or degeneration, optic neuropath, or optic neuritis.

5. Ventricular dysfunction or history of risk factors for Torsades de Pointes (TdP; eg, unexplained syncope, known long QT syndrome, heart failure, and cardiomyopathy). Subjects will be excluded if there is a family history of long QT syndrome. Fridericia's corrected QT interval (QTcF) must not be >450 ms for male subjects and >470 ms for female subjects.
6. Evidence of hepatorenal syndrome and estimated creatinine clearance range <60 mL/min or abnormal sodium and potassium levels, as determined by the Investigator (or designee), calculated using the Cockcroft-Gault equation at Screening and Check-in (Day -1):
  - $\left(\frac{[1.23 \times (140 - \text{age}) \times (\text{weight in kg})]}{[\text{serum creatinine in } \mu\text{mol/L}]}\right)$  for male subjects
  - $\left(\frac{[1.04 \times (140 - \text{age}) \times (\text{weight in kg})]}{[\text{serum creatinine in } \mu\text{mol/L}]}\right)$  for female subjects
7. Clinically significant physical examination abnormality, as determined by the Investigator (or designee).
8. History of diabetes mellitus.
9. Use of any drugs or substances known to be either sensitive substrates or strong inhibitors or inducers of CYP3A4 enzyme or FMO within 30 days prior to study drug administration and throughout the study (until after the Follow-up visit; unless approved by the Investigator [or designee] and Covance Medical Monitor).
10. Use of any OCT-2 and MATE substrates within 30 days prior to study drug administration and throughout the study (until after the Follow-up visit), including but not limited to, amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephadrine, and fexofenadine.
11. Use of any medication known to be toxic to the lens, retina or optic nerve from 30 days prior to study drug administration and throughout the study (until after the Follow-up visit; unless approved by the Investigator [or designee] and Covance Medical Monitor), including but not limited to, deferoxamine, chloroquine/hydroxychloroquine, tamoxifen, phenothiazines, quiniline, thioridazine, topiramate, digoxin, metronidazole, latanoprost, rosiglitazone, ethambutol, and sildenafil.
12. Use or intend to use any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing, unless deemed acceptable by the Investigator (or designee).
13. Consumption of grapefruit/grapefruit juice and Seville oranges within 14 days prior to study drug administration and throughout the study (until after the Follow-up visit).
14. History of alcoholism or drug/chemical abuse within 2 years prior to Check-in (Day -1); current active alcohol abuse or substance abuse will not be permitted.
15. Regular consumption of more than 5 cups of caffeinated drinks per day.

16. Alcohol consumption of >21 units per week for males and >14 units for females. One unit of alcohol equals 12 oz (360 mL) beer, 1½ oz (45 mL) liquor, or 5 oz (150 mL) wine.
17. Positive urine drug screen or positive alcohol test result at Screening and Check-in (Day -1), that is not otherwise explained by permitted concomitant medications. At Screening, a positive alcohol test may be repeated once. At Check-in (Day -1), a positive alcohol test may not be repeated.
18. Positive human immunodeficiency virus test ([Appendix 2](#)).
19. Participation in a clinical study involving administration of an investigational drug (new chemical entity) in the past 30 days or 5 half-lives (whichever is longer) prior to dosing.
20. Smoke more than 10 cigarettes or use the equivalent tobacco- or nicotine-containing products per day.
21. Receipt of blood products within 2 months prior to Check-in (Day -1).
22. Donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, or platelets from 6 weeks prior to Screening.
23. Poor peripheral venous access.
24. Have previously completed or withdrawn from this study or any other study investigating risdiplam, and have previously received the investigational product.
25. Subjects who, in the opinion of the Investigator (or designee), should not participate in this study.

### **Subjects with Normal Hepatic Function Only**

26. Confirmed supine blood pressure >150 mmHg or <90 mmHg and/or supine diastolic blood pressure >90 mmHg or <50 mmHg, or resting (supine) heart rate <45 beats per minute (bpm) or >100 bpm at Screening or Check-in (Day -1). Repeated blood pressure measurements will be allowed at Screening and Day -1.
27. Positive test for hepatitis B or C virus ([Appendix 2](#)).
28. Clinically significant abnormal laboratory values (clinical chemistry, hematology, coagulation, and urinalysis), as determined by the Investigator (or designee).
29. Significant history or clinical manifestation of hepatic disorder, as determined by the Investigator (or designee).
30. History or presence of liver disease or liver injury as indicated by any clinically significant deviations from normal reference ranges in liver function tests, unless approved by the Investigator (or designee).
31. Use or intend to use any prescription medications/products within 14 days prior to dosing, unless deemed acceptable by the Investigator (or designee) and/or Sponsor.
32. Use or intend to use slow-release medications/products considered to still be active within 14 days prior to Check-in (Day -1), unless deemed acceptable by the Investigator (or designee) and/or Sponsor.

33. Use or intend to use any non-prescription medications/products including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations within 7 days prior to Check-in (Day -1), unless deemed acceptable by the Investigator (or designee) and/or Sponsor.

### **Subjects with Hepatic Impairment Only**

34. Confirmed supine blood pressure >159 mmHg or <90 mmHg and/or supine diastolic blood pressure >100 mmHg or <50 mmHg, or resting (supine) heart rate <45 bpm or >100 bpm at Screening or Check-in (Day -1). Repeated blood pressure measurements will be allowed at Screening and Day -1.
35. Values outside the normal range for liver function tests that are not consistent with their hepatic condition, as determined by the Investigator (or designee).
36. Use of a new medication, or a change in dose, for the treatment, or worsening of, hepatic encephalopathy within 3 months prior to Check-in (Day -1).
37. Use of prescription drugs within 14 days of study drug administration, with the exception of therapies for hepatic disease and treatments of associated disorders that have been stable for at least 3 months prior to study drug administration.
38. Recent history of, or the treatment of, esophageal bleeding (within the past 180 days), unless banded.
39. Presence of a portosystemic shunt.
40. Recent history of paracentesis within 90 days prior to Check-in (Day -1).
41. Current functioning organ transplant or are waiting for an organ transplant.
42. Evidence of severe ascites.
43. History within 180 days prior to the Screening visit or current symptoms of hepatic encephalopathy Grade 2 or above.

### **4.3. Subject Number and Identification**

Subjects will have a unique identification number used at Screening. Subjects will be assigned a subject number prior to the first dosing occasion. Assignment of subject numbers will be in ascending order and no numbers will be omitted (eg, Subjects ██████████). Numbering will start at ██████ or ██████ for subjects with mild or moderate hepatic impairment, respectively. Numbering will start at ██████ for subjects with normal hepatic function.

Replacement subjects (Section 4.4) will be assigned a subject number corresponding to the number of the subject he/she is replacing plus ██████ (eg, Subject ██████ replaces Subject ██████).

Subjects will be identified by subject number only on all study documentation. A list identifying the subjects by subject number will be kept in the Site Master File.

### **4.4. Subject Withdrawal and Replacement**

The Investigator has the right to discontinue a subject or withdraw a subject from the study at any time. In addition, subjects have the right to voluntarily discontinue study treatment or

withdraw from the study at any time for any reason. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Any medical condition that the Investigator or Sponsor determines may jeopardize the subject's safety if he/she continues in the study.
- Investigator or Sponsor determines it is in the best interest of the subject.
- Non-compliance with the study or study procedures (eg, dosing instructions, study visits).

If possible, information on the reason for withdrawal from the study should be obtained. The primary reason for withdrawal from the study should be documented on the appropriate electronic Case Report Forms (eCRF).

When a subject voluntarily withdraws from the study, or is withdrawn by the Investigator, samples collected until the date of withdrawal will be analyzed, unless the subject 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 remain as part of the overall research data.

All subjects who received 1 dose of the study drug (risdiplam), whether prematurely withdrawn from the study or not, will be included in the safety analysis.

Subjects who withdraw or are withdrawn from the study for safety reasons, considered to be study drug related by the Investigator, will not be replaced. Subjects who withdraw or are withdrawn from the study for other reasons may be replaced at the discretion of the Investigator (or designee) and the Sponsor's Clinical Pharmacologist.

Under no circumstances will subjects who have already been enrolled in this study, whether completed or withdrawn early, be permitted to be allocated a new subject number and re-enroll in the study.

#### **4.5. Study Termination**

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

- the incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- ethical reasons affecting the continued performance of the study
- difficulties in the recruitment of subjects
- discontinuation of drug development

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

- excessively slow recruitment
- poor protocol adherence
- inaccurate or incomplete data recording
- non-compliance with the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines

## **5. STUDY TREATMENTS**

### **5.1. Study Treatment Definition**

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

In the current study, the IMP is risdiplam. All IMPs required for completion of this study (risdiplam) will be provided by the Sponsor. All study drug administration will be at the study site under supervision of site staff.

### **5.2. Description, Storage, Packaging, and Labeling**

The IMP is a powder for constitution to an oral solution. Each bottle contains 60 mg of risdiplam substance with excipients. The powder is constituted with purified water to yield an oral solution containing 0.75 mg/mL of risdiplam. The following excipients are used: mannitol, isomalt, tartaric acid, sodium benzoate, ascorbic acid, polyethylene glycol 6000, disodium edetate dihydrate, sucralose, and strawberry flavor. All excipients selected for the powder for oral solution formulation comply with pharmacopeia requirements (United States Pharmacopeia–National Formulary [USP/NF] and/or the European Pharmacopoeia [Ph. Eur] and EU Food regulations).

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

Study drug packaging will be overseen by the Roche Clinical Trial Supplies department and will bear a label with the identification required by local law. The packaging and labeling of the study medication and excipient will be in accordance to Roche standards and local regulations. Upon arrival of investigational products at the site, site personnel should check for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the Monitor upon discovery. All drug supplies should be stored in a secure, temperature-controlled area with restricted access.

### **5.3. Study Treatment Administration**

The dose of risdiplam will be administered orally as a drinking solution under fasted conditions. Doses of risdiplam will be preceded by an overnight fast (at least 8 hours).

Subjects will be dosed in numerical order while standing and will not be permitted to lie supine for 2 hours after administration of risdiplam, except as necessitated by the occurrence of an AE(s) and/or study procedures. No food will be allowed for 4 hours postdose and subjects will refrain from consuming water from 1 hour predose until 2 hours postdose, excluding the amount of water consumed at dosing. Subjects shall rinse their mouth with water (and swallow it) after risdiplam administration.

### **5.4. Randomization**

This is a non-randomized study. All subjects will receive the same treatment. The study will use objective PK endpoints, and therefore no bias is anticipated.

### **5.5. Blinding**

Not applicable since this is an open-label study.

### **5.6. Treatment Compliance**

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 subject.
- A predose and postdose inventory of IMP will be performed.

### **5.7. Drug Accountability**

The Investigator (or designee) will maintain an accurate record of the receipt of risdiplam drug substance received. In addition, an accurate drug disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This drug accountability record will be available for inspection at any time. At the completion of the study, the original drug accountability record will be available for review by the Sponsor upon request.

For each batch of unit doses, the empty used unit dose containers will be discarded upon satisfactory completion of the compliance and accountability procedures. Any unused assembled unit doses will be retained until completion of the study.

At the completion of the study, all unused risdiplam drug substance will be returned to the Sponsor or disposed of by the study site, per the Sponsor's written instructions.

## **6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS**

### **6.1. Concomitant Therapies**

All subjects will refrain from the use of any CYP3A, OCT-2, or MATE substrates within 30 days prior to study drug administration and throughout the study (until after the Follow-up visit). Subjects will not be allowed to use any drugs or substances known to be sensitive substrates or strong inhibitors or inducers of CYP3A4 enzyme or FMO within 30 days prior to study drug administration and throughout the study (until after the Follow-up visit).

All subjects will refrain from the use of any medication known to be toxic to the lens, retina or optic nerve from 30 days prior to study drug administration and throughout the study (until after the Follow-up visit).

All subjects will refrain from the use of any medications/products known to alter drug absorption, metabolism, or elimination processes, including St. John's wort, within 30 days prior to dosing.

Paracetamol/acetaminophen (2 g/day for up to 3 consecutive days) is an acceptable concomitant medication.

Females will refrain from use of HRT during the study until the Follow-up visit.

Subjects with normal hepatic function will refrain from use of any prescription or non-prescription medications/products during the study until the Follow-up visit, unless the Investigator (or designee) and/or Sponsor have given their prior consent.

For subjects with hepatic impairment, treatment with chronic stable medications that are necessary for maintaining a subject's clinical status will be permitted if prescribed by the subject's personal physician and approved by the Investigator (or designee), Sponsor, and Covance Medical Monitor. The subject must have been on a stable dose for a minimum of 3 months prior to study drug administration. The use of new medications or changing of doses of current medication is to be avoided from 3 months prior to study drug administration and throughout the study (until after the Follow-up visit), unless required for the treatment of an AE. On Day 1, administration of medications should be withheld for at least 2 hours pre-dose and 4 hours post-dose as clinically appropriate.

Any medication taken by a subject during the course of the study and the reason for its use will be documented in the source data. The administration of any concomitant medication during the study is prohibited without prior approval of the Investigator (or designee), unless its use is deemed necessary for the treatment of an AE or in a medical emergency.

### **6.2. Diet**

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

Subjects will be fasted overnight (at least 8 hours) prior to dosing on Day 1 and 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, subjects 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.

### **6.3. Smoking**

Subjects will not be permitted to smoke from 2 hours predose until 4 hours postdose. Cigarette (or equivalent tobacco- or nicotine-containing products) consumption will be limited to 10 cigarettes per day.

### **6.4. Exercise**

Subjects 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 (ie, will not begin a new exercise program nor participate in any unusually strenuous physical exertion).

### **6.5. Blood Donation**

Subjects are required to refrain from donation of blood from 3 months prior to Screening, plasma from 2 weeks prior to Screening, and platelets from 6 weeks prior to Screening until 3 months after the Follow-up visit.

## 7. STUDY ASSESSMENTS AND PROCEDURES

All assessments must be performed as per the Schedule of Assessments in [Appendix 6](#). At timepoints where more than 1 assessment is required, the following sequence should be followed as applicable, and priority will be given to the PK sample being taken at the scheduled time:

- obtain resting ECG
- collect resting vital signs
- collect blood sample for plasma PK determination or protein binding
- collect blood sample for blood chemistry, hematology, viral serology, coagulation, or pregnancy test
- study drug administration
- administer meal

Every effort will be made to schedule and perform the procedures as closely as possible to the nominal time, giving considerations to appropriate posture conditions, practical restrictions, and the other procedures to be performed at the same timepoint.

### 7.1. Pharmacokinetic Assessments

#### 7.1.1. Pharmacokinetic Blood Sample Collection and Processing

Blood samples (up to approximately  $1 \times 2.0$  mL for risdiplam and its metabolite, M1, per sample) will be collected by venipuncture or cannulation at the times indicated in the Schedule of Assessments in [Appendix 6](#). The date and time of PK sampling must be recorded. Blood samples (approximately 6.0 mL) will also be collected and analyzed for unbound risdiplam and M1 concentrations at the times indicated in the Schedule of Assessments.

Procedures for collection, processing, and shipping of PK and protein binding blood samples will be detailed in a separate document.

#### 7.1.2. Analytical Methodology

Plasma concentrations of risdiplam and its metabolite, M1, will be determined using a specific and validated LC-MS/MS method. Specifics of the analytical method will be provided in a separate document. Plasma concentrations of unbound risdiplam and unbound M1 will be determined by appropriate assays.

## 7.2. Safety and Tolerability Assessments

### 7.2.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in [Appendix 1](#).

The condition of each subject will be monitored from the time of signing the ICF to final discharge from the study. Subjects will be observed for any signs or symptoms and asked about their condition by open questioning, such as ‘How have you been feeling since you were last asked?’, at least once each day while resident at the study site and at each study visit. Subjects will also be encouraged to spontaneously report AEs occurring at any other time during the study.

All non-serious AEs, whether reported by the subject voluntarily or upon questioning, or noted on physical examination, will be recorded from initiation of study drug until study completion. Serious AEs will be recorded from the time the subject signs the ICF until study completion. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

Adverse events recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator’s (or designee’s) discretion.

### 7.2.2. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations (including clinical chemistry, hematology, coagulation, urinalysis, and serology) at the times indicated in the Schedule of Assessments in [Appendix 6](#). Clinical laboratory evaluations are listed in [Appendix 2](#). All subjects will have estimated creatinine clearance determined at Screening and Check-in (Day -1) using the Cockcroft-Gault equation:

- $\left( \frac{[1.23 \times (140 - \text{age}) \times (\text{weight in kg})]}{[\text{serum creatinine in } \mu\text{mol/L}]} \right)$  for male subjects
- $\left( \frac{[1.04 \times (140 - \text{age}) \times (\text{weight in kg})]}{[\text{serum creatinine in } \mu\text{mol/L}]} \right)$  for female subjects

Subjects will be asked to provide urine samples for drugs of abuse screen, and will undergo an alcohol test (either urine or breath) at the times indicated in the Schedule of Assessments in [Appendix 6](#). For all female subjects, a pregnancy test will be performed at the times indicated in the Schedule of Assessments in [Appendix 6](#).

An Investigator (or designee) will perform a clinical assessment of all clinical laboratory data.

Clinical laboratory assessments may be repeated once to confirm any values in the event of technical issues or unexpected results.

### **7.2.3. Vital Signs**

Supine blood pressure, supine pulse rate, and body temperature will be assessed at the times indicated in the Schedule of Assessments in [Appendix 6](#). Vital signs may also be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of vital signs is required.

All measurements will be performed singly, and repeated once if outside the relevant clinical reference range.

Subjects must be supine for at least 10 minutes before blood pressure and pulse rate measurements.

### **7.2.4. 12-Lead Electrocardiogram**

Resting 12-lead ECGs will be recorded in triplicate after the subject has been supine and at rest for at least 10 minutes at the times indicated in the Schedule of Assessments in [Appendix 6](#).

In the event of QT prolongation >500 ms or an increase >60 ms from the predose baseline average, postdose actions will include repeat ECGs on an hourly basis (or more often at the discretion of the Investigator) until stabilized.

Additional 12-lead ECGs may be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of ECGs is required. The Investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

### **7.2.5. Physical Examination**

A full physical examination or symptom-directed physical examination will be performed at the timepoints specified in the Schedule of Assessments in [Appendix 6](#).

## **8. SAMPLE SIZE AND DATA ANALYSIS**

### **8.1. Determination of Sample Size**

Up to 32 evaluable subjects will be enrolled in the study.

No formal sample size calculation has been performed. The sample size determination has been based on historical studies of a similar nature. Eight evaluable subjects per hepatic impairment function group (ie, mild and moderate) and 8 to 16 evaluable subjects with normal hepatic function are planned to complete the study. This is considered a sufficient sample size to evaluate the PK of risdiplam under various degrees of hepatic function.

## 8.2. Analysis Populations

### 8.2.1. Pharmacokinetic Population

The PK population will include all subjects who received a dose of risdiplam and have evaluable PK data. A subject will be excluded from the PK descriptive statistics and statistical analysis if the subject has an AE of vomiting that occurs at or before 2 times median time to maximum concentration or if they have any major protocol deviation(s) thought to impact PK analysis.

### 8.2.2. Safety Population

The safety population will include all subjects who received a dose of risdiplam.

## 8.3. Pharmacokinetic Analyses

Arithmetic and geometric means, geometric coefficient of variation (CV)%, arithmetic standard deviation (SD), median, minimum, maximum, and number of observations will be calculated for all PK concentrations and parameters in each hepatic function group. Geometric mean and geometric CV% will be provided for all PK parameters except  $T_{max}$  and  $\%AUC_{extrap}$ .

Plasma concentrations of risdiplam and its metabolite M1 will be listed and summarized by hepatic function, and individual and mean concentration data will be plotted. The plasma PK parameters of risdiplam and its metabolite M1 will be calculated using standard non-compartmental methods using commercial software such as Phoenix<sup>TM</sup> WinNonlin<sup>®</sup> (Certara USA, Inc., Version 6.4 or higher). Actual elapsed time from dosing will be used to estimate all individual plasma PK parameters for each subject. Additional details will be provided in a separate Statistical Analysis Plan (SAP).

The primary analysis is the evaluation of the PK of risdiplam (and M1, as appropriate) following a single dose in subjects with mild or moderate hepatic impairment ('Test' groups), compared to subjects with normal hepatic function ('Reference' group). The PK parameters in subjects with normal hepatic function will be used as 'Reference' and the PK parameters in subjects with hepatic impairment will be used as 'Test'. Pharmacokinetic parameters will be listed and summarized, including a listing of individual ratios of  $AUC_{inf}$  and  $C_{max}$  of risdiplam and its metabolite M1 in subjects with mild or moderate hepatic impairment to those in subjects with normal hepatic function (Test:Reference) and a summary containing the geometric means of the ratios for  $AUC_{inf}$  and  $C_{max}$ .

The primary PK parameters are  $AUC_{inf}$  and  $C_{max}$  for risdiplam (and M1, as appropriate); all other PK parameters will be regarded as secondary and will not be subject to inferential statistical analysis. An analysis of variance (ANOVA) will be used to estimate the effect of hepatic impairment on the primary PK parameters ( $AUC_{inf}$  [or  $AUC_{last}$  if appropriate] and  $C_{max}$ ) including the factor 'hepatic impairment' (ie, mild, moderate, or none). The PK parameters will be log-transformed prior to analysis. The data from subjects with mild or moderate hepatic impairment and their matched control subjects will be included in the analysis. Geometric mean ratios and the corresponding 90% confidence intervals (CIs) of  $AUC_{inf}$  (or  $AUC_{last}$ , as appropriate) and  $C_{max}$  of risdiplam between the groups of hepatically

impaired subjects and healthy subjects with normal hepatic function will be calculated. Additional statistical analyses, on primary and/or on secondary PK parameters, may be conducted as appropriate.

#### **8.4. Safety Analysis**

In the case of continuous variables, descriptive statistics will be used to summarize results and changes from baseline, as appropriate, by hepatic function group and timepoint. The minimum set of summary statistics for numeric variables will be: number of observations, mean, SD, median, minimum, and maximum. The values of categorical assessments will be tabulated. Categorical data will be summarized in frequency tables with number of observations and percentage. Summaries of a categorical variable will include all recorded values.

All safety and tolerability data will be listed, and a listing of the subjects with hepatic impairment and their matched subject with normal hepatic function will be provided. Each AE will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). All AEs will be listed and summarized using descriptive methodology. The incidence of AEs for each treatment will be presented by severity and by association with the study drug as determined by the Investigator (or designee). Values for clinical laboratory data (including estimated creatinine clearance), vital signs, and 12-lead ECGs will be summarized by impaired hepatic function group. For the 12-lead ECGs evaluated at Screening, the mean will be recorded.

No formal statistical analyses of the safety data are planned.

#### **8.5. Interim Analysis**

Preliminary PK and safety and tolerability data from a minimum of 4 subjects with mild hepatic impairment and 4 matched subjects with normal hepatic function will be reviewed prior to the start of Part 2.

No other interim analyses are planned for this study.

### **9. REFERENCES**

1. F. HOFFMANN-LA ROCHE LTD. RO7034067 – Investigator’s Brochure (Version 5). March 2018.
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):R111-118.
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 U S A.* 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. Food and Drug Administration. Guidance for Industry: Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling [Internet]. Food and Drug Administration; 2003. Available from: <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072123.pdf>
11. European Medicines Agency. Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function. (CPMP/EWP/2339/02) [Internet]. European Medicines Agency; 2005. Available from: [https://www.ema.europa.eu/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-impaired-hepatic-function\\_en.pdf/2009/09/WC500003750.pdf](https://www.ema.europa.eu/documents/scientific-guideline/guideline-evaluation-pharmacokinetics-medicinal-products-patients-impaired-hepatic-function_en.pdf/2009/09/WC500003750.pdf)

## **10. APPENDICES**

## **Appendix 1: Adverse Event Reporting**

### **1. Definition of Adverse Event**

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

### **2. Events Meeting the Adverse Event Definition**

- Any deterioration in a laboratory value (hematology, clinical chemistry, or urinalysis) or other clinical test (eg, electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study treatment.
- 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 (eg, screening invasive procedures such as biopsies).

### **3. Events NOT Meeting the Adverse Event Definition**

- Any clinically significant abnormal laboratory findings (or deemed to be clinically significant) 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 subject'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 subject's condition.
- Medical or surgical procedure (eg, 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.

### **4. Definition of Serious Adverse Events**

If an event is not an AE per definition above, then it cannot be a serious adverse event (SAE) even if serious conditions are met (eg, 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 either:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- results in a congenital anomaly/birth defect
- results in an important medical event (see below).

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this 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.

## **5. Definition of Life-threatening**

An AE is life-threatening if the subject was at immediate risk of death from the event as it occurred (ie, does not include a reaction that might have caused death if it had occurred in a more serious form). For instance, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal.

## **6. Definition of Hospitalization**

Adverse events requiring hospitalization should be considered serious. In general, hospitalization signifies that the subject has been detained (usually involving an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate at 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 as serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

## 7. Recording of Adverse Events and/or Serious Adverse Events

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

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

It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Covance Medical Monitor in lieu of completion of the eCRF.

There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject 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.

## 8. Non-serious Adverse Events of Special Interest

Non-serious adverse events of special interest (NSAESI) are required to be reported by the Investigator to the Sponsor immediately (ie, no more than 24 hours after learning of the event [[Section 13 \(Appendix 1\)](#)]).

Non-serious AEs of special interest for this study include the following:

- Cases of an elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) in combination with either an elevated total bilirubin or clinical jaundice, as defined below:
  - The finding of an elevated ALT or AST in combination with either an elevated total bilirubin or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of potential severe liver injury. Therefore, Investigators must report as an AE the occurrence of either of the following:
    - Treatment-emergent ALT or AST  $>5 \times$  upper limit of normal (ULN) value in combination with total bilirubin  $>2 \times$  ULN (of which  $\geq 35\%$  is direct bilirubin).
    - Treatment-emergent ALT or AST  $>5 \times$  ULN value in combination with clinical jaundice.
- Suspected transmission of an infectious agent by the study treatment, as defined below:
  - Any organism, virus, or infectious particle (eg, prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be

suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study treatment is suspected.

## 9. Assessment of 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 [eg, National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) 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 eCRF.

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

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 (as a guidance for assessing AE severity) using the following categories:

- **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 [Section 4 \(Appendix 1\)](#).

## 10. Assessment of Causality

Investigators should use their knowledge of the subject, 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 re-introduction of study treatment.
- 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 subject 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.

## **11. Follow-up of Adverse Events and Serious Adverse Events**

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 healthcare professionals.

If a subject 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 eCRF.

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

## **12. 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 adverse events
- NSAESI
- pregnancies
- accidental overdoses or medication errors
- medical device complaints

The Investigator must report new significant follow-up information for these events to the Sponsor immediately (ie, 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).

### **13. Reporting Requirements of Serious Adverse Events and Non-serious Adverse Events of Special Interest**

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

#### **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 (eg, SAEs related to invasive procedures such as biopsies). The Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to Investigators should be completed and submitted to the SAE Responsible immediately (ie, no more than 24 hours after learning of the event). Any other AEs should not be reported.

#### **Events that Occur after Study Treatment Initiation**

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

For reports of SAEs and NSAESIs that occur after initiation of study treatment, Investigators should record all case details that can be gathered immediately (ie, within 24 hours after learning of the event) on the appropriate Adverse Event of Special Interest/Serious Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to the Sponsor's Safety Risk Management department.

In the event that the EDC system is unavailable, 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 immediately (ie, no more than 24 hours after learning of the event).

Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

### **14. Reporting of Post-study Adverse Events and Serious Adverse Events**

The Investigator is not required to actively monitor subjects for AEs after the end of the AE reporting period ([Section 15 \[Appendix 1\]](#)).

If the Investigator becomes aware of any other SAE 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.

## **15. Pregnancy**

Male patients will be instructed through the Informed Consent Form to immediately inform the Investigator if their female partner becomes pregnant during the study or within 4 months after their 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 the following sections.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

### **Male Subjects with Partners Who Become Pregnant**

The Investigator will attempt to collect pregnancy information on any male subject's female partner who becomes pregnant while the male subject is in this study. This applies only to male subjects who receive risdiplam.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male subject 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 subject 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 subject'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.

### **Female Subjects Who Become Pregnant**

The Investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a subject's pregnancy. The subject will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the subject and the neonate, which will be forwarded to the Sponsor. Monitoring of the subject should continue until conclusion of the pregnancy. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, and should not be recorded on the Adverse Event eCRF, any pregnancy complication will be reported as an AE or SAE. A

spontaneous abortion is always considered to be an SAE and will be reported as such. Any post-study pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor ([Section 15 \[Appendix 1\]](#)). While the Investigator is not obligated to actively seek this information in former study subjects, he/she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating in the study will discontinue study treatment.

## **16. Abortions**

A spontaneous abortion should be classified as an SAE (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event).

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

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

## **17. Congenital Anomalies/Birth Defects**

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

## **18. 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, 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 document:

- [Risdiplam Investigator's Brochure](#)<sup>1</sup>

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

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

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

## **19. Diagnosis versus Signs and Symptoms**

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

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

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (eg, 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.

## **20. Adverse Events Occurring Secondary to Other Events**

In general, AEs occurring secondary to other events (eg, 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.

## **21. Persistent or Recurrent Adverse Events**

A persistent AE is one that extends continuously, without resolution, between subject 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 subject evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately on the Adverse Event eCRF.

## 22. 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 (eg, dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention (eg, 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 (eg, alkaline phosphatase and bilirubin 5 times ULN associated with cholecystitis), only the diagnosis (ie, 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 (eg, '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.

## 23. 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 (eg, dosage modification, treatment interruption, or treatment discontinuation).
- Results in a medical intervention or a change in concomitant therapy.
- Clinically significant in the Investigator's judgment.

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

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (eg, high blood pressure), only the diagnosis (ie, 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.

#### **24. Abnormal Liver Function Tests**

The finding of an elevated ALT or AST in combination with either an elevated total bilirubin 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:

- For healthy subjects and subjects with mild hepatic impairment:
  - 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
- For subjects with moderate hepatic impairment:
  - treatment-emergent ALT or AST  $>5 \times$  ULN in combination with total bilirubin  $>2 \times$  ULN (of which  $\geq 35\%$  is direct bilirubin)
  - treatment-emergent ALT or AST  $>5 \times$  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 19 \[Appendix 1\]](#)) and reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event), either as an SAE or an NSAESI ([Section 13 \[Appendix 1\]](#)).

#### **25. Deaths**

All deaths that occur during the protocol-specified AE reporting period ([Section 13 \[Appendix 1\]](#)), 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 (eg, 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 (eg, ‘sudden cardiac death’).

## **26. 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 (eg, ‘more frequent headaches’).

## **27. Hospitalization or Prolonged Hospitalization**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition in [Section 4 \[Appendix 1\]](#)), 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 (eg, for study treatment administration or insertion of access device 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 subject 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.

## 28. Cases of Accidental Overdose or Medication Error

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 AE. Each AE associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (ie, no more than 24 hours after learning of the event; [Section 13 \[Appendix 1\]](#)). For risdiplam, AEs associated with special situations should be recorded as described below for each situation:

- Accidental overdose: enter the AE 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 eCRF 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 (eg, 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 2 entries on the Adverse Event eCRF, 1 entry to report the accidental overdose and 1 entry to report the headache. The ‘Accidental overdose’ and ‘Medication error’ boxes would need to be checked for both entries.

**Appendix 2: Clinical Laboratory Evaluations**

<b>Clinical chemistry:</b>	<b>Hematology:</b>	<b>Urinalysis:</b>
Alanine aminotransferase (ALT) Albumin Alkaline phosphatase (ALP) Aspartate aminotransferase (AST) Calcium Chloride Total cholesterol Creatinine Creatine kinase Gamma-glutamyl transferase (GGT) Glucose Potassium Phosphate Sodium Total bilirubin <sup>a</sup> Triglycerides Total protein Uric acid	Hematocrit Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential: Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Blood Glucose Leukocyte esterase Nitrite pH Protein Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive)
	<b>Coagulation:</b>	<b>Other tests:</b>
	Activated partial thrombin time (aPTT) Partial thromboplastin time Prothrombin time (PTT) International normalized ratio (INR)	Estimated creatinine clearance (according to formulas) <sup>b,c</sup>
<b>Serology<sup>d</sup>:</b>	<b>Drug screen<sup>b</sup>:</b>	<b>Hormone panel - females only:</b>
Hepatitis B surface antigen Hepatitis C antibody Human immunodeficiency (HIV-1 and HIV-2) antibodies and p24 antigen	Including but not limited to: Amphetamines/methamphetamines Barbiturates Benzodiazepines Cocaine (metabolite) Methadone Phencyclidine Opiates Tetrahydrocannabinol/cannabinoids Alcohol test	Follicle-stimulating hormone (females aged <55 years only) <sup>d</sup> Estradiol <sup>d</sup> Serum pregnancy test (human chorionic gonadotropin) <sup>e</sup>

a. Direct and indirect bilirubin will be analyzed if total bilirubin is elevated.

b. Only analyzed at Screening and Check-in (Day -1).

c. Estimated creatinine clearance will be calculated as follows:

$([1.23 \times (140 - \text{age}) \times (\text{weight in kg})] / ([\text{serum creatinine in } \mu\text{mol/L}]))$  for male subjects

$([1.04 \times (140 - \text{age}) \times (\text{weight in kg})] / ([\text{serum creatinine in } \mu\text{mol/L}]))$  for female subjects

d. Only analyzed at Screening.

e. Performed at Check-in (Day -1) and at the Follow-up visit for all females.

### Appendix 3: Total Blood Volume

The following blood volumes will be withdrawn for each subject.

	Volume per blood sample	Maximum number of blood samples	Total amount of blood
Clinical chemistry	8.5 mL	9	76.5 mL
Hematology	4.0 mL	9	36.0 mL
Coagulation	4.5 mL	9	40.5 mL
Follicle-stimulating hormone (FSH) <sup>a,b</sup> and estradiol <sup>b</sup>	5.0 mL	1	5.0 mL
Pregnancy test <sup>b,c</sup> , as applicable	3.5 mL	2	7.0 mL
Serology	5.0 mL	1	5.0 mL
Risdiplam pharmacokinetics	2.0 mL <sup>d</sup>	27	54.0 mL
Protein binding	6.0 mL	3	18.0 mL
<b>Total:</b>			<b>242.0 mL</b>

a. Female subjects aged <55 years only.

b. May be included with clinical chemistry, as per local requirements.

c. In all female subjects at Check-in (Day -1) and at the Follow-up visit.

d. Maximum amount of blood to be taken.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 450 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

## **Appendix 4: Contraception Guidance**

### **Definitions**

#### **Women of Non-childbearing Potential:**

1. **Surgically sterile:** females who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to Screening.
2. **Post-menopausal:** females at least 45 years of age with amenorrhea for 12 months without an alternative medical reason with confirmatory follicle-stimulating hormone (FSH) levels within the post-menopausal range designated per the laboratory (FSH will be assessed in females aged <55 years) and estradiol test without hormone replacement therapy [HRT]). The amenorrhea should not be induced by a medical condition such as anorexia nervosa, hypothyroid disease or polycystic ovarian disease, or by extreme exercise. It should not be due to concomitant medications that may have induced the amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormones, anti-estrogens, or selective estrogen receptor modulators. Women aged <55 years whose FSH values are not  $\geq 40$  mIU/L may be included at the discretion of the Investigator and in consultation with the Sponsor.

**Fertile male:** a male that is considered fertile after puberty.

**Infertile male:** permanently sterile male via bilateral orchiectomy.

### **Contraception Guidance**

#### **Female Subjects**

Female subjects who are of non-childbearing potential will not be required to use contraception.

#### **Male Subjects**

Male subjects (whether surgically sterilized or not) with partners of childbearing potential must use a male barrier method of contraception (ie, male condom with spermicide) in addition to a second method of acceptable contraception from Screening until 4 months after their dose of the study drug. Acceptable methods of contraception for female partners include:

- hormonal injection
- combined oral contraceptive pill or progestin/progestogen-only pill
- combined hormonal patch
- combined hormonal vaginal ring

- surgical method (bilateral tubal ligation or Essure<sup>®</sup> [hysteroscopic bilateral tubal occlusion])
- hormonal implant
- hormonal or non-hormonal intrauterine device
- over-the-counter sponge with spermicide
- cervical cap with spermicide
- diaphragm with spermicide.

An acceptable second method of contraception for male subjects is vasectomy that has been performed at least 90 days prior to the Screening visit, with verbal confirmation of surgical success.

For male subjects (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or lactating should be avoided unless condoms are used from the time of the dosing until 4 months after their dose of the study drug. Male subjects are required to refrain from donation of sperm from Check-in (Day -1) until 4 months after their dose of the study drug.

### **Sexual Abstinence and Same-sex Relationships**

For subjects who practice true abstinence, subjects must be abstinent for at least 6 months prior to Screening and must agree to remain abstinent from the time of signing the Informed Consent Form (ICF) until 4 months after their dose of the study drug. If a subject who is abstinent at the time of signing the ICF becomes sexually active they must agree to use contraception as described previously.

Subjects in same-sex relationships at the time of signing the ICF must agree to refrain from engaging in a heterosexual relationship from the time of signing the ICF until 4 months after their dose of the study drug. If a subject becomes engaged in a heterosexual relationship during the study from the time of signing the ICF until 4 months after their dose of the study drug, contraception guidelines as outlined above, will be applicable.

## **Appendix 5: Regulatory, Ethical, and Study Oversight Considerations**

### **Regulatory and Ethical Considerations**

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines.
- Applicable laws and regulations.

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an Institutional Review Board (IRB) by the Investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB and regulatory authority (as locally required) approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
- Notifying the IRB of serious adverse events (SAEs) or other significant safety findings as required by IRB procedures.
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

### **Finances and Insurance**

Financing and insurance will be addressed in a separate agreement.

### **Informed Consent**

Prior to starting participation in the study, each subject will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Subjects will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time. Subjects will be given an opportunity to ask questions about the study prior to providing consent for participation.

Following discussion of the study with Clinical Research Unit (CRU) personnel, subjects will sign 2 copies of the ICF in the presence of a suitably trained member of staff to indicate that they are freely giving their informed consent. One copy will be given to the subject, and the other will be maintained in the subject's records.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

### **Subject Data Protection**

Subjects will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Subject and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual subjects or Investigator(s) will be redacted according to applicable laws and regulations.

The subject 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 subject. The subject must also be informed that his/her study-related data may be examined by Sponsor or Contract Research Organization (CRO) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

### **Disclosure**

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

### **Data Quality Assurance**

The following data quality steps will be implemented:

- All relevant subject data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The Investigator must permit study-related monitoring, audits, IRB 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. Predefined agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a

risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.

- A Study Monitor will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) 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.

### **Investigator Documentation Responsibilities**

All individual, subject-specific study data will also be entered into a 21 CFR Part 11-compliant electronic data capture (EDC) system on an eCRF in a timely fashion.

All data generated from external sources (eg, laboratory and bioanalytical data), and transmitted to the Sponsor or designee electronically, will be integrated with the subject's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each subject who signs an ICF and is enrolled in the study, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the EDC system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, data queries, and site notifications.

### **Publications**

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.

**Appendix 6: Schedule of Assessments**

**Table 2: Schedule of Assessments**

Study Procedures	Screening (Days -28 to -2)	In-clinic Stay		Outpatient Visits						Follow-up (28±3 days postdose)
		Day -1	Days 1 to 14	15	16	18	20	22	24	
Informed consent	X									
Inclusion/exclusion criteria	X	X								
Demographic data	X									
Medical history	X	X <sup>a</sup>								
Child-Pugh classification <sup>b</sup>	X	X								
Assessment of estimated creatinine clearance <sup>c</sup>	X	X								
Urinary drug screen	X	X								
Alcohol test <sup>d</sup>	X	X								
Serology	X									
Pregnancy test <sup>e</sup>		X								X
Follicle-stimulating hormone <sup>f</sup> and estradiol	X									
Height and body weight	X <sup>g</sup>	X								
<b>Study residency:</b>										
Check-in		X								
Check-out			Day 14 <sup>h</sup>							
Nonresidential visit	X			X	X	X	X	X	X	X
<b>Study drug administration:</b>										
Risdiplam			Day 1 (0 hours)							
<b>Pharmacokinetics (PK):</b>										
Blood sampling <sup>i</sup>			Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, and 312 hours postdose	X	X	X	X	X	X	
Protein binding			3, 24, and 144 hours postdose							

Study Procedures	Screening (Days -28 to -2)	In-clinic Stay		Outpatient Visits						Follow-up (28±3 days postdose)
		Day -1	Days 1 to 14	15	16	18	20	22	24	
<b>Safety and tolerability:</b>										
Adverse event recording	X	X	Ongoing	X	X	X	X	X	X	X
Prior/concomitant medication monitoring	X	X	Ongoing	X	X	X	X	X	X	X
Clinical laboratory evaluations	X	X	Day 1: 24, 72, 168, and 264 hours postdose		X		X			X
Vital signs (blood pressure, pulse rate, and body temperature)	X	X	Day 1: predose, 2, 4, 8, and 24 hours postdose Day 14		X		X			X
12-lead electrocardiogram (ECG) <sup>j</sup>	X	X	Day 1: predose, 2, 4, 8, and 24 hours postdose Day 14		X		X			X
Full physical examination	X	X								
Symptom-directed physical examination			Prior to discharge on Day 14		X		X			X

Abbreviations: ECG= electrocardiogram(s); PK = pharmacokinetic(s).

- a. Interim medical history.
- b. Subjects with hepatic impairment only.
- c. Estimated creatinine clearance will be calculated using the Cockcroft-Gault equation:  

$$([1.23 \times (140 - \text{age}) \times (\text{weight in kg})] / ([\text{serum creatinine in } \mu\text{mol/L}]))$$
 for male subjects  

$$([1.04 \times (140 - \text{age}) \times (\text{weight in kg})] / ([\text{serum creatinine in } \mu\text{mol/L}]))$$
 for female subjects
- d. May be performed in either urine or breath. At Screening, a positive alcohol test may be repeated once. At Check-in (Day -1), a positive alcohol test may not be repeated.
- e. In all female subjects; performed in serum at Check-in (Day -1) and at the Follow-up Visit.
- f. Females aged <55 years only.
- g. Height measured at Screening only.
- h. Subjects will check-out of the Clinical Research Unit (CRU) following the 312 hours postdose PK blood sample.
- i. Blood samples for risdiplam PK analysis will be taken at predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours postdose.
- j. 12-lead ECGs will be recorded in triplicate with at least 1 minute between recordings.