EU RISK MANAGEMENT PLAN FOR EVRYSDI®/RISDIPLAM

RMP version to be assessed as part of this application:

RMP Version number: 2.0

Data lock point for this RMP: 18 August 2023

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
13-Oct-2023 07:47:41	Company Signatory (PV)	PPD
13-Oct-2023 14:31:25	QPPV	Gellert, Birgitt (gellertb)

Table of Contents

List of Tables

List of Annexes

Rationale for Submitting an Updated RMP

The EU Risk Management Plan (RMP) Version 2.0 was prepared for the removal of the important potential risk of retinal toxicity with risdiplam due to the absence of evidence of retinal toxicity based on thorough ophthalmological monitoring in clinical studies to date. As such, the amendments made in EU RMP v2.0 will be restricted only to sections relevant for the removal of important potential risk of retinal toxicity. The other changes will be performed in an upcoming RMP update.

Summary of Significant Changes in This RMP (v2.0):

Part	Summary of significant changes	Rationale
I	The indication and dosage section in the Product Overview table updated to current status	To align with the latest SmPC
SII.1.1 and SII.5	Updated to indicate that retinal toxicity is no longer considered an important potential toxicity.	Retinal toxicity has not been observed in clinical studies at the pivotal dose
Table 17 (SIV.1)	Rationale updated to clarify that no findings of retinal toxicity observed following extensive monitoring across clinical studies.	New information following review of retinal toxicity
Part II, SV.1 and Annex 7	Post-authorization exposure updated with data from the latest PBRER (Report No. 1122884; DLP: 6 August 2023). The cumulative patient exposure per region has been moved to Annex 7.	New information available
Part II, SVII.2	Added rationale for removing retinal toxicity from the list of safety concerns (important potential risk). Reference to DSR Report No. 1127141 added.	New information following review of retinal toxicity
Part II, SVII.3.1 and Table 22 (Part II, SVIII)	Updated to indicate that retinal toxicity is no longer considered an important potential toxicity.	New information following review of retinal toxicity
Part III (III.2 and III.3), Part V (V.1 and V.3), Part VI (II.A IIB, and II.C.2)	Updated to indicate that retinal toxicity is no longer considered an important potential toxicity.	New information following review of retinal toxicity
Annex 2	Clarified in the table that “Retinal toxicity” evaluation has been completed although studies are ongoing in the Pharmacovigilance study program.	New information following review of retinal toxicity
Annex 7	New literature references added.	New information available.
Annex 7	Summary tabulations of prospective and retrospective ICSRs on pregnancy have been appended.	Compliance with EMA Pregnancy and Breastfeeding Guidance (GVP P.III)

Part	Summary of significant changes	Rationale
Annex 8	Annex 8 was updated to reflect the changes to this RMP.	Reflect key changes during RMP update.

DLP = data lock point; DSR = Drug Safety Report; PBRER = Periodic Benefit Risk Evaluation Report; RMP = Risk Management Plan; SmPC = Summary of Product Characteristic(s).

Other RMP Versions under Evaluation

Not applicable.

Details of Currently Approved RMP

RMP Version Number: 1.5

Approved with Procedure Number: EMEA/H/C/005145/II/0005/G

Date of approval (opinion date): 20 July 2023

See page 1 for signature and date

Dr. Birgitt Gellert (QPPV) | Date

See page 1 for signature and date

PPD | Date

PART I: PRODUCT(S) OVERVIEW

Table 1 Product(s) Overview

Active Substance(s) (INN or common name)	Risdiplam
Pharmacotherapeutic group(s) (ATC Code)	M09AX10
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the EEA	Evrysdi
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: small molecule *SMN2* splicing modifier
	Summary of mode of action: Evrysdi modulates *SMN2* splicing to include exon 7 into the mRNA transcript, thereby increasing the expression of full-length protein from the *SMN2* gene.
	Important information about its composition: Evrysdi is a powder for oral solution. Each mL of the constituted solution contains 0.75 mg risdiplam. Evrysdi contains less than 1 mmol sodium (23 mg) in a maximum daily dose volume of 6.6 mL of 0.75 mg/mL oral solution, i.e. essentially 'sodium-free'.
Hyperlink to the Product Information	Refer to EU PI
Indication(s) in the EEA	Current: Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies.

Dosage in the EEA	Current: Evrysdi is taken orally once daily using the re-usable oral syringe provided, at approximately the same time each day. The recommended once daily dose of Evrysdi for SMA patients is determined by age* and body weight as follows: • < 2 months of age: 0.15 mg/kg body weight • 2 months to < 2 years of age: 0.20 mg/kg body weight • ≥ 2 years of age and < 20 kg body weight: 0.25 mg/kg body weight • ≥ 2 years of age and ≥ 20 kg body weight: 5 mg * based on corrected age for preterm infants
Pharmaceutical form(s) and strengths	Current: 0.75 mg/mL powder for oral solution Proposed (if applicable): Not applicable
Is or will the product be subject to additional monitoring in the European Union?	Yes

EEA = European Economic Area; INN= International non-proprietary name; SMA= spinal muscular atrophy.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
CHMP	Committee for Medicinal Products for Human Use
DSR	Drug Safety Report
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
E.U. RMP	E.U. Risk Management Plan
GVP	Good Pharmacovigilance Practice
IB	Investigator's Brochure
IBD	international birth date
MAA	Marketing Authorization Application
PV	Pharmacovigilance
PI	Product Information
PIP	Pediatric Investigation Plan
RMP	Risk Management Plan
SAE	serious adverse event
SMA	spinal muscular atrophy
SMQ	Standardised MedDRA Query
SmPC	Summary of Product Characteristics

PART II: SAFETY SPECIFICATION

PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1SPINAL MUSCULAR ATROPHY

Spinal muscular atrophy (SMA) is an autosomal recessive disorder caused by homozygous mutations of the Survival of Motor Neuron 1 gene (*SMN1*) that results in lack of functional SMN protein which leads to severe dysfunction of motor neurons of the spinal cord (Verhaart et al. 2017b). There is a wide range of clinical severity in SMA, and the main determinant of disease phenotype is the copy number of the *SMN2* gene, a low-functioning paralogue of *SMN1* (Belter et al. 2018).

SMA is a spectrum of motor and functional disabilities, characterized by age of onset and highest motor milestone achieved. Patients are usually categorized into the following four main subtypes based on clinical criteria, including achieving (or failing to achieve) physical motor milestones, age of onset, and lifespan (Cobben et al. 2008; D'Amico et al. 2011; Farrar et al. 2013; Finkel et al. 2014; Lunn and Wang 2008; Munsat and Davies 1992; Sproule 2014; Zerres et al. 1997):

- Type 1 SMA (Werdnig-Hoffmann disease, approximately 50-60% of SMA births): severe infantile type, with an onset before 6 months of age and failure to achieve the ability to sit independently, usually requiring feeding and/or ventilation support by month 12, with the eventual use of permanent ventilation and death due to respiratory distress, usually within 2 years if untreated.
- Type 2 SMA (approximately 20-25% of SMA births): intermediate chronic infantile type with onset between the age of 7 and 18 months, unable to stand or walk independently; these patients are initially able to maintain a sitting position without help but eventually become wheelchair-dependent and show a reduced life expectancy compared with the general population (up to 30-40 years, if treated appropriately).
- Type 3 SMA (Kugelberg-Welander disease, approximately 10% of SMA births): mild chronic juvenile type with a broad span of age at onset from 18 months into the third decade of life, able to stand and walk independently for some period of time. This phenotype comprises weaker patients, who progress rapidly to lose ambulation and become functionally like patients with Type 2, and stronger patients, who are ambulatory for a longer time, but who eventually become progressively weaker and wheelchair-dependent. Most Type 3 SMA patients live into adulthood and show a normal life span.
- Type 4 SMA: rare mild form with adult onset and normal life expectancy.

A fifth type, denoted as Type 0, has been proposed for extremely severe SMA that manifests during fetal life and results in death within a few weeks after birth (Kolb and Kissel 2015).

Consistent with disease etiology, several studies have reported a phenotype-genotype relationship among patients with SMA, showing that high copy number of *SMN2* ameliorates the clinical severity in patients (Feldkotter et al. 2002; Mailman et al. 2002). The majority of patients with Type 1 SMA have two *SMN2* copies; patients with Type 2 SMA usually have three *SMN2* copies; patients with Type 3 SMA have three or four *SMN2* copies; and patients with Type 4 SMA have four or more *SMN2* copies (Crawford et al. 2012). *SMN2* copy number is currently regarded as a determinant of SMA disease severity.

An overview of the clinical characteristics of different subtypes is provided in Table 2.

The epidemiologic burden of SMA is not equally divided over the subtypes, because of the difference in survival patterns across SMA subtypes (Verhaart et al. 2017b). Type 1 SMA has the highest birth incidence but also the lowest point prevalence, as it is the most severe form and historically, more than 90% of Type 1 SMA patients do not survive after 2 years of age. Patients with Type 2 SMA, have a longer life expectancy, resulting in high prevalence as compared with Type 1 SMA (Verhaart et al. 2017b).

Table 2 Clinical classification of spinal muscular atrophy

Type	Age of onset		Incidence (%)	Prevalence (%)	Maximum Motor Function	*SMN2* Copy Number	Life Expectancy
0	Fetal		<1	0	Nil	1	Days-Weeks
1	<6 Months	1A: 0-2 Weeks 1B: <3 Months 1C: >3 Months	60	15	Never sits	1, 2, 3	<2 years
2	6-18 Months		25	70	Sits, never walks	2, 3, 4	Adulthood
3	1.5-10 Years	3A: <3 Years 3B: >3 Years	15	15	Walks Regression	3, 4, 5	Normal
4	>35 Years		<1	1	Walks Slow decline	4, 5, 6	Normal

Modified according to (Butchbach 2016; Castro and Iannaccone 2014; Feldkotter et al. 2002; Finkel et al. 2015).

SI.1.1 Incidence

In Europe, 3776 patients were genetically diagnosed within a 5-year period from 2011 to 2015. The median incidence of SMA from 18 European countries in the period 2011-2015 was 11.9 per 100,000 (range 6.3-25.5 per 100,000 [~1 in 3900-16,000]). In Germany and Croatia, several laboratories have indicated that they perform cross-border testing, which could account for the higher reported incidence of 25.5 per 100,000 and 21.1 per 100,000, respectively (Verhaart et al. 2017a).

A recent systematic review published in 2017 (Verhaart et al. 2017b) found only a few incidence estimates for North America with most of them being outdated or originating from very local studies (Burd et al. 1991; Prior et al. 2010; Winsor et al. 1971). These annual estimates ranged from 6.5 per 100,000 in Canada (Winsor et al. 1971) to 14.9 per 100,000 in the U.S. (Prior et al. 2010). Despite conducting additional literature searches, no recent incidence rates have been identified so far for North America.

Table 3 presents incidence estimates of genetically diagnosed SMA cases, across European and American countries.

The epidemiologic burden of SMA is not equally divided over the subtypes. A review of the epidemiology literature covering regional and national studies performed in Europe, reported an overall incidence rate of 10 per 100,000 live births. The break down by SMA type was Type 1 SMA: 5.9 per 100,000, Type 2: 2.7 per 100,000; Type 3: 1.4 per 100,000 live births (Ogino et al. 2004).

Table 3 Incidence of Spinal Muscular Atrophy

Country	Years	Number of patients diagnosed with SMA	Number of live births	Incidence (per 100,000)	95% CI for incidence (per 100,000)
Finland*	2011-2015	30	289,746	10.4	7.0–14.8
Denmark*	2011-2015	29	292,640	9.9	8.6–14.3
UK*	2011-2015	438	4,020,416	10.9	9.9–12.0
Ireland*	2011-2015	24	358,933	6.7	4.3–10.0
The Netherlands*	2011-2015	89	885,145	10.1	8.1–12.4
Belgium*	2011-2015	73	643,834	11.3	8.9–14.3
France*	2011-2015	816	3,935,757	20.7	19.3–22.2
Germany*	2011-2015	857	3,357,275	25.5	23.8–27.3
Italy*	2011-2015	550	2,565,747	21.4	19.7–23.3
Slovenia*	2011-2015	17	107,884	15.8	9.2–25.2
Croatia*	2011-2015	44	208,850	21.1	15.3–28.2
Bulgaria*	2011-2015	77	343,462	22.4	17.7–28.0
Hungary [a]*	2015	21	92,761	22.6	14.0–34.6
Slovakia*	2011-2015	45	284,463	15.8	11.5–21.2
Czech Republic*	2011-2015	64	538,446	11.9	9.2–15.2
Poland*	2011-2015	240	2,005,665	12.0	10.5–13.6
Ukraine*	2011-2015	240	2,439,376	9.8	8.6–11.2
Cyprus*	2011-2015	3	47,582	6.3	1.3–18.4
United States# (North Dakota)	1980–1987	14	94,092	14.9	Not reported
United States** (Ohio)	Not reported	4	40,103	10.0	Not reported
Canada (Ontario)	1955-1965	4	61,752	6.5	Not reported

Sources: *(Verhaart et al. 2017a) / # (Burd et al. 1991) / **(Prior et al. 2010)

SI.1.2 Prevalence

A large prevalence study (Verhaart et al. 2017a) used two global SMA registries: the Global SMA Patient Registry and the Care and Trial Site Registry (CTSR), together covering 46 countries. In these data sources, SMA diagnoses relied on genetic testing for SMN1 and/or clinical examination. In 2015, the global prevalence rates of all-type SMA ranged from 0.01 to 2.43 per 100,000 in the Global Patient Registry and from 0.00 to 4.11 per 100,000 in the CTSR. Except five older studies focusing on very small areas (Czeizel and Hamula 1989; Forsgren et al. 1983; Merlini et al. 1992; Mostacciuolo et al. 1992; Tangsrud and Halvorsen 1988), all other selected studies provided consistent prevalence estimates which were included within the aforementioned range. Of the 21 European countries investigated (Verhaart et al. 2017a), prevalence estimates

for all-type SMA were 0.64 and 0.70 per 100,000 in the Global SMA Patient Registry and the CTSR, respectively. The total number of SMA patients in 2005 was thus comprised between 2,458 and 3,441 for a total population catchment area of 490,278,605 inhabitants. Denmark had the highest prevalence rates for both registries (2.43 and 4.11 per 100,000 respectively) while Ireland presented the lowest rate (i.e., 0.00 per 100,000 in the CTSR). In the U.S. and Canada, the point prevalence as on 1 September 2015 ranged from 0.23 to 0.44 per 100,000 population (Verhaart et al. 2017a) (Table 4).

Although SMA Type 1 is expected to account for more than half of all new SMA cases, evidence from literature sources for SMA Type 1 showed a prevalence of only 0.10 (in the UK) to 0.28 (in Sweden) per 100,000 population. Due to severe motor impairment, patients with SMA type 1 have a very short life expectancy. The prevalence for SMA Type 2 ranged from 0.57 (in UK) to 3.66 (in Norway) per 100,000 population, while the prevalence for SMA Type 3 ranged from 0.35 (in Norway) to 1.39 (in Sweden) per 100,000 (Verhaart et al. 2017b) (Table 5). With the advent of disease modifying therapies, these prevalences will probably shift considerably in future decades.

Table 4 Prevalence of SMA estimated through Global SMA registry and Care and Trial Site Registry

	Global SMA Registry			CTSR		
Region/ Country	**Population**	**No of patients**	**Prevalence (per 10^5)**	**Population**	**No of patients**	**Prevalence (per 10^5)**
Europe	381,180,652	2,458	0.64 (range: 0.24-2.43)	490,278,605	3,441	0.70 (range: 0.0 - 4.11)
Southern America	378,281,507 (3 countries)	234	0.06 (range: 0.03-0.31)	225,795,669 (2 countries)	10	0.0 (range: 0.0 - 0.04)
USA	321,773,631	738	0.23	-	1 416	0.44
Canada	35,939,927	84	0.23	-	136	0.38
China	1,376,048,943	179	0.01	-	338	0.02
Japan	126,573,481	-	-	-	94	0.07

Source: (Verhaart et al. 2017a)

Table 5 Prevalence of SMA by subtypes

Country	Time point	Population	Prevalence (per 100,000 population)			
			SMA (overall)	SMA Type 1	SMA Type 2	SMA Type 3
Norway	1 January 1983	573,762	4.18	0.17	3.66	0.35
Sweden	1 January 1995	359,676	2.78	0.28	1.11	1.39
UK	1 August 2007	2,991,517	1.87	0.10	0.57	1.20
Italy	31 December 1989	152,529	6.56	-	-	-
Canada	1962-1964	2,748,500	0.74	-	-	-

Source: (Verhaart et al. 2017b)

SI.1.3 Demographics

The Cure SMA database is one of the largest patient-reported databases for people affected with SMA. Individuals with self-reported SMA were identified from the database with a date of first contact to Cure SMA between 1 January 2010 and 31 December 2016 in the U.S. A total of 1966 SMA patients were included in the study. Of these individuals, 51.9% had Type 1, 32.3% had Type 2, and 15.8% had Type 3 SMA (Belter et al. 2018). Males and females were represented equally, and no statistically significant difference was observed between gender and type of SMA. Demographic information of SMA patients available from the Cure SMA database is represented in Table 6.

According to Global SMA Patient Registry, among all the SMA patients worldwide, 66% were from Europe, 18% from North America, 10% from Asia, and 5% from Central and South America. Patients were predominantly of Type 2 etiology (45%), followed by Type 3 (32%), Type 1 (18.4%), and 5% unknown. Demographic information of SMA patients available from Global SMA and CTSR registry is represented in Table 7.

Table 6 Demographic characteristics of SMA patients from Cure SMA database (1 January 2010 to 31 December 2016)

		All (n=1966)	Type 1 (n=1021)	Type 2 (n=635)	Type 3 (n=310)
Gender	Male	966	497 (51.5%)	315 (32.6%)	154 (15.9%)
	Female	934	492 (52.7%)	298 (31.9%)	144 (15.4%)
	Unknown	66	33 (50.7%)	22 (33.3%)	12 (18.2%)
Current Age	< 5 years	754	433 (57.4%)	267 (35.4%)	54 (7.2%)
	6-10 years	417	99 (23.7%)	218 (52.3%)	100 (24.0%)
	11-59 years	192	11 (5.7%)	62 (32.3%)	119 (62.0%)
	≥ 60 years	5	0	0	5 (100.0%)
Deceased n (%)		441	424 (96.2%)	16 (3.6%)	1 (0.2%)
Age at diagnosis (months)		25.5	5.2	22.1	97.8

Source: (Belter et al. 2018)

Table 7 Demographic characteristics of SMA patients from Global SMA and Care and Trial Site Registry database

		Global SMA Registry	CTSR
SMA Type	Type 1	18.4%	16%
	Type 2	45%	48%
	Type 3	32%	37%
Gender	Male	50%	-
	Female	48%	-
	Unknown	2%	-
Age distribution	0-2 years	12%	14%
	3-11 years	39%	36%
	12-17 years	13%	21%
	18-45 years	26%	26%
	> 45 years	9%	4%
Geographic distribution	Europe	66%	59%
	North America	18%	24%
	Asia	10%	15%
	Central and South America	5%	2%

Source: (Verhaart et al. 2017a)

SI.1.4 Main Existing Treatment Options

The intrathecally administered *SMN2*-targeting anti-sense oligonucleotide nusinersen (SPINRAZA®) has been approved for the treatment of SMA in pediatric and adult patients. Onasemnogene abeparvovec (ZOLGENSMA®), a gene-replacement therapy that uses a non-replicating adeno-associated virus (AAV) capsid to deliver a functional copy of the *SMN* gene by intravenous infusion, has been approved in the United States, European Union and other jurisdictions for patients with SMA <2 years of age. Despite the availability of these treatment options, a clear unmet medical need remains for this patient population (Noone et al. 2019).

SI.1.5 Risk Factors for the Disease

SMA is a monogenic neuromuscular autosomal recessive disorder secondary to loss-of-function mutations in both alleles of the survival motor neuron 1 (*SMN1*) gene with subsequent loss of SMN protein expression. In humans, there are two SMN genes, the *SMN1* gene and its paralog *SMN2*. The *SMN2* pre-messenger RNA (mRNA) undergoes alternative splicing that excludes exon 7 from 85%–90% of mature *SMN2* transcripts, which produces an unstable SMNΔ7 protein that is rapidly degraded so that full-length *SMN2* mRNA is generated in only 10%–15% of splicing events (Markowitz et al. 2012; Monani et al. 1999). 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 SMN protein produced by the *SMN2* gene.

SI.1.6 Natural History of the Indicated Condition in the (Untreated) Population

Natural history demonstrates that 50% of infants with Type 1 SMA will have died or required permanent daily noninvasive ventilation support by 10.5 months of age and 92% by 20 months of age (Finkel et al. 2014). Patients with Type 2 SMA have a decline in motor function over time, most prominently during the ages of 6 to 16 years, as reported in a number of publications with different motor function measures, i.e., the Motor Function Measure 32-item version (MFM32) (Vuillerot et al. 2013), the Hammersmith Functional Motor Scale Expanded (Mercuri et al. 2018), and the Revised Upper Limb Module (Pera et al. 2019). Patients with Type III SMA decline in motor function over time most prominently during the ages of 10 to 15 years and nearly a third will lose their ability to walk between ages 3–28 years (Vuillerot et al. 2013). Type 4 SMA represents less than 1% of all SMA patients and is the mildest form of the recognized disease continuum, characterized by mild proximal muscle weakness predominantly affecting the leg and hip muscles which may progress to the shoulders and arms. Life expectancy is not affected in Type 4 SMA (Arnold et al. 2015). With the advent of disease modifying therapies (SI.1.4Main Existing Treatment Options) the natural history of SMA is dramatically changing.

A cross-sectional study of pregnancy among confirmed SMA patients indicated that preterm labor and delivery by cesarean section were more common in mothers with

SMA, particularly SMA Type 2. About two-thirds of pregnant patients reported increased weakness during pregnancy, which persisted in 42% even after delivery (Elsheikh et al. 2017). A recent literature review indicated that premature labor and C-section rates are higher in SMA patients; however, the incidence of maternal and fetal complications among SMA patients was not higher than the general population (Abati et al. 2018). The literature surrounding the risks of adverse pregnancy outcomes among SMA patients is based on case reports or retrospective studies of small number of patients and the maternal and fetal risks of SMA are largely unknown.

SI.1.7 Important Comorbidities

SMA is a genetic disorder therefore non-SMA related comorbidities in patients with SMA share the same distribution as in the general population.

The section below describes therefore the most relevant clinical features of SMA.

Overall, SMA comprises a wide spectrum of clinical conditions characterized by a selective degeneration of spinal motor neurons within the CNS, along with a complex profile of accompanying symptoms that point to the crucial systemic role of the SMN protein (Faravelli et al. 2015).

Table 8 below provides an overview of symptoms at presentation by SMA Type.

Table 8 Subtypes of SMA

SMA type	Age at onset	Age at diagnosis	Defining clinical features at presentation	Maximal motor function achieved
0	Fetal	Birth	• Paucity of movement in limbs, face, trunk, no suck • Muscle atrophy • Areflexia • Congenital contractures • Requirement for mechanical ventilation support at birth	Nil
1-A	Fetal	First 2 weeks of life	• Hypotonia: severe, generalized • Weakness of limbs, neck • Areflexia, ±tongue fasiculation • Poor feeding, requiring support • Labored breathing/requirement for mechanical ventilation may be needed since the neonatal period	Nil
1-B	Infancy	By age 3 months	• Hypotonia: severe generalized • Weakness of limbs, neck • Areflexia, tongue fasciculation • Bell-shaped thorax, paradoxical breathing pattern	Never rolls or sits independently
1-C	Infancy	3–6 months	• Hypotonia: severe, generalized • Weakness: proximal > distal, lower > upper limbs • May gain neck support • Areflexia, tongue fasciculation • ±Bell-shaped thorax, paradoxical breathing pattern	Never rolls or sits independently
2	Infancy	6–18 months	• Hypotonia: mild-moderate • Weakness: proximal > distal, lower > upper limbs > trunk • ±Areflexia • Finger polymyoclonus tremor	Sits, may stand, unable to walk independently
3-A	Early childhood	18–36 months	• Plateau in motor development • Reflexes reduced or absent • Finger polymyoclonus tremor	Walks Never runs or jumps well

SMA type	Age at onset	Age at diagnosis	Defining clinical features at presentation	Maximal motor function achieved
			• Majority lose ambulation before or around puberty	
3-B	Later childhood	3–10 years	• Milder decline in gross motor function compared with 3A	Walks, runs, jumps and can participate in sport
4	Adult	35+ years	• Difficulty with gross motor function	Normal until early adult years

Note: Adapted from 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy (Finkel et al. 2015)

Newborns with SMA Type 0 present with failure to swallow and breathe, facial diplegia, and joint contractures.

Patients with Type 1 SMA display generalized muscular weakness with severe hypotonia, often displaying 'floppy infant syndrome' (ragdoll-like limpness). Infants can present with a typical frog-leg position owing to hypotonia of proximal muscles. Impaired ribcage expansion can cause a bell-shape-like conformation of the thorax, with a relative sparing of the diaphragm. Deep tendon reflexes can be decreased or absent. Difficulties in breathing and feeding are invariably present. Tongue fasciculation and weak cry are consequences of the involvement of bulbar motor neurons. High level cognitive functions seem to be spared. Congenital heart defects with potential impairment of the cardiac autonomic innervation have been reported in severe Type 1 SMA (Faravelli et al. 2015).

Children with Type 2 SMA show delay in reaching developmental milestones for gross motor skills. Bulbar function impairment manifesting as swallowing difficulties which may lead to poor weight gain, difficulty in chewing, nasal regurgitation, slurring of speech, difficulty in handling secretions, aspiration of liquids, dysphonia (defective use of the voice, inability to produce sound due to laryngeal weakness) and dysarthria. Intercostal muscles are weak, and some are also diaphragmatic breathers. They have difficulty coughing and clearing tracheal secretion. They have fine tremors with extended fingers or when attempting hand grips. Kyphoscoliosis eventually develops, and bracing or spinal surgery is needed.

Patients with Type 3 SMA present with varying degrees of muscular hypotonia and weakness, with a preferential wasting of proximal muscle groups. Bulbar motor neuron involvement is less frequent than in more severe forms of SMA. Loss of ambulation usually occurs before or around puberty.

Individuals with Type 4 SMA can manifest signs of spinal motor neuron degeneration, such as flaccid hypotonia, fasciculations, muscular atrophy and decreased deep tendon reflexes. The disease course is stable and mild (Wang et al. 2007).

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

SII.1 TOXICOLOGY AND SAFETY PHARMACOLOGY

Overall, toxicology findings can be grouped into two distinct categories according to the duration of treatment with risdiplam needed to induce these effects:

- Retinal degeneration, which occurs after prolonged dosing and whose mechanism is not fully understood
- Adverse effects related to secondary splice targets, occurring with acute/subacute dosing and which include effects on organs with rapid cell turnover and teratogenic effects.

While retinal degeneration is a delayed type of toxicity, which is not reversible in terms of photoreceptor loss, effects mediated by interaction with secondary splice targets are more immediate in their onset (time course similar to the onset of the effect on the primary splice target *SMN2*) and reversible in their nature.

A no observed adverse effect level (NOAEL) was established for risdiplam in all pivotal toxicity studies for genotoxicity, repeat dose toxicity, juvenile toxicity, reproductive toxicity and carcinogenicity.

In vitro and in vivo safety pharmacology studies have not shown any evidence for any effects of risdiplam on cardiovascular, CNS or respiratory functions.

An overview of the key toxicities observed in animal studies and their safety margins (or ratios of exposure for retinal changes and male germ cell effects) at mean exposure in SMA patients is provided in Table 9. An overview of key toxicology findings with translatability to humans is given below (Table 10 and following sections).

Table 9 Overview of Exposure Ratios (Safety Margins) for Key Toxicities (Adverse Effects) of Risdiplam at Mean Exposure in SMA Patients (SUNFISH and FIREFISH)

Type of Toxicity	Exposure Ratio (Margin) at NOAEL vs Exposure of 2000 ng·h/mL (AUC_{0-24})[a]
Micronucleus induction in rat bone marrow	~1.5[b]
Testis toxicity in rats and monkeys	~0.8 (for juvenile rats) ~1-1.5 for adult rats and monkeys
Epithelial findings (skin, eyelid, larynx, GI tract) in monkeys (with chronic dosing)	>2.5
Hematology changes (RBC and lymphocytes) in monkeys, rats and mice	>4
Retina changes in monkeys	~1
Overall NOAEL (2-4 weeks of treatment in mice)	~8
Overall NOAEL (13 weeks of treatment: juvenile rat)	~3
Overall NOAEL (26 weeks of treatment: adult albino rat)	~1
Overall NOAEL (39 weeks of treatment: juvenile/pubertal monkey)	~1
Effects on embryofetal development: Embryofetal toxicity (delayed development, lower fetal weight) in rats	>2
Embryofetal (lethality and teratogenic) effects in rabbits with maternal toxicity	~4

[a] Clinical exposures (mean AUC_{0-24}) were 1930 ng•h/mL in BP39056 (FIREFISH) and 2070 ng•h/mL in BP39055 (SUNFISH) Part 2 at the pivotal dose.

[b] Refers to NOGEL at the lower confidence interval of MN induction (~3000 ng•h/mL)

Table 10 Translatability of Animal Toxicity Findings to Humans

Observed Toxicities/Effects	Translatability to Human
Retinal toxicity	Evidence for cellular disturbances in vitro in human RPE; however, retinal toxicity has not been observed in clinical studies at the pivotal dose and thus, the safety of the pivotal dose as set originally based on the NOEL for retinal toxicity in monkeys is confirmed under clinical conditions.
Skin/Upper and lower GI tract	Yes, likely: related to secondary splice targets. Human in vitro skin model shows comparable pathology (data elaborated with RO6885247[a]).
Micronucleus induction and bone marrow depression	Yes, likely: related to secondary splice targets. Micronucleus induction in human cell line in vitro.
Male germ cell degeneration	Yes, likely: related to secondary splice targets and seen across species and *SMN2* splicing modifiers.
Changes in secondary splice targets and related toxicities	Yes, likely: similar changes in target organs in animals in vivo and in patient cells in vitro.
Embryofetal toxicity	Yes, likely: related to secondary splice targets. Hydrocephalus is a known translatable effect. Embryofetal toxicity is considered an important potential risk.
Delay in gestation/parturition	Yes, likely: COX1 and COX2 inhibition is a possible cause of the observed effects in rats. However, humans are less sensitive.

GI = gastrointestinal; NOEL = no observed effect level; RPE = retinal pigment epithelium.

[a] (Mueller and Hermann 2015).

SII.1.1 Delayed (Retinal) Toxicity

Retinal findings, which are likely of delayed nature (diagnosed with approximately 5 months of treatment and lack of earlier data) and potentially related to the physicochemical properties of risdiplam (rather than secondary splice targets), were diagnosed in-life in all monkeys after daily oral treatment above no observed effect level (NOEL). These findings were partly irreversible (in terms of photoreceptor degeneration), and started to occur at exposures higher than twice the mean exposure guidance set for the ongoing clinical trials.

The exact mechanism for the delayed type of retinal toxicity seen in the monkey with risdiplam is presently unknown. Impairment of autophagosomal function has been observed in vitro in human RPEs and this in vitro property of risdiplam is possibly related to the retinal effects seen in monkeys. Comprehensive clinical monitoring data focused on the nature of the observations in monkeys and with a sufficient duration of chronic dosing and obtained under the conditions of the clinical trials confirm the absence of retinal toxicity and thus do not point towards an effect of risdiplam on the retina in patients with SMA (SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks).

SII.1.2 Adverse Effects Related to Secondary Splice Targets

Risks related to secondary splice target effects with early onset and involving genes, other than *SMN2*, mainly play a role in cell division and apoptosis:

- Decreased sperm count and degeneration of spermatocytes (at systemic exposures similar to the mean exposure in clinical trials [2010 ng•h/mL, AUC_{0-24}]).
- Micronucleus formation in bone marrow with a clear NOAEL, including mechanistic information related to secondary effects to apoptosis at approximately 1.5-fold of the mean exposure in clinical trials.
- Bone marrow suppression with decreased cellularity at higher exposures than those for micronucleus induction, i.e., above 4-fold of the mean exposure in patients.
- Skin and mucosa (mainly parakeratosis) at 2.5-fold above mean exposure in patients. These effects were dose-dependent, with early onset within several days and up to approximately 2 weeks of treatment and reversible following discontinuation of risdiplam.

All of these risks are considered of human relevance (see Table 10). Above the NOAEL, findings were consistently observed in a substantial subset of animals treated. All effects were shown to be reversible in animal studies or are deemed to be fully reversible based on scientific rationales and class effect data.

Degeneration of germ cells, which is considered to be of special clinical relevance, is discussed in more detail below.

Male Germ Cells

The potential risk of adverse effects on human sperm has not been characterized in clinical studies. Consistent observation of this effect in monkeys and rats, including similar findings for other small molecule *SMN2* splice modifiers, suggest that this risk is a class effect and that it may translate to humans and could occur at the therapeutic exposures. Spermatocyte degeneration is most likely an effect of risdiplam on splice targets other than *SMN2*. The effect seems to be reversible by nature since no effects were noted on Sertoli cells or on primordial germ cells, which therefore retain their function to differentiate into spermatozoa once normal *FOXM1* expression (and/or another affected splice target) has resumed. Indeed, the effect was reversible in animal studies after discontinuation of treatment, as confirmed with other *SMN2* splice modifiers of the same class. Thus, in terms of clinical management of this effect, any impact on fertility in human males is expected to be reversible after one cycle of spermatogenesis. Therefore, normal fertility function would be restored within 4 months (one cycle of spermatogenesis plus 5 half-lives of risdiplam after the last dose).

SII.1.3 Reversibility of Toxicological Findings

All of the findings of toxicological significance (retina, male germ cells, hematology, digestive system, skin) induced by risdiplam in mice, rats or monkeys were studied for

reversibility. Full or partial reversibility was shown for all of these findings with the exception of the effects on photoreceptor degeneration in the retina in the monkey. Only partial reversibility was shown for male sperm cell changes in some studies primarily due to recovery periods chosen being too short for a full spermatogenic cycle (8-week recovery periods in the 13-week juvenile rat and 26-week adult rat studies); in other cases, animals were not adult (monkey studies). However, full reversibility for male germ cell changes is postulated [1093542] based on evidence of partial reversibility in the rat and studies with another splice modifier with similar mode of action on *SMN2* and secondary splice targets, RO6885247, in the monkey.

SII.1.4 Genotoxicity and Carcinogenicity

Risdiplam was not mutagenic in bacterial tests and there was no evidence of primary DNA-damage in vivo following risdiplam administration. Consistent with its effects on cell division and apoptosis, risdiplam-induced MN in bone marrow as part of a non-DNA reactive mechanism. Since the effect is not on the DNA, it is considered to be reversible and damage cannot be passed onto subsequent cell generations. At higher doses, the damage manifests as reduction in cellularity in bone marrow, an effect, which is monitored in SMA patients with hematology investigation.

Risdiplam is not tumorigenic in animals when tested in a transgenic model suitable to address non-genotoxic and genotoxic mechanisms to tumorigenesis. Risdiplam is used to treat a severe, life threatening disease, and hence a standard 2-year carcinogenicity study in the rat was deferred to be initiated after submission for approval to facilitate an accelerated clinical development and availability for patients. The study has been initiated with dosing started in Q3 2020 and is planned to be reported in Q3 2023 in order to facilitate a full risk-benefit assessment with the availability of the full rodent carcinogenicity data upon lifetime treatment, as set out in the ICH S1 guidelines. Roche commits to provide the results of this study to the CHMP.

SII.1.5 Reproductive Toxicity

Studies with radiolabeled risdiplam in pregnant and lactating rats indicate that risdiplam may cross the placental barrier in pregnant women and may be excreted in milk in breastfeeding women. These findings are consistent with its physicochemical properties, such as high permeability.

Consistent with its effects on cell division and apoptosis, treatment of pregnant rabbits with risdiplam has been associated with maternal toxicity and teratogenicity, with a NOAEL at exposures of ~4 times the mean exposure guidance in clinical trials. No teratogenicity was observed in rats up to ~5 times the clinical mean exposure guidance, but embryofetal toxicity (reduced fetal weight and delayed fetal development) was noted, with a NOAEL slightly in excess of 2-fold the mean exposure guidance without maternal toxicity. Even though teratogenicity was only noted in the rabbit at a maternally toxic

dose level, the possibility of a dysmorphogenic potential of risdiplam in the human cannot be discounted.

Although COX1 and COX2 inhibition can affect parturition in human (Urrego et al. 2019), it is thought that secondary pharmacodynamic effects of risdiplam on COX1/COX2 shown in vitro may not be relevant for in vivo conditions in human even at the maximal free plasma concentrations achieved with the recommended doses. The IC_{50} for COX1 and COX2 inhibition by risdiplam is ~800 ng/mL, compared with the maximum free C_{max} of ~27 ng/mL observed for risdiplam in clinical studies in SMA patients of reproductive age.

SII.1.6 Safety Pharmacology and Abuse Liability

A complete in vitro and in vivo safety pharmacology study package has not shown any evidence for any effects of risdiplam on cardiovascular, CNS or respiratory functions.

Receptor interactions of potential animal and human relevance based on their IC_{50} and further functional assessment were found for risdiplam and its major human metabolite M1 only for COX1 and COX2 and for acetylcholinesterase. However, side effects known in the context of inhibition of COX1 and COX2 (bleeding, ulceration, erosions in the GI tract) have not been observed in animal studies with risdiplam. Similarly, effects known for inhibition of acetylcholinesterase (cholinergic effects) have not been seen in the animal safety pharmacology and toxicity studies with risdiplam. Effects of COX1 and COX2 on parturition are discussed in SII.1.5 Reproductive Toxicity.

Receptor-ligand binding studies do not indicate abuse-related signals.

SII.1.7 Phototoxicity

The phototoxic potential of risdiplam is considered low or negligible because free plasma/tissue concentrations of more than 9000 ng/mL (the maximal concentration evaluated in an in vitro test) are not expected in the clinical use of risdiplam.

SII.2 AGE DIFFERENCES IN PLASMA PROTEIN BINDING

Major differences in tolerability after daily oral gavage treatment with risdiplam between the pre- and post-weaning phase were observed in rats, with deaths occurring after a few days of treatment starting on PND4 at doses that were tolerated well when treatment was started post-weaning. These differences were correlated with increased free plasma exposure due to differences in plasma protein binding and clearance, with pre-weaning pups showing a much higher plasma free fraction and longer half-life of risdiplam in plasma than post-weaning and adult rats. The age-dependency was less pronounced in mice and monkeys.

In contrast to juvenile animals, risdiplam showed similar plasma protein binding in human blood sampled at various ages from birth to adulthood (non-SMA and Type 1, 2,

and 3 SMA patients). Hence, no major differences in tolerability due to age-related variation in plasma protein binding are expected for the pediatric SMA population.

SII.3 METABOLISM AND MAJOR METABOLITE M1

Any possible clinical risk stemming from the covalent binding potential of risdiplam detected in vitro is considered low based on the clinical dose of maximally 5 mg and the low in vitro potency for covalent interactions.

Human exposure to the major human metabolite (M1) is qualified in all key toxicology studies (repeat dose toxicity, juvenile toxicity, genotoxicity, carcinogenicity, reproductive toxicity) at the respective NOAELs. In vitro, M1 is devoid of any significant primary (*SMN2* splicing) or secondary (*FOXM1* splicing) pharmacological effect or potential for pharmacodynamic drug-drug interaction (DDI) at therapeutic doses of risdiplam.

SII.4 DRUG-DRUG INTERACTION

The effect of coadministration of risdiplam on the pharmacokinetics of MATE1 and MATE2-K substrates in humans is unknown. Based on in vitro data, risdiplam may increase plasma concentrations of drugs eliminated via MATE1 or MATE2-K, such as metformin and fexofenadine.

In vitro investigations suggested a potential for DDI effects, by either risdiplam or M1, on concomitant medications which are CYP3A4 substrates. The clinical relevance of CYP3A4 inhibition was evaluated in a DDI study (BP41361) with midazolam in healthy volunteers. In this study, the administration of risdiplam slightly increased the exposure of midazolam (a sensitive CYP3A substrate). As such, this study confirmed that there is no clinically relevant DDI between risdiplam and CYP3A4 substrates. Based on physiologically based pharmacokinetic (PBPK) modeling, a similar magnitude of effect is expected in children and infants as young as 2 months old.

SII.5 OVERALL CONCLUSION

Retinal toxicity observed in monkey was initially considered an important potential risk (see SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP) but is no longer considered a potential risk due to absence of findings following thorough ophthalmological monitoring in 486 patients for up to 5.15 years (Drug Safety Report [DSR] No. 1127141).

Further, sperm cell toxicity and embryofetal toxicity are identified risks in nonclinical studies which are deemed relevant for human use and embryofetal toxicity is considered an important potential risk (see SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks). Further risks for GI, skin and hematology as described in Table 10 have been fully addressed in the clinical studies conducted so far.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

Overview of Studies in the RMP

Study BP39056 (FIREFISH) is a two-part, multicenter, single-arm, open-label study to investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and efficacy of risdiplam in infants (aged 1 to 7 months at enrollment) with Type 1 SMA. The study consists of a dose-finding Part 1 and a confirmatory Part 2 at the dose selected in Part 1. A total of 21 patients were enrolled in Part 1 of the study. Following selection of the dose for Part 2, patients in Part 1 entered an extension phase to continue treatment at the dose selected for Part 2 (referred to as the pivotal dose). Patients in Part 1 did not enter Part 2 of the trial.

Part 2 is a pivotal, single-arm study of risdiplam in 41 infants with Type 1 SMA treated for 24 months, followed by an open-label extension (OLE). The primary analysis of Part 2 was conducted once the last patient in Part 2 completed 12 months of treatment.

Safety data from a total of 62 patients with Type 1 SMA (21 patients from Part 1; 41 patients from Part 2) up to the clinical cutoff date (CCOD) of 12 November 2020 are available and included in this analysis. This is the timepoint at which all patients in Part 2 had completed the 24-month assessment of treatment with risdiplam and all patients in Part 1 had been dose-escalated to the pivotal dose. As of the CCOD, 55 patients had completed the 24-month treatment period of Part 2 and entered the OLE phase.

Study BP39055 (SUNFISH) is a two-part, multicenter, randomized, placebo-controlled, double-blind study to investigate safety, tolerability, PK/PD, and efficacy of risdiplam in patients with Type 2 and 3 SMA (aged 2 to 25 years). The study consists of a dose-finding Part 1 and a confirmatory Part 2 at the dose selected in Part 1. A total of 51 patients were enrolled in Part 1 of the study. Patients who were assigned to placebo were switched to active treatment at the dose tested in their respective cohort after a minimum 12-week placebo-controlled treatment period. After selection of the dose for Part 2 (referred to as the pivotal dose), all patients in Part 1 received the pivotal dose as part of an OLE phase. Patients in Part 1 did not enter Part 2 of the trial.

Overall, safety data from 231 patients with Type 2 or Type 3 SMA are included in the safety analyses. These data include:

- 51 patients from Part 1 of the study included in the analyses at the CCOD of 15 January 2020. 35 patients were treated with risdiplam from randomization and 16 patients were switched from placebo during or after the dose selection period. At the CCOD in January 2020, all patients from Part 1 of the study (except one who had withdrawn consent) were in the OLE and had been treated for a minimum of 2 years with the pivotal dose.
- 180 patients (RIS: n=120, PLB=60) from Part 2 of the study at the CCOD of 30 September 2020, when the last patient in Part 2 completed 24 months of treatment.

Part 2 patients randomized to placebo were switched to risdiplam after completion of 12 months of study treatment.

Study BP39054 (JEWELFISH) is an open-label, non-comparative study in SMA patients previously enrolled in Roche Study BP29420 (MOONFISH) with the splicing modifier RO6885247 (development discontinued) or previously treated with SPINRAZA® (nusinersen), Zolgensma® (onasemnogene abeparvovec, AVXS-101), or olesoxime (previous Roche acquired development compound, since discontinued) in which treatment with risdiplam is evaluated over a 24-month period. Study enrollment has been completed with 174 patients; these 174 patients had previously received either nusinersen (N=76), RO6885247 (N=13), olesoxime (N=71), or AVXS-101 (N=14). Safety data up to the CCOD of 29 January 2021 (corresponding to the date when the last patient in the study completed the Month 12 visit) from 173 out of these 174 patients enrolled are included in the analyses.

Study BN40703 (RAINBOWFISH) is a study to assess the efficacy, safety, tolerability, and PK/PD of risdiplam in pre-symptomatic infants from birth to 6 weeks who were genetically diagnosed with SMA. The study is currently recruiting; up to the CCOD of 1 July 2021, 18 patients had been enrolled.

Table 11 summarizes key design features, safety populations, and data cutoff dates for all four studies in this RMP.

Clinical trial exposure data are presented for risdiplam by duration of exposure (Table 12), age group and gender (Table 13), ethnic or racial origin (Table 14), pivotal dose (Table 15), and pivotal dose by individual dose level (Table 16). Included are 483 patients with symptomatic or presymptomatic SMA from BP39056 (FIREFISH), BP39055 (SUNFISH), BP39054 (JEWELFISH) and BN40703 (RAINBOWFISH).

Table 11 Clinical Studies Included in the RMP

Pivotal Studies in SMA Contributing Safety Data					
Study Number	**Study Design**	**Population**	**Objectives**	**Dose, Route, Regimen**	**Number of Patients**
BP39056 (FIREFISH), ongoing pivotal Phase 2/3 study	Open-label, two-part operationally seamless [1] multicenter study	Infants with Type 1 SMA aged 1–7 months at enrollment		Once daily oral	
	Part 1: Open-label dose-escalation phase with a 24-month treatment period, followed by an open-label extension (OLE) phase [2].		Part 1: Safety, tolerability, PK and PD, dose selection for Part 2	Part 1 Starting dose for first infant: 0.00106 mg/kg single dose. Once daily treatment with 0.0106, 0.04, 0.08, 0.2, 0.25 mg/kg. After the selection of the starting dose for Part 2 the protocol was amended to switch all patients to the dose of 0.2 mg/kg	Part 1: 21 patients CCOD (24-month analysis): 12 Nov 2020
	Part 2: Open-label single-arm with a 24-month treatment period, followed by an OLE phase [2].		Part 2: Efficacy, safety and tolerability, PK and PD	Part 2 Starting dose (adjusted upon PK review) Infants >1–<3 months: 0.04 mg/kg Infants 3–<5 months: 0.08 mg/kg Infants ≥ 5 months: 0.2 mg/kg The dose for all infants <2 years has been adjusted to 0.2 mg/kg. Infants ≥2 years: 0.25 mg/kg OLE phase in Parts 1 and 2 (after 24 months of treatment): pivotal dose - 0.2 mg/kg for infants < 2 years and 0.25 mg/kg for infants ≥2 years	Part 2: 41 patients CCOD (24-month analysis): 12 Nov 2020

Table 11 Clinical Studies Included in the RMP (cont.)

BP39055 (SUNFISH), ongoing pivotal Phase 2/3 study	Two-part operationally seamless [1] randomized, multicenter, placebo-controlled, double-blind, study	Patients with Type 2 and 3 SMA aged 2 -25 years at enrollment		Once daily oral	
	Part 1: double-blind, randomized (2:1), placebo-controlled, exploratory dose-finding phase, followed by open-label phase to complete 24 months. Afterwards patients can enter an OLE phase	Part 1: Type 2 and Type 3 SMA (ambulant and non-ambulant) patients	Part 1: Safety, tolerability, PK and PD, dose selection for Part 2	Part 1 Initial doses Age 12-25 years: 3 mg or 5 mg Age 2-11 years: 0.02, 0.05, 0.15 or 0.25 mg/kg Minimum of 12-weeks placebo-controlled treatment, after which patients on placebo switched to risdiplam at the dose tested in their cohort. After the dose selection for Part 2, all patients switched to the pivotal dose.	Part 1: 51 patients in 2 age groups: 2–11 years (n = 31) 12–25 years (n = 20) CCOD (24-month analysis): 15 Jan 2020:
	Part 2: double-blind, randomized (2:1), placebo-controlled, parallel group treatment period, followed by an OLE phase	Part 2: Type 2 and non-ambulant Type 3 SMA patients	Part 2: Efficacy, safety and tolerability, PK and PD	Part 2: Pivotal dose 0.25 mg/kg for patients with body weight (BW) < 20 kg 5 mg for patients with BW ≥ 20 kg 24-month treatment period; patients on placebo switched in a blinded manner to active treatment after 12 months of treatment. OLE phase in Parts 1 and 2: pivotal dose	Part 2: 180 patients CCOD (24-month analysis): 30 Sep 2020

Table 11 Clinical Studies Included in the RMP (cont.)

Supportive Study in SMA Contributing Safety Data					
BP39054 (JEWELFISH), ongoing supportive Phase 2 study	Multicenter, open-label, non-comparative, single-arm, exploratory study in SMA patients previously enrolled in BP29420 (MOONFISH) or previously treated with nusinersen, onasemnogene abeparvovec or olesoxime; 24-month treatment period	Type 1, 2 or 3 SMA patients aged 6 months– 60 years	Safety, tolerability, PK and PD	Once daily oral Initial dose was 3 mg (patients 12–60 years). Dosing was amended in line with the pivotal dose selection in Studies BP39055 (SUNFISH) and BP39056 (FIREFISH) Age 2–60 years: 5 mg for patients with BW ≥ 20 kg; 0.25 mg/kg for patients with BW < 20 kg Age 6 months to < 2 years: 0.2 mg/kg	N=174 patients CCOD (12-month analysis): 29 Jan 2021
BN40703 (RAINBOWFISH), ongoing supportive Phase 2 study	Multicenter, open-label, single-arm; 24-month treatment period plus extension phase	Pre-symptomatic (birth to 6 weeks of age) with genetically diagnosed SMA. 10 patients with 2 copies of *SMN2* gene and CMAP ≥ 1.5 mV	Efficacy, safety and tolerability, PK, PD	Once daily oral administration Dose selected to achieve the target exposure of a mean AUC ≤ 2000 ng • h/mL	Up to 25 patients planned N=18 at the 1 July 2021 CCOD

CCOD=clinical cutoff date; OD=once daily; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; SMA=spinal muscular atrophy.

[1] Studies BP39056 (FIREFISH) and BP39055 (SUNFISH) were conducted in an operationally seamless manner in some of the participating countries.

[2] In Studies BP39056 (FIREFISH), BP39055 (SUNFISH), BP39054 (JEWELFISH), and BN40703 (RAINBOWFISH), the OLE period will run for 3 years. Thereafter, treatment will continue until the drug is available commercially in the patient's country.

Table 12 Duration of Exposure, Safety-Evaluable Patients by Age Group

Duration of Exposure, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety

Duration of exposure (Months)	0 to <43 Days (N=18)		43 Days to <2 Years (N=67)		2 to <12 Years (N=189)		12 to <18 Years (N=119)		18 Years or Older (N=90)	
	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*
0 - 2	4 (22.2%)	0.33	2 (3.0%)	0.19	1 (0.5%)	0.07	0	NE	1 (1.1%)	0.07
>2 - 6	3 (16.7%)	1.03	2 (3.0%)	0.40	1 (0.5%)	0.27	0	NE	2 (2.2%)	0.67
>6 - 12	6 (33.3%)	4.77	3 (4.5%)	2.63	11 (5.8%)	9.74	8 (6.7%)	7.32	12 (13.3%)	10.48
>12 - 18	1 (5.6%)	1.40	4 (6.0%)	4.74	58 (30.7%)	71.15	51 (42.9%)	64.15	30 (33.3%)	37.98
>18 - 24	4 (22.2%)	6.98	4 (6.0%)	7.58	22 (11.6%)	40.38	14 (11.8%)	23.42	18 (20.0%)	30.13
>24 - 30	0	NE	31 (46.3%)	69.64	74 (39.2%)	164.53	28 (23.5%)	61.71	14 (15.6%)	31.92
>30 - 36	0	NE	14 (20.9%)	39.17	19 (10.1%)	52.19	12 (10.1%)	33.62	6 (6.7%)	16.45
>36 - 42	0	NE	4 (6.0%)	12.57	3 (1.6%)	9.02	5 (4.2%)	16.23	5 (5.6%)	16.23
>42	0	NE	3 (4.5%)	11.18	0	NE	1 (0.8%)	3.91	2 (2.2%)	7.14
Total patients numbers/person time	18 (100%)	14.51	67 (100%)	148.10	189 (100%)	347.37	119 (100%)	210.37	90 (100%)	151.08

* Person time is the sum of exposure across all patients in Years.
Clinical Cut off dates: Jewelfish 29JAN2021. Sunfish Part 1 15JAN2020. Sunfish Part 2 30SEP2020. Firefish Part 1&2 12NOV2020. Rainbowfish 01JUL2021.

Program: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/program/rmp_t01.sas
Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/output/rmp_t01_SE.out
05NOV2021 12:33 Page 1
of 1

Table 13 Extent of Exposure by Age Group and Gender, Safety-Evaluable Patients

Extent of Exposure by Age Group and Gender, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety

	Patients			Person time*		
Age Group	Male	Female	Total	Male	Female	Total
0 to <43 Days	8 (3.3%)	10 (4.1%)	18 (3.7%)	4.47	10.04	14.51
43 Days to <2 Years	28 (11.6%)	39 (16.1%)	67 (13.9%)	56.15	91.94	148.10
2 to <12 Years	96 (39.8%)	93 (38.4%)	189 (39.1%)	174.68	172.69	347.37
12 to <18 Years	58 (24.1%)	61 (25.2%)	119 (24.6%)	98.62	111.75	210.37
18 Years or Older	51 (21.2%)	39 (16.1%)	90 (18.6%)	88.48	62.60	151.08
Total patients numbers/person time	241 (100%)	242 (100%)	483 (100%)	422.41	449.02	871.43

* Person time is the sum of exposure across all patients in Years.
Clinical Cut off dates: Jewelfish 29JAN2021. Sunfish Part 1 15JAN2020. Sunfish Part 2 30SEP2020. Firefish Part 1&2 12NOV2020. Rainbowfish 01JUL2021.

Program: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/program/rmp_t03.sas
Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/output/rmp_t03_SE.out
05NOV2021 12:35 Page 1
of 1

Table 14 Extent of Exposure by Race, Safety-Evaluable Patients

Extent of Exposure by Race, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety

	0 to <43 Days (N=18)		43 Days to <2 Years (N=67)		2 to <12 Years (N=189)		12 to <18 Years (N=119)		18 Years or Older (N=90)	
Race	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*
Asian	2 (11.1%)	0.59	18 (26.9%)	34.94	28 (14.8%)	52.50	9 (7.6%)	17.79	8 (8.9%)	9.80
Black or African American	0	NE	1 (1.5%)	1.06	2 (1.1%)	4.25	0	NE	0	NE
White	15 (83.3%)	13.61	38 (56.7%)	89.49	141 (74.6%)	256.65	96 (80.7%)	169.61	68 (75.6%)	117.44
Multiple	0	NE	0	NE	1 (0.5%)	1.22	1 (0.8%)	2.01	0	NE
Unknown	1 (5.6%)	0.31	10 (14.9%)	22.61	17 (9.0%)	32.76	13 (10.9%)	20.97	14 (15.6%)	23.84
Total patients numbers/person time	18 (100%)	14.51	67 (100%)	148.10	189 (100%)	347.37	119 (100%)	210.37	90 (100%)	151.08

* Person time is the sum of exposure across all patients in Years.
Clinical Cut off dates: Jewelfish 29JAN2021. Sunfish Part 1 15JAN2020. Sunfish Part 2 30SEP2020. Firefish Part 1&2 12NOV2020. Rainbowfish 01JUL2021.

Program: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/program/rmp_t05.sas
Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/output/rmp_t05_SE.out
05NOV2021 12:35 Page 1
of 1

Table 15 Extent of Pivotal Dose Exposure by Dose Level, Safety-Evaluable Patients

Extent of Pivotal Dose Exposure by Dose Level, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety

	0 to <43 Days (N=18)		43 Days to <2 Years (N=67)		2 to <12 Years (N=189)		12 to <18 Years (N=119)		18 Years or Older (N=90)	
Dose Received	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*
Pivotal Dose	18 (100%)	14.02	64 (95.5%)	130.71	189 (100%)	332.56	119 (100%)	196.84	90 (100%)	145.10
Non-Pivotal Dose	6 (33.3%)	0.49	66 (98.5%)	17.05	21 (11.1%)	11.99	13 (10.9%)	10.66	8 (8.9%)	3.56
Total patients numbers/person time	18 (100%)	14.50	67 (100%)	147.76	189 (100%)	344.54	119 (100%)	207.50	90 (100%)	148.66

* Person time is the sum of exposure across all patients in Years, based on the number of doses actually received.
Pivotal Dose: All exposures of 0.2 Mg/Kg given to a patient less than 2 years of age, 0.25 Mg/Kg given to a patient 2 years of age or older with a body
weight of less than 20 Kg, or 5 Mg given to a patient 2 years of age or older with a body weight of greater than or equal to 20 Kg.
Non-Pivotal Dose: All exposures of 0.00106 Mg/Kg, 0.0106 Mg/Kg, 0.02 Mg/Kg, 0.04 Mg/Kg, 0.05 Mg/Kg, 0.08 Mg/Kg, 0.15 Mg/Kg, or 3 Mg. It also includes any exposure of 0.2 Mg/Kg given to a patient 2 years of age or older, or an exposure of 0.25 Mg/Kg given to a patient under the age of 2 years old.
Clinical Cut off dates: Jewelfish 29JAN2021. Sunfish Part 1 15JAN2020. Sunfish Part 2 30SEP2020. Firefish Part 1&2 12NOV2020. Rainbowfish 01JUL2021.

Program: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/program/rmp_t02.sas
Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/output/rmp_t02_SE.out
05NOV2021 12:34 Page 1 of 1

Table 16 Extent of Pivotal Dose Exposure by Individual Dose Level, Safety-Evaluable Patients

Extent of Pivotal Dose Exposure by Individual Dose Level, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety

	0 to <43 Days (N=18)		43 Days to <2 Years (N=67)		2 to <12 Years (N=189)		12 to <18 Years (N=119)		18 Years or Older (N=90)	
Dose Received	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*	Patients	Person time*
Pivotal Dose	18 (100%)	14.02	64 (95.5%)	130.71	189 (100%)	332.56	119 (100%)	196.84	90 (100%)	145.10
0.2 Mg/Kg	18 (100%)	14.02	63 (94.0%)	77.78	0	NE	0	NE	0	NE
0.25 Mg/Kg	0	NE	60 (89.6%)	52.93	100 (52.9%)	134.75	3 (2.5%)	2.92	0	NE
5 Mg	0	NE	0	NE	135 (71.4%)	197.81	118 (99.2%)	193.92	90 (100%)	145.10
Non-Pivotal Dose	6 (33.3%)	0.49	66 (98.5%)	17.05	21 (11.1%)	11.99	13 (10.9%)	10.66	8 (8.9%)	3.56
Total patients numbers/person time	18 (100%)	14.50	67 (100%)	147.76	189 (100%)	344.54	119 (100%)	207.50	90 (100%)	148.66

* Person time is the sum of exposure across all patients in Years, based on the number of doses actually received.
Pivotal Dose: All exposures of 0.2 Mg/Kg given to a patient less than 2 years of age, 0.25 Mg/Kg given to a patient 2 years of age or older with a body
weight of less than 20 Kg, or 5 Mg given to a patient 2 years of age or older with a body weight of greater than or equal to 20 Kg.
Non-Pivotal Dose: All exposures of 0.00106 Mg/Kg, 0.0106 Mg/Kg, 0.02 Mg/Kg, 0.04 Mg/Kg, 0.05 Mg/Kg, 0.08 Mg/Kg, 0.15 Mg/Kg, or 3 Mg. It also includes any exposure of 0.2 Mg/Kg given to a patient 2 years of age or older, or an exposure of 0.25 Mg/Kg given to a patient under the age of 2 years old.
Clinical Cut off dates: Jewelfish 29JAN2021. Sunfish Part 1 15JAN2020. Sunfish Part 2 30SEP2020. Firefish Part 1&2 12NOV2020. Rainbowfish 01JUL2021.

Program: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/program/rmp_t02_indlev.sas
Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_202106_sNDA_latest/prod/output/rmp_t02_indlev_SE.out
05NOV2021 12:34 Page 1 of 1

PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Specific exclusion criteria discussed in this section are those from the two pivotal studies which are the basis for the approval of the use of risdiplam in SMA (BP39055 [SUNFISH] and BP39056 [FIREFISH], Table 11) and supporting Study BN40703 (RAINBOWFISH). Exclusion criteria are generally consistent among these studies. The key exclusion criteria are summarized in Table 17, and patients who met any of the criteria were excluded from study entry.

Table 17 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Concomitant or previous administration of a *SMN2*-targeting anti-sense oligonucleotide, *SMN2* splicing modifier or gene therapy either in a clinical study or as part of medical care	Confounding factors such as previous treatment for SMA can impact the data and ability to understand the efficacy profile of the drug under study (risdiplam).	No	Safety in patients on previous treatment with *SMN2* splicing modifiers or gene therapy is available from BP39054 (JEWELFISH).
Any history of cell therapy	Confounding factors such as previous cell therapy can impact the data and ability to understand the efficacy profile of the drug under study (risdiplam).	No	Significant exposure to stem cell therapy in SMA is not expected.
Multiple or fixed contractures and/or hip subluxation or dislocation at birth	Any possible confounding conditions that can impact the data and ability to understand the efficacy profile of the drug under study (risdiplam) were excluded	No	Patients with contractures are not expected to be at higher risk of adverse reactions to risdiplam.
Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 months	Any possible confounding conditions that can impact the data and ability to understand the efficacy profile of the drug under study (risdiplam) were excluded	No	Patients with scoliosis or hip surgery in the last year are not expected to be at higher risk of adverse reactions to risdiplam.
Unstable gastrointestinal, renal, hepatic, endocrine, or cardiovascular system diseases	These diseases may preclude patients from participating and staying in the study and would confound safety or efficacy assessments	No	There are no gastrointestinal, cardiovascular, renal or endocrine adverse drug reactions (ADRs) Study BP40995 did not show any significant impact of mild to moderate hepatic impairment on the PK of risdiplam.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
For patients aged <2 years, hospitalization for a pulmonary event within 2 months prior to screening and pulmonary function not fully recovered at the time of screening	Any possible confounding conditions that can impact the data and ability to understand the efficacy profile of the drug under study (risdiplam) were excluded.	No	In patients below 2 years of age (Patients with Type 1 SMA Pool), SAEs which were mostly infections and respiratory complications resolved despite ongoing treatment with risdiplam. Also the rate of SAEs declined over time. Overall this does not suggest a less favourable safety profile of risdiplam in patients with hospitalization due to pulmonary event.
Pregnant women	Based on the findings from animal studies, risdiplam crosses the placental barrier and may cause fetal harm. Pregnant women were excluded because risdiplam has shown embryofetal toxicity in animals.	No	There are no clinical data from the use of risdiplam in pregnant women and embryofetal toxicity is assessed as an important potential risk. Sections 4.4 (Special warnings and precautions for use; Embryofetal toxicity) and 4.6 (Fertility, pregnancy and lactation) of the SmPC advises women of reproductive potential to avoid pregnancy.
Lactating women	It is not known whether risdiplam is excreted in human breast milk. Studies in rats show that risdiplam is excreted into milk. Lactating women were excluded due to unknown effects of risdiplam on the breastfed baby.	No	There are no clinical data from use of risdiplam in breastfeeding mothers during lactation Section 4.6 (Fertility, pregnancy and lactation) of the SmPC advises women to either discontinue breastfeeding or discontinue risdiplam therapy.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Clinically significant abnormal blood pressure or heart rate	Any possible confounding conditions that can impact the data and ability to understand the safety profile of the drug under study (risdiplam) were excluded.	No	No indication that safety profile of risdiplam adversely affected by tachycardia/bradycardia or increased/decreased blood pressure given there are no cardiovascular risks associated with risdiplam.
Presence of clinically significant ECG abnormalities before study drug administration	Any possible confounding conditions that can impact the data and ability to understand the safety profile of the drug under study (risdiplam) were excluded.	No	No increased risk in patients with clinically significant ECG abnormalities expected based on absence of any significant ECG findings or cardiovascular risks in risdiplam clinical trials and absence of any exposure-dependent ECG abnormalities in particular QT prolongation.
History of malignancy if not considered cured	These diseases may preclude patients from participating and staying in the study and would confound safety or efficacy assessments.	No	Based on nonclinical 6-month carcinogenicity study in rasH2 transgenic mice, risdiplam is not expected to increase rate of malignancies. A carcinogenicity study in rats with lifetime dosing (~2 years) is ongoing.
Any major illness within one month before the screening examination or any febrile illness within one week prior to screening and up to first dose administration	These diseases may preclude patients from participating and staying in the study and would confound safety or efficacy assessments.	No	Risdiplam has been safe and well tolerated in all clinical studies. Also risdiplam did not show an increased risk for infections or serious infections and adverse events generally resolved despite ongoing treatment with risdiplam It is considered part of routine practice to assess a patient's fitness for treatment and therefore no specific guidance is included in the SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Taking any nutrients known to modulate CYP3A activity (e.g., grapefruit juice; Seville orange) within 2 weeks prior to administration of study drugs	In vitro data indicate that risdiplam can be metabolized by CYP3A4. Included in order to reduce variability in risdiplam exposure.	No	Exposure safety response analysis has shown that risdiplam is safe and well tolerated without indication for any exposure-dependent risks.
The infant (and the mother, if breastfeeding the infant) with prior use of any inhibitor or inducer of CYP3A4 or any known FMO1 or FMO3 inhibitors or substrates	In vitro data indicate that risdiplam can be metabolized by flavin monooxygenase 1 and 3 (FMO1 and 3), and as well by CYP3A4. Included in order to reduce variability in risdiplam exposure.	No	Exposure safety response analysis has shown that risdiplam is safe and well tolerated without indication for any exposure-dependent risks.
Patients aged >6 years with significant risk for suicidal behavior	May preclude patients from participating and staying in the study and would confound suicidality assessment.	No	Risdiplam does not increase risk for suicidal ideation or behavior.
Use of any MATE substrates within 2 weeks before dosing	Risdiplam and its metabolite are inhibitors of the human multidrug and toxin extrusion (MATE)1 and MATE2-K transporters. Criterion included to avoid putting patients at risk for toxicities related to concomitant medications transported by MATE 1 and MATE2-K.	No	The safety profile of risdiplam is not altered, but rather patients are at increased risk of toxicities due to concomitant drugs which are substrate of these transporters. Potential for DDI is addressed in Section 4.5, Interaction with other medicinal products and other forms of interaction, in the SmPC.
Any inhibitor or inducer of FMO1 or FMO3 taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing	In vitro data indicate that risdiplam can be metabolized by flavin monooxygenase 1 and 3 (FMO1 and 3) thus criterion included to avoid additional PK variability.	No	Exposure safety response analysis has shown risdiplam is safe and well tolerated without indication for any exposure-dependent risks. DDI via this pathway is not expected.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Use of other medications known to or suspected of causing retinal toxicity	Criterion included into all trials to avoid confounding of ophthalmological assessments conducted during the studies to assess the potential risk of retinal toxicity observed in chronic toxicology study in monkeys.	No	No findings of retinal toxicity observed across all clinical studies. Information to prescribers on retinal toxicity in nonclinical studies provided in label, no restriction required re use of concomitant drugs with potential retinal toxicity.
Use of other medications with known phototoxicity liabilities	Criterion added in order to avoid confounding assessment of potential phototoxicity.	No	Because of the absorption of risdiplam in the UV range, the potential for phototoxicity was studied in vitro on a neutral red uptake test with 3T3 cells. The phototoxic potential of risdiplam is considered low or negligible as free plasma/tissue concentrations of more than 9 μg/mL are not expected in the clinical use of risdiplam. No impact of the UV absorption potential on the retinal toxicity of risdiplam is expected, as the retina is not exposed to wavelengths shorter than ~400 nM. In clinical studies with risdiplam, no adverse events indicating potential phototoxicity were observed.
Ascertained or presumptive hypersensitivity (e.g., anaphylactic reaction) to risdiplam or to the constituents of its formulation	Criterion added in order to avoid hypersensitivity to the active substance or to any of the excipients	No	Hypersensitivity to risdiplam or to any of the constituents of its formulation is a potential risk (not important) and is included as a contraindication in the SmPC.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale *(if not included as missing information)*
Recent history (less than one year) of ophthalmological diseases	Criterion added in order to avoid confounding assessment of potential risk for retinal toxicity.	No	No findings of retinal toxicity observed following extensive monitoring across all clinical studies.
Patients requiring invasive ventilation or tracheostomy	Any possible confounding conditions that can impact the data and ability to understand the efficacy profile of the drug under study (risdiplam) were excluded.	No	The safety profile of risdiplam is expected to be similar in those with and without invasive ventilation/tracheostomy.
Requiring awake non-invasive ventilation or with awake hypoxemia ($SaO_2 < 95\%$) with or without ventilator support	Any possible confounding conditions that can impact the data and ability to understand the efficacy profile of the drug under study (risdiplam) were excluded.	No	In clinical studies, awake non-invasive ventilation or with awake hypoxemia ($SaO_2 < 95\%$) with or without ventilator support did not impact the safety profile of risdiplam.
A history of respiratory failure or severe pneumonia, and have not fully recovered their pulmonary function at the time of screening	Any possible confounding conditions that can impact the data and ability to understand the efficacy profile of the drug under study (risdiplam) were excluded.	No	Respiratory failure or severe pneumonia is not expected to impact the safety profile of risdiplam in clinical studies.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical trial development program for risdiplam conducted for the rare disease population of SMA was unable to detect the following adverse drug reactions:

- Rare adverse reactions
- Adverse reactions caused by prolonged exposure
- Adverse reactions caused by cumulative exposure
- Adverse reactions that have a long latency

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDERREPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

Use in Pregnancy and Lactation

Table 18 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Study BP40995 evaluated the PK and safety of risdiplam in subjects with mild or moderate hepatic impairment.
Patients with renal impairment	Not included in the clinical development program.
Patients with cardiovascular impairment	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Refer to Table 14.
Subpopulations carrying relevant genetic polymorphisms	Not specifically studied in the clinical development program.
Pediatric population	Children aged 20 days to 17 years have been studied in clinical trials at the pivotal dose. Please refer to Table 12.
Aged >60 years	Not included in the clinical development program.

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

Risdiplam is currently approved in approximately 100 countries. Due to inventory, it was not possible to use standard patient number calculation from Company Internal sales data.

For the United States, cumulative exposure was calculated as “the sum of all new commercial patients each month from the international birth date (IBD; 7 August 2020) until July 2023” and “the sum of all patients on free goods from IBD until July 2023.”

Note: All expanded access program patients in the U.S. were converted to commercial patients. The number of patients on free goods were derived from commercial patients under the assumption that free goods this year accounts to 20% of total sales.

Total estimated patient exposures were directly reported by affiliates for 28 countries (out of 82) having sales. For the remaining 54 countries, patient numbers were estimated using extrapolation based on reported patient numbers and volume from Company Internal sales data. Age splits were derived by countries that reported patient splits. It is the average of actual age splits reported by aforementioned 28 countries (Table 19). The source for the gender split was the epidemiology model (Table 20).

For Japan, patient exposure is in 'patient numbers'. The estimation of the market exposure to risdiplam in this RMP was based on direct reporting from physicians. Age splits were based on Japanese Real-world data. The source for the gender split was published data (Ito et al. 2022).

Table 19 Cumulative Patient Exposure – Age Split by Regions

Region	≤20 days	20 days to ≤2 years	>2 years to ≤18 years	above 18 years
EEA	0%	1%	39%	60%
ROW	0%	12%	61%	27%
U.S.	1%	5%	39%	55%

EEA = European Economic Area; RoW = Rest of World; U.S. = United States

The age split data reflected in this table details the cumulative and interval patient exposure from marketing experience.

Table 20 Cumulative Patient Exposure – Gender Split (U.S., EEA and RoW)

Region	Male	Female	Unknown
EEA, ROW, U.S.	50%	50%	0%

EEA = European economic area; RoW = rest of world; U.S. = United States.

SV.1.2 Exposure

Since the IBD of 7 August 2020 until 6 August 2023, an estimated cumulative total of 10,885 patients have received risdiplam from marketing experience; see Annex 7 for further details.

PART II: MODULE SVI— ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Although risdiplam penetrates well into the brain, it is not expected to lead to abuse or dependency for the following reasons:

- There is neither nonclinical nor current clinical evidence supporting any CNS effects which would induce misuse for illegal purposes:
- Although risdiplam may potentially bind to neuromelanin in the brain in analogy to its binding to retinal melanin, this property is common to many drugs. Given that it has been shown that melanin-binding per se did not confer retinal toxicity in pigmented rats, the binding of risdiplam to neuromelanin does not imply toxicity.
- In nonclinical studies no pathological changes were observed in sections in brain tissue, in particular high melanin-containing substantia nigra of the mid-brain after chronic treatment in monkeys.
- There is no evidence for accumulation of risdiplam in the brain given that it reaches equal total concentrations in brain tissue and plasma. Furthermore, the free concentrations in plasma and in cerebrospinal fluid (CSF) are comparable in animals.
- The molecular mechanism of splicing modification of the *SMN2* gene or other secondary splice targets seen in vitro or in animal studies/tissues does not suggest an engagement of neuronal signaling pathways involved in dependency and abuse. An in vitro screen specifically designed to capture targets known to be involved in abuse and dependence has not shown effects on such targets at concentrations in the range of potential concentrations in patients with SMA [1087510].
- Numerous nonclinical studies with risdiplam demonstrated that there were no observed behavioral changes suggestive of abuse potential or detrimental effects on the dopaminergic neurons of the substantia nigra.

A thorough review of safety information obtained in patients and subjects exposed to risdiplam concluded that there was no indication of abuse or dependence-related AEs.

Based on the mechanistic, bio-distribution, nonclinical, and clinical data, the MAA concludes that risdiplam does not have CNS activity associated with abuse potential and dependence and therefore no additional abuse and dependence-related studies are required.

PART II: MODULE SVII— IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for NOT including an identified or potential risk in the list of safety concerns in the RMP:

Known risks that have an impact on the benefit-risk profile but are not associated with additional pharmacovigilance or risk-minimization activities, beyond labeling:

- Potential risk of effects on male fertility
- Potential risk of toxicities of MATE1/2-K substrates with narrow therapeutic margin concomitantly administered with risdiplam

Risks observed in nonclinical trials that were not confirmed to be potential or identified risk in the clinical trials conducted in humans:

- Potential risk of hematological effects

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks: None
Important Potential Risk of Retinal toxicity

Risk-benefit impact:

A comprehensive panel of ophthalmological assessments was performed including imaging to detect structural changes of the retina as well as visual function testing to detect potential functional impairment in central or peripheral vision. No adverse event or ophthalmologic assessment finding suggestive of risdiplam-induced retinal toxicity were reported in any patient exposed to risdiplam up to the CCOD for each study. With the extensive ophthalmological monitoring up to at least 8 weeks in 405 patients, for at least 1 year in 273 patients, for at least 2 years in 72 patients and for at least 3 years in 12 patients, there is evidence of an absence of retinal toxicity in patients exposed to risdiplam for up to 3 years.

In comparison, delayed retinal toxicity became apparent in a nonclinical monkey study after an estimated 2-5 months (see SII.1.1 Delayed (Retinal) Toxicity). Moreover, the theoretical impact of non-reversible retinal toxicity on the individual patient is expected to consist primarily of impaired peripheral vision/night vision. Based on nonclinical observations, significant impairment of central vision or blindness would not be expected. This potential risk may result in persistent disability. The clinical significance of this potential disability must be viewed in the context of the severity of the underlying disease but could be considered as significant in particular for patients with milder clinical course of SMA.

Important Potential Risk: Effect on epithelial tissues

Risk-benefit impact:

The benefit-risk impact of this potential risk is low given that the events observed would be reversible and would be observed only in case of overdose. Temporary discontinuation of treatment with subsequent re-initiation at the recommended dose would ensure management of this risk and allow the patient to continue benefiting from the therapeutic effects of risdiplam.

Important Potential Risk: Embryofetal toxicity

Risk-benefit impact:

There are no adequate data on the developmental risks associated with use of risdiplam in pregnant women.

In studies in pregnant rats treated with risdiplam, embryofetal toxicity with lower fetal weight and delayed development was evident. The NOAEL for this effect was approximately two fold above the exposure levels reached at the therapeutic dose of risdiplam in patients. In studies with pregnant rabbits, dysmorphogenic effects were observed at exposures also associated with maternal toxicity. These consisted of four fetuses (4%) from 4 litters (22%) with hydrocephaly. The NOAEL was approximately four times the exposure levels reached at the therapeutic dose of risdiplam in patients. In a pre- and post-natal study in rats treated daily with risdiplam, risdiplam caused a slight delay in gestation length.

Although this potential risk could result in persistent disability in infants born from mothers with SMA treated with risdiplam, the nonclinical data suggest that normal pregnancies could be possible. Normal pregnancies have been reported in patients with SMA who often wish to have own children (Abati et al. 2018). The potential risk of embryofetal toxicity can therefore have a significant impact on the overall benefit-risk of risdiplam in female patients wishing to conceive.

1.1.1.1 Missing Information of Long-term Safety

Risk-benefit impact:

There is no evidence for any risks associated with chronic treatment of risdiplam in clinical studies (where patients have been treated for up to 42 months). In nonclinical studies, risks associated with long-term treatment have not been identified (up to 9 months of chronic treatment in monkeys, equivalent to several years of human life, and 6 months in rats, equivalent to more than 10 years of human life).

There remains, however, the possibility of delayed onset of currently unknown risks other than potential retinal toxicity, justifying the inclusion of long-term safety as missing information.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Important Potential Risk of Retinal Toxicity:

The risk of retinal toxicity is no longer considered a potential risk due to the absence of findings following thorough ophthalmological monitoring in 486 patients for up to 5.15 years (Refer to DSR No. 1127141 for additional information).

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Information on Important Identified Risks

There are no important identified risks for risdiplam.

Information on Important Potential Risks

Embryofetal Toxicity

Potential mechanisms:

The potential effect on embryofetal development is secondary to risdiplam's effect on cell division and apoptosis associated with alternative splicing of secondary splice target genes (*FOXM1* and *MADD* genes).

Evidence source(s) and strength of evidence:

Consistent with its effects on cell division and apoptosis, treatment of pregnant rabbits with risdiplam has been associated with maternal toxicity and teratogenicity, with a NOAEL at exposures of ~4 times the mean exposure guidance in clinical trials. No teratogenicity was observed in rats up to ~5 times the clinical mean exposure guidance, but embryofetal toxicity (reduced fetal weight and delayed fetal development) was noted, with a NOAEL slightly in excess of 2-fold the mean exposure guidance without maternal toxicity. Even though teratogenicity was only noted in the rabbit at a maternally toxic dose level, the possibility of a dysmorphogenic potential of risdiplam in the human cannot be discounted.

Characterization of the risk:

There are no data on the developmental risks associated with use of risdiplam in pregnant women. In animal studies of rats and rabbits, administration of risdiplam resulted in adverse effects on development including embryofetal mortality, malformations, decreased fetal body weights, and reproductive impairment in offspring.

Risk factors and risk groups:

Women who have been exposed to risdiplam during pregnancy or 1 month prior to the start of pregnancy.

Preventability:

The pregnancy status of female patients of reproductive potential should be verified prior to initiating treatment with risdiplam.

Females of reproductive age should use effective contraception during treatment with risdiplam and for at least 1 month after their last dose.

Impact on the benefit-risk balance of the product:

Although this potential risk could result in persistent disability in infants born from mothers with SMA treated with risdiplam, the nonclinical data suggest that normal pregnancies could be possible. Normal pregnancies have been reported in patients with SMA who often wish to have own children (Abati et al 2018). The potential risk of embryofetal toxicity can therefore have a significant impact on the overall benefit-risk balance of risdiplam in female patients of childbearing potential wishing to conceive.

Public health impact:

No public health impact is expected.

Effect on Epithelial Tissues

Potential mechanisms:

The potential effect on epithelial tissues is secondary to risdiplam's effect on cell division and apoptosis associated with alternative splicing of secondary splice target genes (*FOXM1* and *MADD* genes).

Evidence source(s) and strength of evidence:

In chronic toxicology studies in rodents and monkeys, adverse effects on epithelial tissues (skin, larynx, eyelid, and gastrointestinal tract) were observed. These effects were observed within days or weeks of treatment, were dose-dependent in severity, and occurred with high incidence. The first clinical sign in monkeys was mild parakeratosis at exposures more than 2.5-fold the exposure observed at the pivotal dose selected for patients with SMA. These findings were reversible upon discontinuation of dosing with risdiplam but persisted with continuous dosing and worsened at high doses with breakage of the skin barrier when animals were dosed through.

Characterization of the risk:

In the 'All Patients with SMA' population, skin findings were either not suggestive of events observed in nonclinical studies (mainly parakeratosis) and/or resolved despite ongoing treatment, which precludes a causal association with risdiplam.

Risk factors and risk groups:

Skin events suggestive of effects on epithelial tissues have not been observed in humans and, therefore, risk factors and risk groups cannot be identified in humans and must be extrapolated from nonclinical studies.

Significant overdoses may be considered as risk factors for effects on epithelial tissues based on the exposure dependency of findings in the nonclinical studies. Overdoses are a potential risk factor for effects on epithelial tissues.

Preventability:

The maximum amount of risdiplam dispensed by prescription can cover the needs for a maximum treatment period of 64 days of treatment, which prevents occurrence of significant overdoses for prolonged periods.

Impact on the benefit-risk balance of the product:

This potential risk does not occur at the recommended dose and would be reversible upon treatment discontinuation in the event of overdose.

Public health impact:

No public health impact is expected.

SVII.3.2. Presentation of the Missing Information

Information on Missing Information

Long-term safety

Evidence source:

To date, with patients monitored for up to 47 months, no long-term safety risk has been identified. Other than retinal toxicity, nonclinical studies do not indicate any other risk associated with chronic treatment with risdiplam (see SII.1.1 Delayed (Retinal) Toxicity).

The anticipated risk / consequence of risks associated with chronic treatment are currently unknown.

Safety in patients < 1 month of age

Evidence source:

Fifteen patients < 1 month (30 days) have been enrolled in Study BN40703 (RAINBOWFISH); however, there were no patients < 20 days treated with the pivotal dose from Day 1 of the study. As such PK and safety in patients below 20 days has not been assessed to date and therefore safety in patients below 1 month is considered missing information.

Evrysdi is already approved for patients with SMA from birth in several countries including the U.S. Although the worldwide exposure in patients <1 month is unknown, solicited information is available from U.S. physicians regarding 12 newborns <20 days of age at the time of risdiplam treatment start. The patients ranged from 1 to 18 days of age at first administration and were dosed according to the United States Prescribing Information (USPI) at 0.15 mg/kg. The physicians orally reported that treated newborns did well on risdiplam, progressed normally, and reached milestones on time. One newborn was reported with an upper respiratory tract infection assessed as unrelated to risdiplam by the physician. Five out of the 12 babies (~42%) discontinued risdiplam between 2 weeks and 4 months of age due to starting gene therapy, while all others remained on risdiplam treatment.

This information is consistent with the Global Safety Database which does not provide evidence for adverse safety outcomes in patients starting risdiplam <1 month of age.

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 21 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryofetal toxicity Effect on epithelial tissues
Missing information	Long-term safety Safety in patients <1 month of age

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

ROUTINE PHARMACOVIGILANCE ACTIVITIES BEYOND ADVERSE REACTIONS REPORTING AND SIGNAL DETECTION

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

No other forms of routine pharmacovigilance activities have been put in place for risdiplam.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Safety concerns: Long-term safety and Effect on Epithelial tissues

Table 22 Study BP39056 (FIREFISH) Open-Label Extension Summary

Study/activity short name and title: A two-part, multicenter, single-arm, open-label study to investigate the safety, tolerability, PK, pharmacodynamics (PD) and efficacy of risdiplam in infants with Type 1 SMA.
Study objectives: Part 1 To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in infants with Type 1 SMA, and to select the dose for Part 2. Part 2 To assess the efficacy of risdiplam measured as the proportion of infants sitting without support after 12 months of treatment, as assessed in the Gross Motor Scale of the Bayley Scales of Infant and Toddler development. OLE: Continued general safety in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE).
Study design: This is a seamless open-label, single-arm, multicenter clinical study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of risdiplam in Type 1 SMA infants. Patients will then be given the opportunity to enter the OLE phase of the study (for both Parts 1 and 2). The patient's treatment in the OLE may continue for an additional 3 years after 2 years of study treatment (patients will be treated for a total duration of at least 5 years).
Study populations: This study includes both male and female Type1 SMA infants aged ≥ 1 month and ≤ 7 months at the time of enrollment.
Milestones: Initial protocol: Version 1, 22 June 2016 Current protocol: Version 7, 17 June 2020 Interim Clinical Study Report (CSR): 02 August 2019 (Part 1 data) Primary CSR: 06 April 2020 (Part 2 data) Update CSR: Submitted Q3 2021 Final CSR: Estimated Q3 2024

Table 23 Study BP39055 (SUNFISH) Open-Label Extension Summary

Study/activity short name and title: A two-part, multicenter, randomized, placebo-controlled, double-blind study to investigate safety, tolerability, PK/PD, and efficacy of risdiplam in patients with Type 2 and 3 SMA (aged 2 to 25 years).
Study objectives: Part 1: To evaluate the safety, tolerability, PK and PD of risdiplam in patients with Type 2 and Type 3 (ambulant or non-ambulant) SMA, and to select the dose for Part 2 of the study. Part 2: To evaluate efficacy of risdiplam compared to placebo in terms of motor function in Type 2 and non-ambulant Type 3 SMA patients, as assessed by the change from baseline in the total score of the MFM at 12 months. OLE: Continued general safety in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE).
Study design: The study consists of two parts: Part 1 is a double-blinded, placebo-controlled, dose-finding part. Patients will be randomized to risdiplam active treatment or placebo (2:1 ratio), administered once daily. Part 2, the confirmatory part, will start once the dose has been selected in Part 1 by the IMC and has been confirmed by the iDMC. Patients will then be given the opportunity to enter the OLE phase of the study (for both Parts 1 and 2). The patient's treatment in the OLE may continue for an additional 3 years after 2 years of study treatment (patients will be treated for a total duration of at least 5 years).
Study populations: • Part 1 includes patients with Type 2 and 3 SMA (ambulant and non-ambulant) aged 2-25 years. • Part 2 of the study includes Type 2 and non-ambulant Type 3 SMA patients aged 2-25 years.
Milestones: Initial protocol: Version 1, 03 May 2016 Current protocol: Version 6, 22 June 2020 Interim CSR: 31 July 2019 (Part 1 data) Primary CSR: 27 February 2020 (Part 2 data) Update CSR: 09 June 2020 (Part 1 data) Update CSR: Submitted in Q2 2021 (Part 2 data) Final CSR: Estimated Q2 2024

Table 24 Study BP39054 (JEWELFISH) Open-Label Extension Summary

Study/activity short name and title: An open-label, non-comparative study in SMA patients previously enrolled in Roche Study BP29420 (MOONFISH) with the splicing modifier RO6885247 (development discontinued) or previously treated with SPINRAZA® (nusinersen), Zolgensma® (onasemnogene abeparvovec, AVXS-101), or olesoxime (previous Roche acquired development compound, since discontinued) in which treatment with risdiplam is evaluated over a 24-month period.
Study objectives: To evaluate the safety and tolerability of risdiplam To investigate the PK of risdiplam and metabolites as appropriate OLE: Continued general safety in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE).
Study design: This is a multicenter, exploratory, non-comparative and open-label study to investigate the safety, tolerability, PK and PK/PD relationship of risdiplam in adults and children and infants with SMA previously enrolled in Study BP29420 (Moonfish) with the splicing modifier RO6885247 or previously treated with nusinersen, AVXS-101 (AAV 9 based gene therapeutic that delivers a normal copy of the SMN1 gene), or olesoxime. Patients will then be given the opportunity to enter the OLE phase of the study. The patient's treatment in the OLE may continue for an additional 3 years after 2 years of study treatment (patients will be treated for a total duration of at least 5 years).
Study populations: The study population consists of adult and pediatric patients with SMA aged 6 months to 60 years who have been previously enrolled in Study BP29420 (MOONFISH) or previously treated with nusinersen, AVXS-101, or olesoxime.
Milestones: Initial protocol: 2 November 2016 Current protocol: Version 4, 23 June 2020 Interim CSR: 23 July 2019 Interim CSR: 10 June 2020 Interim CSR: Submitted in Q3 2021 Primary CSR: Estimated in Q4 2022 Final CSR: Estimated Q4 2025

Table 25 Study BN40703 (RAINBOWFISH) Open-Label Extension Summary

Study/activity short name and title: An open-label study of risdiplam in infants with genetically diagnosed and presymptomatic spinal muscular atrophy (RAINBOWFISH).
Study objectives: This study will evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants genetically diagnosed with SMA but not yet presenting with symptoms. OLE: Continued general safety in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE).
Study design: The study is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, pharmacokinetics, and pharmacodynamics of risdiplam in infants aged from birth to 6 weeks who have been (at first dose) genetically diagnosed with SMA but are not yet presenting with symptoms. Patients will then be given the opportunity to enter the OLE phase of the study. The patient's treatment in the OLE may continue for an additional 3 years after 2 years of study treatment (patients will be treated for a total duration of at least 5 years).
Study populations: Infants aged from birth to 6 weeks who have been (at first dose) genetically diagnosed with SMA but are not yet presenting with symptoms.
Milestones Final CSR: Estimated Q3 2027

Safety concern: Long-term safety

Table 26 Study BP42817 (QTc Study) Summary

Study/activity short name and title: A Phase I, double-blind, placebo and positive-controlled crossover study to investigate the effects of risdiplam on QTc interval in healthy subjects.
Study Objectives: To estimate the effects of single oral doses of risdiplam on QT interval of the ECG (QT)/QT corrected for heart rate (QTc) interval in healthy subjects.
Study design: This will be a 2-part, randomized, double-blinded study in healthy male adult subjects. In each part, potential subjects will be screened within 28 days prior to study entry (i.e., prior to Check-in) to confirm eligibility to participate in the study. Subjects will be admitted to the clinical site on Day -1 and reside in the clinic after dosing for 8 days in Part A or 3 days in Part B.
Study populations: Male healthy subjects aged 18 to 50 years of age, inclusive, at Screening.
Milestones: Final protocol: Submitted in Q2 2021 Final report: Estimated in Q3 2023

Safety concern: Embryofetal toxicity

Table 27 Study BN42833 (Risdiplam Pregnancy Surveillance Study) Summary

Study/activity short name and title: A Phase IV, non-interventional surveillance study.
Study Objectives: To collect and describe selected pregnancy outcomes (i.e., live birth, spontaneous abortions, stillbirths, elective abortions, and preterm births) and pregnancy complications in women with SMA exposed to risdiplam during the defined exposure window. To collect and describe selected fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, and postnatal growth and development) at birth and through up to the first year of life of infants born to women exposed to risdiplam during the defined pregnancy exposure window.
Study design: This pregnancy surveillance program will collect primary data from risdiplam-exposed pregnant women and their healthcare providers (HCPs), as well as their infant's HCP.
Study populations: Any currently pregnant woman with SMA exposed to risdiplam, as defined above, will be eligible.
Milestones: Protocol v1: Submitted to EMA in Q3 2021 Protocol v2: Submitted to EMA in Q4 2021 Final report: Estimated Q4 2031

Safety concern: Safety in Patients < 1 Month of Age

Table 28 Study BN44619 (PUPFISH) Summary

Study/activity short name and title: A phase II, open-label study to investigate the pharmacokinetics and safety of risdiplam in infants with SMA.
Study Objectives: To characterize the risdiplam PK profile. To evaluate the safety of risdiplam.
Study design: Non-randomized, open-label, single-arm interventional study.
Study populations: Patients with SMA aged < 20 days at first dose.
Milestones: Final report: Estimated Q1 2026

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 29 Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones/Due Date(s)
Category 3—Required additional pharmacovigilance activities (by a competent authority such as CHMP/PRAC or NCA)—i.e., studies that investigate a safety concern or evaluate the effectiveness of risk minimization activities			
BP39056 (FIREFISH) OLE Ongoing	Target population: infants (aged 1 to 7 months at enrollment) with Type 1 SMA OLE: Continued general safety as well as ophthalmological monitoring.	Long-term safety Effect on epithelial tissues	Initial protocol: Version 1, 22 June 2016 Current protocol: Version 7, 17 June 2020 Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the OLE phase Final CSR: Estimated Q3 2024
BP39055 (SUNFISH) OLE Ongoing	Target population: patients with Type 2 and 3 SMA (aged 2 to 25 years) OLE: Continued general safety as well as ophthalmological monitoring.	Long-term safety Effect on epithelial tissues	Initial protocol: Version 1, 03 May 2016 Current protocol: Version 6, 22 June 2020 Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the OLE phase Final CSR: Estimated Q2 2024

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones/Due Date(s)
BP39054 (JEWELFISH) OLE Ongoing	Target population: patients previously enrolled in Roche Study BP29420 (MOONFISH) who were previously treated with the splicing modifier RO6885247 (development discontinued) or patients previously treated with SPINRAZA® (nusinersen), Zolgensma® (onasemnogene abeparvovec, AVXS-101), or olesoxime (previous Roche acquired development compound, since discontinued) OLE: Continued general safety as well as ophthalmological monitoring.	Long-term safety Effect on epithelial tissues	Initial protocol: 2 November 2016 Current protocol: Version 4, 23 June 2020 Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the OLE phase Final CSR: Estimated Q4 2025
BN40703 (RAINBOWFISH) OLE Ongoing	Target population: infants with genetically diagnosed and presymptomatic spinal muscular atrophy OLE: Continued general safety as well as ophthalmological monitoring.	Long-term safety Effect on epithelial tissues	Initial protocol: 13 July 2018 Current protocol: Version 4, 30 March 2021 Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the OLE phase Final CSR Estimated: Q3 2027

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones/Due Date(s)
BN42833 Phase IV, non-interventional pregnancy surveillance study Planned	To collect and describe selected pregnancy outcomes (i.e., live birth, spontaneous abortions, stillbirths, elective abortions, and preterm births) and pregnancy complications in women with SMA exposed to risdiplam during the defined exposure window. To collect and describe selected fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, and postnatal growth and development) at birth and through up to the first year of life of infants born to women exposed to risdiplam during the defined pregnancy exposure window.	Embryofetal toxicity	Protocol v1 (Submitted to EMA in Q3 2021) Current Protocol: Version 2, 30 November 2021 (Submitted to EMA in Q4 2021) Final report: Estimated Q4 2031
BP42817 Phase I, double-blind, placebo- and positive-controlled crossover study to investigate the effects of risdiplam on QTc interval in healthy subjects Ongoing	To estimate the effects of single oral doses of risdiplam on QT interval of the ECG (QT)/QT corrected for heart rate (QTc) interval in healthy subjects.	Missing information: long-term safety	Current Protocol: Version 1, 21 May 2021 (Submitted to EMA in Q2 2021) Final report: Estimated Q3 2023
BN44619 Phase II, open-label study Planned	To evaluate the pharmacokinetics and safety of risdiplam in patients with SMA under 20 days of age at first dose.	Missing information: Safety in patients $<$1 month of age	Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the study. Final report: Estimated Q1 2026

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

Table 30 Planned and Ongoing Post-Authorization Imposed Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones Due Date
Efficacy studies that are conditions of the marketing authorization			
BN43428 A Prospective, Observational, Post-Authorization Efficacy Study to Assess Long-term Effectiveness of Risdiplam in Patients with Genetically Confirmed 5q SMA Planned	•To describe the real-world, long-term effectiveness of risdiplam on disease progression and to compare the impact of potential effect modifiers (symptomatic status, *SMN2* copy number) on long-term effectiveness •To compare the real-world, long-term effectiveness outcomes between a cohort of risdiplam-treated patients and a cohort of DMT-naive patients (untreated with any DMT approved for SMA)	Long-term efficacy	Current protocol: Version 1.0, 30 July 2021 Final report: Estimated Q4 2030

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN
V.1 ROUTINE RISK-MINIMIZATION MEASURES

Table 31 Description of Routine Risk-Minimization Measures by Safety Concern

Safety concern	Routine risk-minimization activities
Embryofetal toxicity	**Proposed routine risk communication is described in:** • Section 4.4 of the SmPC (Special warnings and precautions for use) • Section 4.6 of the SmPC (Fertility, pregnancy and lactation) • Section 5.3 of the SmPC (Preclinical safety data; Reproductive toxicity) • Section 2 of the Package Leaflet (What you need to know before you or your child take Evrysdi; Pregnancy, contraception, breastfeeding and male fertility) **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • Section 4.6 of the SmPC (Fertility, pregnancy and lactation) **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription
Effect on Epithelial tissues	**Proposed routine risk communication is described in:** • Section 5.3 of the SmPC (Preclinical safety data; Effect on epithelial tissues) **Routine risk-minimization activities recommending specific clinical measures to address the risk:** No specific clinical measures are recommended to address the effect on epithelial tissues. **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription
Long-term safety	No risk-minimization measures required
Safety in patients $<$1 month of age	No risk-minimization measures required

V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

Routine risk-minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 SUMMARY OF RISK-MINIMIZATION MEASURES

Table 32 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Potential Risk: Effect on Epithelial tissues	**Routine risk minimization measures:** • SmPC Section 5.3 (Preclinical safety data; Effect on Epithelial tissues) **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** OLE until 5 years of treatment for all patients in following studies: • Study BP39056 (FIREFISH) • Study BP39055 (SUNFISH) • Study BP39054 (JEWELFISH) • Study BN40703 (RAINBOWFISH)
Important Potential Risk: Embryofetal toxicity	**Routine risk minimization measures:** • SmPC Section 4.4 (Special warnings and precautions for use) • SmPC Section 4.6 (Fertility, pregnancy and lactation) • SmPC Section 5.3 (Preclinical safety data) • Section 2 of the Package Leaflet (What you need to know before you or your child take Evrysdi; Pregnancy, contraception, breastfeeding and male fertility) **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.6 (Fertility, pregnancy and lactation)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Study BN42833 (Risdiplam Pregnancy Surveillance Study)

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Other risk minimization measures beyond the Product Information: Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** • None	
Missing Information: Long-term safety	**Routine risk minimization measures:** • None **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study BP42817 (QTc Study) OLE until 5 years of treatment for all patients in following studies: • Study BP39056 (FIREFISH) • Study BP39055 (SUNFISH) • Study BP39054 (JEWELFISH) • Study BN40703 (RAINBOWFISH)
Missing information: Safety in patients $<$1 month of age	**Routine risk minimization measures:** • None **Other risk minimization measures beyond the Product Information:** **None** **Additional risk-minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** Study BN44619 (PUPFISH)

REFERENCES

Abati E, Corti S. Pregnancy outcomes in women with spinal muscular atrophy: A review. J Neurol Sci. 2018 May 15;388:50-60.

Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve 2015;51:157-67.

Belter L, Cook SF, Crawford TO, et al. An overview of the Cure SMA membership database: Highlights of key demographic and clinical characteristics of SMA members. J Neuromuscul Dis 2018;5:167-76.

Burd L, Short SK, Martsolf JT, et al. Prevalence of type I spinal muscular atrophy in North Dakota. Am J Med Genet 1991;41:212-5.

Butchbach ME. Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases. Front Mol Biosci 2016;3:7.

Castro D, Iannaccone ST. Spinal muscular atrophy: therapeutic strategies. Curr Treat Options Neurol 2014;16:316.

Cobben JM, Lemmink HH, Snoeck I, et al. Survival in SMA type I: a prospective analysis of 34 consecutive cases. Neuromuscul Disord 2008;18:541-4.

Crawford TO, Paushkin SV, Kobayashi DT, et al. Evaluation of SMN protein, transcript, and copy number in the biomarkers for spinal muscular atrophy (BforSMA) clinical study. PLoS One 2012;7:e33572.

Czeizel A, Hamula J. A hungarian study on Werdnig-Hoffmann disease. J Med Genet 1989;26:761-3.

D'Amico A, Mercuri E, Tiziano FD, et al. Spinal muscular atrophy. Orphanet J Rare Dis 2011;6:71.

Elsheikh BH, Zhang X, Swoboda KJ, et al. Pregnancy and delivery in women with spinal muscular atrophy. Int J Neurosci 2017;127(11):953-957.

Faravelli I, Nizzardo M, Comi GP, et al. Spinal muscular atrophy--recent therapeutic advances for an old challenge. Nat Rev Neurol 2015;11:351-9.

Farrar MA, Vucic S, Johnston HM, et al. Pathophysiological insights derived by natural history and motor function of spinal muscular atrophy. J Pediatr 2013;162:155-9.

Feldkotter M, Schwarzer V, Wirth R, et al. Quantitative analyses of SMN1 and SMN2 based on real-time lightCycler PCR: fast and highly reliable carrier testing and prediction of severity of spinal muscular atrophy. Am J Hum Genet 2002;70:358-68.

Finkel R, Bertini E, Muntoni F, et al. 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands. Neuromuscul Disord 2015;25:593-602.

Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. Neurology 2014;83:810-7.

Forsgren L, Almay BG, Holmgren G, et al. Epidemiology of motor neuron disease in northern Sweden. Acta Neurol Scand 1983;68:20-9.

Ito M, Yamauchi A, Urano M, et al. Epidemiological investigation of spinal muscular atrophy in Japan. Brain and Development 2022;44:2–16.

Kolb SJ, Kissel JT. Spinal Muscular Atrophy. Neurol Clin 2015;33:831-46.

Lunn MR, Wang CH. Spinal muscular atrophy. Lancet 2008;371:2120-33.

Mailman MD, Heinz JW, Papp AC, et al. Molecular analysis of spinal muscular atrophy and modification of the phenotype by SMN2. Genet Med 2002;4:20-6.

Markowitz JA, Singh P, Darras BT. Spinal muscular atrophy: a clinical and research update. Pediatr Neurol 2012;46:1-12.

Mercuri E, Darras BT, Chiriboga CA, et al. Nusinersen versus Sham Control in Later-Onset Spinal Muscular Atrophy. N Engl J Med 2018;378:625-35.

Merlini L, Stagni SB, Marri E, et al. Epidemiology of neuromuscular disorders in the under-20 population in Bologna Province, Italy. Neuromuscul Disord 1992;2:197-200.

Monani UR, Lorson CL, Parsons DW, et al. A single nucleotide difference that alters splicing patterns distinguishes the SMA gene SMN1 from the copy gene SMN2. Hum Mol Genet 1999;8:1177-83.

Mostacciuolo ML, Danieli GA, Trevisan C, et al. Epidemiology of spinal muscular atrophies in a sample of the Italian population. Neuroepidemiology 1992;11:34-8.

Mueller L, Hermann A. A human keratinocyte tissue model differentiates between phototoxicity and direct skin toxicity. The Toxicologist, Supplement to Toxicological Sciences 2015;144:89.

Munsat TL, Davies KE. International SMA consortium meeting. (26-28 June 1992, Bonn, Germany). Neuromuscul Disord 1992;2:423-8.

Noone J, Whitmire S, Buchenberger D, et al., editors. Clinical experience of spinal muscular atrophy (SMA) treatment: A combination of perspectives from a large survey. 23rd International SMA Research Meeting; 2019; Anaheim, CA.

Ogino S, Wilson RB, Gold B. New insights on the evolution of the SMN1 and SMN2 region: simulation and meta-analysis for allele and haplotype frequency calculations. Eur J Hum Genet 2004;12:1015-23.

Pera MC, Coratti G, Mazzone ES, et al. Revised upper limb module for spinal muscular atrophy: 12 month changes. Muscle Nerve 2019;59:426-30.

Periodic Benefit-Risk Evaluation Report for Risdiplam Reporting Interval 7 February 2023 through 6 August 2023. Report No. 1122884. 6 October 2023.

Prior TW, Snyder PJ, Rink BD, et al. Newborn and carrier screening for spinal muscular atrophy. Am J Med Genet A 2010;152A:1608-16.

Review of the potential risk of retinal toxicity for risdiplam. Drug Safety Report RDR No: 1127141. Dated October 2023.

Sproule DM. Spinal Muscular Atrophy. In: Aminoff MJ DR, editor. Encyclopedia of the Neurological Sciences: Academic Press; 2014. p. 281-5.

Tangsrud SE, Halvorsen S. Child neuromuscular disease in southern Norway. Prevalence, age and distribution of diagnosis with special reference to "non-Duchenne muscular dystrophy". Clin Genet 1988;34:145-52.

Urrego D, Liwa AC, Cole WC, et al. Cyclooxygenase inhibitors for treating preterm labour: What is the molecular evidence? (1). Can J Physiol Pharmacol 2019;97:222-31.

Verhaart IEC, Robertson A, Leary R, et al. A multi-source approach to determine SMA incidence and research ready population. J Neurol 2017a;264:1465-73.

Verhaart IEC, Robertson A, Wilson IJ, et al. Prevalence, incidence and carrier frequency of 5q-linked spinal muscular atrophy - a literature review. Orphanet J Rare Dis 2017b;12:1-15.

Vuillerot C, Payan C, Iwaz J, et al. Responsiveness of the motor function measure in patients with spinal muscular atrophy. Arch Phys Med Rehabil 2013;94:1555-61.

Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. J Child Neurol 2007;22:1027-49.

Winsor EJ, Murphy EG, Thompson MW, et al. Genetics of childhood spinal muscular atrophy. J Med Genet 1971;8:143-8.

Zerres K, Rudnik-Schoneborn S, Forrest E, et al. A collaborative study on the natural history of childhood and juvenile onset proximal spinal muscular atrophy (type II and III SMA): 569 patients. J Neurol Sci 1997;146:67-72.

PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

Summary of Risk Management Plan for EVRYSDI (RISDIPLAM)

This is a summary of the risk-management plan (RMP) for Evrysdi. The RMP details important risks of Evrysdi, how these risks can be minimized, and how more information will be obtained about Evrysdi's risks and uncertainties (missing information).

Evrysdi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Evrysdi should be used.

This summary of the RMP for Evrysdi should be read in the context of all this information, including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Evrysdi's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Evrysdi is authorized for the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies (see SmPC for the full indication). It contains risdiplam as the active substance, and it is given as a solution by mouth or feeding tube.

Further information about the evaluation of Evrysdi's benefits can be found in Evrysdi's EPAR, including in its plain-language summary, available on the EMA Web site, under the medicine's Web page:

https://www.ema.europa.eu/en/medicines/human/EPAR/evrysdi

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Evrysdi, together with measures to minimize such risks and the proposed studies for learning more about Evrysdi's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorized pack size—The amount of medicine in a pack is chosen so as to ensure that the medicine is used correctly.
- The medicine's legal status—The way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Evrysdi is not yet available, it is listed under “missing Information” below.

II.A List of Important Risks and Missing Information

Important risks of Evrysdi are risks that need special risk-management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Evrysdi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine, and in patients <1 month of age).

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	Embryofetal toxicity Effect on epithelial tissues
Missing information	Long-term safety Safety data in patients <1 month of age

II.B Summary of Important Risks

Important Potential Risk: Embryofetal toxicity	
Evidence for linking the risk to the medicine	Consistent with its effects on cell division and apoptosis, treatment of pregnant rabbits with risdiplam has been associated with maternal toxicity and teratogenicity, with a NOAEL at exposures of ~4 times the mean exposure guidance in clinical trials. No teratogenicity was observed in rats up to ~5 times the clinical mean exposure guidance, but embryofetal toxicity (reduced fetal weight and delayed fetal development) was noted, with a NOAEL slightly in excess of 2-fold the mean exposure guidance without maternal toxicity. Even though teratogenicity was only noted in the rabbit at a maternally toxic dose level, the possibility of a dysmorphogenic potential of risdiplam in the human cannot be discounted.
Risk factors and risk groups	Women who have been exposed to risdiplam during pregnancy or 1 month prior to the start of pregnancy

Important Potential Risk: Embryofetal toxicity	
Risk-minimization measures	**Routine risk minimization measures:** • SmPC Section 4.4 (Special warnings and precautions for use) • SmPC Section 4.6 (Fertility, pregnancy and lactation) • SmPC Section 5.3 (Preclinical safety data) • Section 2 of the Package Leaflet (What you need to know before you or your child take Evrysdi; Pregnancy, contraception, breastfeeding and male fertility) **Routine risk-minimization activities recommending specific clinical measures to address the risk:** • SmPC Section 4.6 (Fertility, pregnancy and lactation)
	Other risk minimization measures beyond the Product Information: Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BN42833 Risdiplam Pregnancy Surveillance Study **See Section II.C of this summary for an overview of the post-authorization development plan.**

Important Potential Risk: Effect on Epithelial tissues	
Evidence for linking the risk to the medicine	In chronic toxicology studies in rodents and monkeys, adverse effects on epithelial tissues (skin, larynx, eyelid, and gastrointestinal tract) were observed. These effects were observed within days or weeks of treatment, were dose-dependent in severity, and occurred with high incidence. The first clinical sign in monkeys was mild parakeratosis at exposures more than 2.5-fold the exposure observed at the pivotal dose selected for patients with SMA. These findings were reversible upon discontinuation of dosing with risdiplam but persisted with continuous dosing and worsened at high doses with breakage of the skin barrier when animals were dosed through.
Risk factors and risk groups	Risk factors and risk groups: Skin events suggestive of effects on epithelial tissues have not been observed in humans therefore risk factors and risk groups cannot be identified in humans and must be extrapolated from nonclinical studies. Overdoses are a potential risk factor for effects on epithelial tissues based on findings in the nonclinical studies.

Important Potential Risk: Effect on Epithelial tissues	
Risk-minimization measures	**Routine risk minimization measures:** • Section 5.3 of the SmPC (Preclinical safety data; Effect on epithelial tissues) **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** • None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** OLE until 5 years of treatment for all patients in following studies: • Study BP39056 (FIREFISH) • Study BP39055 (SUNFISH) • Study BP39054 (JEWELFISH) • Study BN40703 (RAINBOWFISH) **See Section II.C of this summary for an overview of the post-authorization development plan.**

Missing Information: Long-term safety	
Risk-minimization measures	**Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. No additional risk-minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BP42817 (QTc Study) OLE until 5 years of treatment for all patients in following studies: • Study BP39056 (FIREFISH) • Study BP39055 (SUNFISH) • Study BP39054 (JEWELFISH) • Study BN40703 (RAINBOWFISH) **See Section II.C of this summary for an overview of the post-authorization development plan**

Missing Information: Safety in patients <1 month of age	
Risk-minimization measures	**Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. No additional risk-minimization measures
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Study BN44619 **See Section II.C of this summary for an overview of the post-authorization development plan.**

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

The following studies are conditions of the marketing authorization.

Study short name: Non Interventional Post-Authorization Efficacy Study (PAES) BN43428

Purpose of the study

A long-term prospective, observational study to further evaluate disease progression in SMA patients (both pre-symptomatic and symptomatic) with 1 to 4 *SMN2* copies treated with risdiplam, in comparison to natural history data in untreated patients.

II.C.2 Other Studies in Post-Authorization Development Plan

Study short name: Study BP39056 (FIREFISH) Open-Label Extension

Purpose of the study

Continued general safety and effects on epithelial tissues in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE).

Study short name: Study BP39055 (SUNFISH) Open-Label Extension

Purpose of the study

Continued general safety and effects on epithelial tissues in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE).

Study short name: Study BP39054 (JEWELFISH) Open-Label Extension

Purpose of the study

Continued general safety and effects on epithelial tissues in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE).

Study short name: Study BN40703 (RAINBOWFISH) Open-Label Extension

Purpose of the study

Continued general safety and effects on epithelial tissues in the OLE phase of ongoing clinical studies in SMA patients will occur for treatment duration of 5 years (study duration of 2 years, followed by 3 years OLE).

Study short name: Study BN42833 (Risdiplam Pregnancy Surveillance Study)

Purpose of the study

To collect and describe selected pregnancy outcomes (i.e., live birth, spontaneous abortions, stillbirths, elective abortions, and preterm births) and pregnancy complications in women with SMA exposed to risdiplam during the defined exposure window.

To collect and describe selected fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, and postnatal growth and development) at birth and through up to the first year of life of infants born to women exposed to risdiplam during the defined pregnancy exposure window.

Study short name: Study BP42817 (QTc Study)

Purpose of the study

To estimate the effects of single oral doses of risdiplam on QT interval of the ECG (QT)/QT corrected for heart rate (QTc) interval in healthy subjects.

Study short name: Study BN44619 (PUPFISH)

Purpose of the study

To generate pharmacokinetic (PK) and safety data on the use of risdiplam treatment in patients with spinal muscular atrophy (SMA) aged under 20 days of age at first dose.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

No other forms of routine pharmacovigilance activities have been put in place for risdiplam.

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (IF APPLICABLE)

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

This annex is not applicable as there are no proposed additional risk minimization activities for risdiplam.