25 February 2021
EMA/216061/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Evrysdi

International non-proprietary name: risdiplam

Procedure No. EMEA/H/C/005145/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Quality

AIBN	Azobisisobutyronitrile
CHMP	Committee for Medicinal Products for Human use
CMA	Critical material attribute
CPP	Critical process parameter
CQA	Critical quality attribute
DSC	Differential scanning calorimetry
DVS	Dynamic vapour sorption
EC	European Commission
EU	European Union
GC	Gas chromatography
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC	In-process control
IR	Infrared
KF	Karl Fischer titration
LDPE	Low density polyethylene
MAH	Marketing authorisation holder
NMR	Nuclear magnetic resonance
NOR	Normal operating range
PAR	Proven acceptable range
PBPK	Physiologically based pharmacokinetic
PDE	Permitted daily exposure
PET	Preservative efficacy test
Ph. Eur.	European Pharmacopoeia
PIBA	Push in bottle adaptor
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative humidity
SmPC	Summary of product characteristics
TGA	Thermogravimetric analysis
UV	Ultraviolet
XRF	X-ray fluorescence
XRPD	X-ray powder diffraction

Non clinical

ADME	absorption-distribution-metabolism-excretion
API	active pharmaceutical ingredient
APLP2	amyloid precursor-like protein 2
AUC_{0-24}	area under the concentration-time curve from zero up to 24 h
$AUC_{0-\infty}$	area under the concentration-time curve from zero up to infinity with extrapolation in the terminal phase
BCRP	breast cancer resistance protein
BMD	benchmark dose
CEDL	lower confidence interval of the critical effect dose
CES	critical effect size
CHMP	Committee for Medicinal Products for Human Use
C_{max}	observed maximum concentration
CNS	central nervous system
COX	cyclooxygenase
CSF	cerebrospinal fluid
CTD	common technical document
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DRF	dose range finding (study)
EC_{50}	50% effective concentration
EC_{90}	90% effective concentration
ECG	electrocardiogram
EFD	embryofetal development
ERG	electroretinogram
ESE	exonic splicing enhancer site
F	female
FAF	fundus autofluorescence
FL	full length
FMO	flavin monooxygenase
FOXM1	forkhead box protein M1 (previously termed HFH11)

GD	gestation day
GFAP	glial fibrillary acidic protein
GI	gastrointestinal
GLP	Good Laboratory Practice
H&E	haematoxylin and eosin (staining)
hERG	human Ether-a-go-go Related Gene
IC_{50}	50% inhibitory concentration
IHC	immunohistochemistry
ILM	inner limiting membrane
INL	inner nuclear layer
IP	intraperitoneal
iPSCs	induced pluripotent stem cells
IV	intravenous
K_i	inhibitor constant
LC-MS/MS	liquid chromatography coupled to tandem-mass spectrometry
LLNA	local lymph node assay
LOAEL	lowest observed adverse effect level
LOEC	lowest observed effect concentration
M	male
MAA	Marketing Authorisation Application
MAD	mutual acceptance of data
MADD	MAP kinase-activating death domain
MATE	multidrug and toxin extrusion transporter
MDR1	multidrug resistance protein 1
MMD	microcystoid macular degeneration
MN	micronucleus
MN-PCE	micronucleated polychromatic erythrocytes
MNT	micronucleus test
MoA	mechanism of action
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
MW	molecular weight
NCE	normochromatic erythrocytes
NMJ	neuromuscular junction
NOAEL	no observed adverse effect level
NOEL	no effect level
NOGEL	no-genotoxic effect level
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OCT	organic cation transporter
ONL	outer nuclear layer
PARP	poly-ADP-ribose-polymerase
PBPK	physiologically based pharmacokinetics
PCE	polychromatic (young) erythrocytes
PD	pharmacodynamics
PDCO	Paediatric Committee
PK	pharmacokinetics
PKPD	pharmacokinetics-pharmacodynamics
PND	postnatal day
PO	orally
ppm	parts per million
PPND	pre- and postnatal development
qPCR	quantitative real-time PCR
QWBA	quantitative whole-body autoradiography
RPE	retinal pigment epithelium
SD	standard deviation
sdOCT	spectral domain-optical coherence tomography
SLC25A17	solute carrier family 25, member 17
SMA	spinal muscular atrophy
SMN	survival of motor neuron
STRN3	striatin, calmodulin binding protein 3
$t_{1/2}$	half-life
TDI	time-dependent inhibition
tg	transgenic
TK	toxicokinetics
t_{max}	time to reach C_{max}
UV	ultraviolet
VEP	visual evoked potential
vGluT1	vesicular glutamate transporter 1
V_{ss}	volume of distribution at steady-state
wt	wild type

Clinical (PK/PD)

ADME	absorption, distribution, metabolism, elimination
AE(s)	adverse event(s)
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the curve
$AUC_{0\text{-}24h}$	AUC from time 0 to 24 hours
AUC_{last}	AUC from time 0 to the last measurable concentration
AUC_{inf}	AUC from time 0 extrapolated to infinite time
BA	bioavailability
BE	bioequivalence
BLQ	below the limit of quantification
BMI	body mass index
BW	body weight
C_{av}	average concentration
CCOD	clinical cut-off date
CL/F	apparent total body clearance
C_{max}	maximum observed concentration
CNS	central nervous system
CoA	certificate of analysis
C_{trough}	concentration at the end of a dosing interval
CV%	percent of coefficient of variation
CWRES	conditional weighted residual
DDI	drug-drug interaction
ddPCR	digital polymerase chain reaction
ECG	electrocardiogram
EC50	half maximal effective concentration
E_{max}	maximum response achievable
ETA	individual deviation from the population mean
FL	full length
f_u	fraction of the drug unbound to plasmatic proteins
GAM	generalised additive modelling
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GLSM	geometric least squares mean
GOF	goodness-of-fit
HPLC	high-performance liquid chromatography
HS	healthy subjects
iAUC	incremental area under the curve
IIV	inter-individual variability
IPRED	individual prediction
IS	internal standard
IWRES	individual weighted residual
k_{tr}	absorption transit rate
LC	liquid chromatography
LC-MS/MS	liquid chromatography with tandem mass spectrometric detection
LLOQ	lower limit of quantification
LOQ	limit of quantification
LTS	long-term stability
M1	metabolite M1 or RO7112063
MATE	multidrug and toxin extrusion protein
MFM	motor function measure
m.m.	molecular mass
$MRAUC_{inf}$	metabolic ratio based on AUC_{inf}
$MRAUC_{last}$	metabolic ratio based on AUC_{last}
MRC_{max}	metabolic ratio based on C_{max}
mRNA	messenger ribonucleic acid
MS	mass spectrometry
NOAEL	no observed adverse effect level
OAT	organic anion transporter
OCT	organic cation transporter
OFV	objective function value
PBPK	physiologically based pharmacokinetics
PCR	polymerase chain reaction
Pc-VPC	prediction corrected-visual predictive check
PD	pharmacodynamic(s)
P-gp	P-glycoprotein

PK	pharmacokinetic(s)
PPK	population pharmacokinetics
PRED	population predicted value
QC	quality control
QD	once daily
Q/F	apparent intercompartmental clearance
RE%	percent of relative error
RO7112063	metabolite M1
RO7034067	risdiplam
RSE	relative standard error
SAD	single ascending dose
SAE(s)	serious adverse event(s)
SD	standard deviation
SE	standard error
SEM	standard error of the mean
SMN	survival of motor neuron
TEAE(s)	treatment-emergent adverse event(s)
$t_{1/2}$	terminal half-life
T_{max}	time of the maximum observed plasma concentration
ULOQ	upper limit of quantification
V_c/F	apparent central volume of distribution
V_p/F	apparent peripheral volume of distribution
V_{ss}	volume of distribution at steady state
VPR	visual predictive check
λz	apparent terminal elimination rate constant
$\%AUC_{extrap}$	percentage of AUC due to extrapolation

Clinical (Efficacy/Safety)

AAV9	adeno-associated virus 9
ADR	adverse drug reaction
AE	adverse event
BSID-III	Bayley Scales of Infant and Toddler Development - Third Edition
CSR	clinical study report
CCOD	clinical cut-off date
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CNS	central nervous system
DDI	drug-drug interaction
EMA	European Medicine Agency
FDA	U.S. Food and Drug Administration
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE-2	Hammersmith Infant Neurological Examination Module 2
MFM	Motor Function Measure
MFM32	Motor Function Measure 32-Item
mRNA	messenger ribonucleic acid
NatHis-SMA	Natural History SMA Study
NOAEL	no observed adverse effect level
PD	pharmacodynamics
PK	pharmacokinetics
PY	patient-years
RULM	Revised Upper Limb Module
SAE	serious adverse event
SMA	spinal muscular atrophy
SMAIS	SMA Independence Scale
SMN	survival of motor neuron
SMN1	SMN1 gene
SMN2	SMN2 gene
SOC	system organ class

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration GmbH submitted on 21 July 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Evrysdi, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 29 July 2020.

Evrysdi, was designated as an orphan medicinal product EU/3/19/2145 on 26 February 2019 in the following condition: "Treatment of spinal muscular atrophy".

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Evrysdi as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Evrysdi

Evrysdi was granted eligibility to PRIME on 13/12/2018 in the following indication: Treatment of SMA.

The applicant applied for the following indication "Treatment of spinal muscular atrophy (SMA)".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP EMEA-002070-PIP01-16-M04 some measures are still ongoing.

In accordance with Article 23(2)(a)(b)(c) of Regulation (EC) No 1901/2006, as amended, Roche Registration GmbH requested the European Medicines Agency (EMA) to check as to whether some studies conducted are in compliance with the agreed paediatric investigation plan as set in the EMA's decision P/0089/2020 of 18 March 2020.

The PDCO issued an opinion on compliance for the PIP as set out in the EMA's Decision P/0089/2020 of 18/03/2020.

Information relating to orphan market exclusivity

Orphan designation

The European Commission granted orphan designation to the above-mentioned medicinal product on 26 January 2019 for "Treatment of spinal muscular atrophy" (EU/3/19/2145). This was based on an opinion of the Committee for Orphan Medicinal Products (COMP) of 24 February 2019.

The review of maintenance of the criteria of orphan medicinal product designation at the stage of Marketing Authorisation by the COMP is currently ongoing.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.
Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Evrysdi (risdiplam) is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Spinraza (nusinersen).

Having considered the arguments presented by the applicant and with reference to Article 8 of Regulation (EC) No 141/2000, Evrysdi (risdiplam) is considered not similar (as defined in Article 3 of Commission Regulation (EC) No. 847/2000) to Zolgensma (onasemnogene abeparvovec).

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Spinraza® (nusinersen) in the treatment of 5q spinal muscular atrophy, does not prevent the granting of the marketing authorisation of Evrysdi (risdiplam). This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Therefore, with reference to Article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Zolgensma® (onasemnogene abeparvovec) in the treatment of patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene, does not prevent the granting of the marketing authorisation of Evrysdi (risdiplam). This finding is without prejudice to the outcome of the scientific assessment of the marketing authorisation application.

Applicant's request(s) for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance risdiplam contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Protocol assistance

The applicant received the following Protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
23 June 2016	EMA/CHMP/SAWP/428115428432/2016	Prof. Minne Casteels, Dr André Elferink
23 June 2016	EMA/CHMP/SAWP/428115/2016	Prof. Minne Casteels, Dr Caroline Auriche
20 July 2017	EMA/CHMP/SAWP/432183/2017	Dr Susan Morgan, Dr Stephan Lehr
14 December 2017	EMA/CHMP/SAWP/793439/2017	Dr Susan Morgan, Dr Odoardo Olimpieri
27 June 2019	EMA/CHMP/SAWP/344156/2019	Dr Marion Haberkamp, Prof. Mario Miguel Rosa, Dr Armando Magrelli

The Protocol assistance pertained to the following aspects:

The applicant received Scientific Advice on the development of risdiplam for treatment of Type 1 (infantile-onset) Spinal Muscular Atrophy from the CHMP on 23/06/2016 (Procedure No.: EMEA/H/SA/3320/1/2016/PED/III) . The Scientific Advice pertained to the following non-clinical aspects:

- the juvenile toxicity studies in rats covering all developmental stages and chronic toxicity data in young monkeys (treatment phase) will be available to support the initiation of Study BP39055, an adaptive study in Type 2/3 SMA patients, and initiation of a subsequent study, BP39056, in Type 1 SMA patients and the applicant may initiate the planned adaptive studies, both with intended daily oral treatment duration of up to 2 years, with toxicity studies in juvenile rats covering all developmental stages and a chronic toxicity study in young monkeys

The applicant received Scientific Advice on the development of risdiplam for treatment of Type 2 and Type 3 (later-onset) Spinal Muscular Atrophy from the CHMP on 24/06/2016 (Procedure No.: EMEA/H/SA/3320/2/2016/III) . The Scientific Advice pertained to the following non-clinical and clinical aspects:

- Non-clinical question: the juvenile toxicity studies in rats covering all developmental stages and chronic toxicity data in young monkeys (treatment phase) will be available to support the initiation of Study BP39055, an adaptive study in Type 2/3 SMA patients, and initiation of a subsequent study, BP39056, in Type 1 SMA patients.
- Clinical pharmacology: the strategy for the exploratory part (Part 1) in assessing the safety, tolerability, PK and PD of RO7034067 and to select the dose to be investigated in the confirmatory part (Part 2) of the proposed clinical study in Type 2 and Type 3 SMA patients (Study BP39055).
- Clinical: the proposed design of the confirmatory part (Part 2) of the adaptive study (BP39055) to support registration of RO7034067 in patients with Type 2 and non-ambulant Type 3 SMA, including the following: a) primary endpoint, statistical analysis, and sample size; b) secondary endpoints; c) duration of treatment. The proposed clinical safety monitoring plans, including the use of OCT imaging as the primary retinal monitoring tool, in the adaptive study in patients with Type 2 and Type 3 SMA. The applicant's proposal to progress in an operationally seamless manner from the exploratory part (Part 1) to the confirmatory part (Part 2) of the proposed adaptive study, BP39055, in Type 2 and 3 SMA patients. The registration package for RO7034067 for the treatment of SMA at the time of MAA.

The applicant received Scientific Advice on the development of risdiplam for treatment of spinal muscular atrophy Type 1 from the CHMP on 20/07/2017 (Procedure No.: EMEA/H/SA/3320/3/2017/PED/I) . The Scientific Advice pertained to the following quality aspects:

- Selection of drug substance starting materials and control strategy for mutagenic impurities.

The applicant received Scientific Advice on the development of risdiplam for treatment of spinal muscular atrophy Type 1 from the CHMP on 14/12/2017 (Procedure No.: EMEA/H/SA/3320/3/FU/1/2017/PED/I). The Scientific Advice pertained to the following quality aspects:

- The concentration of sodium benzoate as a preservative in the proposed market formulation and its acceptability for the SMA Type 1 patient population, particularly newborn infants and infants up to 2 months of age.

The applicant received Scientific Advice on the development of risdiplam for treatment of spinal muscular atrophy from the CHMP on 25/02/2019 (Procedure No.: EMEA/H/SA/3320/4/2019/PA/III. The Scientific Advice pertained to the following non-clinical and clinical aspects:

- Non-Clinical: the assessment that the effect of risdiplam on male germ cells in animals is a class effect that has been fully characterised with other SMN2 gene splicing modifying agents; further studies in adult monkeys with sperm staging and confirmation of full reversibility are not warranted for risdiplam; the proposal for Post Authorisation Measures a) Two-year carcinogenicity study in rats b) Open label extension of ongoing studies c) Clinical drug-drug interaction (DDI) study (BP41361) d) Hepatic impairment study (BP40995)
- Clinical: an MAA for risdiplam on the basis of efficacy and safety data from FIREFISH Part 1 in patients with Type 1 SMA (at least 12 months of treatment) and SUNFISH Part 1 in patients with Type 2 and 3 SMA (at least 18 months of treatment on risdiplam or placebo, with at least 12 months of treatment on the Part 2 dose of risdiplam). The MAA for risdiplam is intended to support the following indication: Risdiplam is indicated for the treatment of spinal muscular atrophy (SMA). The efficacy and safety results from FIREFISH Part 1 and SUNFISH Part 1 provide sufficient and clinically meaningful evidence to characterise the benefits and risks of risdiplam for the treatment of SMA at the doses proposed, and support the review of the MAA.
- The applicant registries' approach to monitor the safety and effective use of risdiplam.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bruno Sepodes Co-Rapporteur: Armando Genazzani

The application was received by the EMA on	21 July 2020
Accelerated Assessment procedure was agreed-upon by CHMP on 28 May 2020	28 May 2020
The procedure started on	13 August 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	14 October 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 October 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	20 October 2020
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	29 October 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 November 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	23 December 2020
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	18 January 2021

The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	N/A
The Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Questions to all CHMP members on	23 January 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	26 January 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	2 February 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	15 February 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	24 February 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Evrysdi on	25 February 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The therapeutic indication that was applied for was: "Treatment of spinal muscular atrophy (SMA)"

2.1.2. Epidemiology and risk factors, screening tools/prevention

Spinal muscular atrophy (SMA) is a monogenic neuromuscular disorder resulting in severe weakness of the limbs, trunk, bulbar and respiratory muscles secondary to failure to gain and maintain functional motor nerve innervation of skeletal muscles. SMA is characterised by the dysfunction of alpha motor neurons within the anterior horn of the spinal cord, leading to skeletal muscle weakness and atrophy. It is the leading genetic cause of mortality in infants and young children, with an estimated incidence of 1 in 6,000 to 1 in 10,000 live births and carrier frequency of 1 in 40–60 individuals.

2.1.3. Biologic features, Aetiology and pathogenesis

SMA is an 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 ribonucleic acid (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. Therefore, full-length *SMN2* mRNA is generated in only 10%–15% of splicing events. 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 functional SMN protein produced by the *SMN2* gene. Children born with multiple copies of the *SMN2* gene have milder phenotypes, further demonstrating that the pathophysiology of the disease is due to insufficient production of functional SMN protein.

The severity of spinal muscular atrophy is highly variable and patients with heterogeneous clinical features can be classified into phenotypes (Types 0 through 4) on the basis of age at onset and the most advanced motor milestone achieved during development; Types 1, 2 and 3 represent approximately 99% of the SMA population. Type 0 (congenital SMA) is very rare and most of these patients do not survive beyond 6 months of age. Type 4 SMA (adult onset) accounts for only approximately 1% of all SMA cases. Patients consistently in all SMA Types have proximal greater than distal limb weakness and lower limb greater than upper limb weakness.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Patients with Type 1 (infantile-onset) SMA present before the age of 6 months and most commonly have 2 *SMN2* copies. At diagnosis, these infants demonstrate reduced motor function compared with age-matched healthy infants and uniformly lose motor function over time as assessed with a standard instrument for infants with SMA known as the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. Infants with Type 1 SMA never gain major motor milestones such as sitting independently. In addition, they have progressive loss of independent swallowing and respiratory function requiring feeding tubes and ventilatory support. This leads to an increased risk for aspiration pneumonia and recurrent respiratory infections, with repetitive hospitalisations and a very high risk of death. Natural history shows that 50% of infants with Type 1 SMA will have died or required permanent daily non-invasive ventilation support by 10.5 months of age and 92% by 20 months of age.

Patients with Type 2 SMA present after the age of 6 months and before the age of 18 months and most commonly have 3 *SMN2* copies. These children will be able to sit independently and possibly stand but never walk independently given the greater amount of weakness in their lower limbs. Natural history demonstrates that these patients have a decline in motor function over time, most prominently between the ages of 6 and 16 years, as reported in a number of publications with different validated motor function measures, i.e., the Motor Function Measure 32-item version (MFM32), the Hammersmith Functional Motor Scale Expanded (HMFSE), and the Revised Upper Limb Module (RULM). Affected Type 2 patients also experience other SMA-related comorbidities, including severe scoliosis, which may require surgery, possibly as young as 8–10 years old. Joint contractures are also a prominent clinical feature as the disease progresses. These contractures lead to stiffness and tightening, with the knees, hips and elbows being the main joints affected (Gusset 2020). Collectively, these complications limit patients' independence and their ability to perform important activities of daily living.

Patients with Type 3 SMA present after the age of 18 months and before 36 months and most commonly have 3 or 4 *SMN2* copies. These children are able to sit, stand, and walk independently. Natural history demonstrates that these patients decline in motor function over time most prominently during the ages of 10–15 years and nearly a third will lose their ability to walk between ages 3□28 years. In both Type 2 and Type 3 SMA patients, pulmonary function declines over time and patients may need non-invasive ventilation support.

Patients with Type 4 SMA present in adulthood and have 4–6 *SMN2* copies. The clinical presentation is during adulthood. Type 4 SMA is very rare and represents less than 1% of all SMA patients and is the mildest form of the recognised disease continuum; it is characterised by mild proximal muscle weakness, predominantly affecting the leg and hip muscles which may progress to the shoulders and arms. SMA Type 4 muscle weakness progresses steadily and slowly over time, but rarely affects swallowing or breathing. Life expectancy is not affected in Type 4 SMA.

2.1.5. Management

Currently approved treatments have not been shown to increase SMN protein through the whole body including the CNS, which is hypothesised to result in greater efficacy than increases of functional SMN protein in the CNS alone. Patients with SMA still lack an approved therapy with an easy and sustainable route of administration that can be accessed without frequent clinic visits, invasive procedures, or concomitant use of additional medicines. Such therapies are critical for achieving treatment compliance and thus, the likelihood of treatment benefit, particularly as SMA is a life-long chronic disease.

The intrathecally administered *SMN2*-targeting antisense oligonucleotide nusinersen (Spinraza®) is approved for the treatment of SMA in paediatric and adult patients. Onasemnogene abeparvovec (Zolgensma→) is a one-time intravenously administered, gene replacement therapy that uses a non-replicating adeno-associated virus 9 (AAV9) capsid to deliver a functional copy of the *SMN* gene by intravenous infusion; it is approved in the United States and Japan for paediatric patients with SMA <2 years of age. In the European Union (EU), onasemnogene abeparvovec is approved conditionally for the treatment of patients up to 21 kg in weight with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the *SMN2* gene.

The COVID-19 pandemic and measures to promote physical distancing, as well as changes in hospital priorities that postpone elective procedures, have made more difficult the use of nusinersen or Onasemnogene abeparvovec.

Nusinersen (Spinraza®)

Results of Phase 3 studies in infantile-onset SMA and in later-onset SMA overall demonstrate benefit in patients receiving active drug versus sham control. However, by the end of the Phase 3 study (ENDEAR) in infantile-onset SMA, 49% of the treated patients did not exhibit an improvement in their motor milestones and 39% did not reach event-free survival. For nusinersen intrathecal administration, many of the infants and young children with SMA would require anaesthesia to undergo the lumbar puncture procedures, and sedation is known to potentiate adverse respiratory reactions. Very common adverse reactions linked to lumbar puncture include headache, vomiting and backache, identified during clinical trials of nusinersen in patients with later-onset SMA. Post-marketing experience with nusinersen has also identified serious infections, such as meningitis, communicating hydrocephalus, aseptic meningitis and hypersensitivity (frequency unknown). It is also noted that renal toxicity, thrombocytopenia, and coagulation abnormalities, including acute severe thrombocytopenia, have been observed after administration of other antisense oligonucleotides administered by subcutaneous or IV injection in infant and adult patients. Additionally, intrathecal injection may not be possible for patients who have developed severe scoliosis, or who have undergone a spinal surgery procedure, complications that are present in the majority of Type 2 and non-ambulatory Type 3 patients.

In Study BP39054 (JEWELFISH), 77 SMA patients (1–60 years of age) had previously received nusinersen. Of these patients, 45% (35 patients) reported inability to continue to receive nusinersen secondary to tolerability concerns, treatment-related safety concerns, difficulty in accessing a suitable clinical site to perform the injection or inability to undergo intrathecal administration. This means that patients who have already had access to nusinersen may be precluded to continue receiving this therapy due to medical reasons.

Onasemnogene abeparvovec

The product uses a non-replicating adeno-associated virus 9 (AAV9) capsid to deliver a functional copy of the SMN gene by intravenous infusion. Treatment includes baseline testing for AAV9 antibodies, treatment with systemic corticosteroids (for 30 days or longer with required down-titration over 28 days) and close safety monitoring of liver function, platelet count and cardiac parameters (troponin-I levels) for a period of at least 3 months post treatment, all of which could limit administration for some patients. Overall, there is limited experience in patients 2 years of age and older or with body weight above 13.5 kg; the safety and efficacy of onasemnogene abeparvovec in older patients have not been established and, if dosed, the high viral loads required could carry safety risks. Given the selected population studied to date (albeit ongoing trials) and potential uncertainty around long-term duration of efficacy and safety, the impact of this treatment on the overall broad population living with SMA is not yet fully known.

In addition, based on currently available information from the EU approval process there appears to exist only small batch sizes available due to the batch allocation strategy being used for the product. Thus, the supply of the drug may be limited. In addition, given that Zolgensma is dosed according to body weight, the capacity to meet demand for older heavier patients may be an added challenge.

Non-Therapeutic Management

Concomitant non-therapeutic management strategies for SMA rely on prevention and treatment of comorbidities, such as swallowing and feeding difficulties, scoliosis and thoracic deformity, contractures, and respiratory insufficiency. Treatments such as pulmonary hygiene, non-invasive ventilation, placement of feeding tubes, mobility and seating support, and physical and occupational therapies are supportive, with the goals of improving overall survival, quality of life and of minimizing disability. Other forms of intervention such as immunisation, provision of antibiotics and vitamin supplementation are also part of the standard of care in SMA. Over time, palliative management for the most severe Type 1 SMA patients has been introduced more frequently at home with increased levels of technical supportive care such as enteral nutrition, oxygenotherapy, and analgesic and sedative treatments. According to a natural history study, none of the assessed patients with Type 1 SMA had major motor milestone developments, even after the implementation of basic standards of care in SMA to improve survival and patients' care, illustrating the benefits of developing disease-target therapies.

About the product

Risdiplam, an *SMN2* mRNA splicing modifier, is an orally (liquid formulation) administered small molecule with systemic distribution.

SMA is caused by a deficiency in SMN protein, and therefore the need to systemically increase SMN protein is at the core of the disease intervention across the continuum of SMA phenotypes. Risdiplam modulates *SMN2* splicing to include exon 7 into the mRNA transcript, thereby increasing the expression of full-length SMN protein from the *SMN2* gene. Systemic administration versus intracerebroventricular administration of an antisense oligonucleotide (ASO) *SMN2* splicing modifier was compared in a transgenic animal model where systemic administration conferred a much longer survival benefit and most animals given systemic administration showed no signs of motor dysfunction. Therefore, a systemic increase in SMN protein with risdiplam is hypothesised to bring greater efficacy in patients with SMA than treatments targeting increases of functional SMN protein in the CNS alone.

Treatment with risdiplam indeed prevents the manifestation of the SMA phenotype in a dose-dependent manner in the severely affected SMNΔ7 mice. A 2- to 3-fold increase in SMN protein was associated with a significant prolongation of animal survival. Analyses of SMN protein in blood,

peripheral (muscle), and central (brain) tissues of animals show that similar SMN protein increase is obtained in these key organs of interest as compared to blood.

Specificity of Risdiplam and Therapeutic Margin

The potency of risdiplam is the result of its high specificity for the SMN2 exon 7 splicing process which is believed to be achieved through binding to two distinct sites of the SMN2 pre-mRNA. In patients, therapeutic effect in terms of shifting the splicing to inclusion of exon 7 is achieved at a mean exposure not exceeding the no observed adverse effect level (NOAEL) for off-target effects observed in nonclinical toxicity studies.

Toxicities associated with off-target effects based on nonclinical studies are of two types:

- Early onset and reversible off-target effects in rodent and non-rodent species: Risdiplam also binds to a few secondary splice targets, which all share the same mRNA 5' splice site. The most prominent secondary splice targets contributing to the toxicities (effects on epithelial tissues, effect on male germ cells, embryofetotoxicity/teratogenicity and haematological effects) are FOXM1 and MADD due to their role in cell cycle and apoptosis (2.4 Nonclinical Overview, Section 6.7.2). With the exception of effects on male germ cells, the exposure at NOAEL for these reversible toxicities is at least 2.5-fold higher than the exposure required to achieve significant therapeutic effect (at a 2-fold increase in functional SMN protein).
- Delayed onset, not fully reversible retinal toxicity observed in non-rodent (monkey) only: Specific investigations show that secondary splice targets are unlikely to be involved but rather a specific biological process in the monkey such as impairment of autophagosomal function. Exposures at the NOAEL for retinal toxicity achieve significant therapeutic effect (at a 2-fold increase in functional SMN protein).

Type of application and aspects on development

The CHMP agreed with the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the severity of the disorder and the fact that the available treatments do not adequately cover the whole population. SMA therapies are approved in Europe (nusinersen and onasemnogene abeparvovec), but still a proportion of patients remain untreated.

Risdiplam is an oral solution, to be applied as at home therapy, an easier route of administration, to best support a life-long chronic disease. Risdiplam offers a rapid and sustained increase in SMN protein synthesis through the whole body including the CNS, an important aspect especially in SMA1 where a rapidly progressive disease requires a quick time to effect agent. From a public health perspective, an at home therapy is less burdensome than therapies that require regular hospital visits, invasive procedures, trained and highly skilled medical staff for their administration, concomitant use of other drug therapies with associate AEs, and availability of imagining technology to support drug administration, such as CT.

Considering the inevitable accumulation of disability that all patients with SMA face, and the unmet need, there is a need for patients in Europe to gain access to a sustainable non-parenteral treatment that can be administered to all eligible (as per the approved indication) SMA patients regardless of type and comorbidities, within a reasonable timeframe.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a powder for oral solution containing 0.75 mg/ml of risdiplam as active substance.

Other ingredients are: mannitol (E421), isomalt (E953), strawberry flavour, tartaric acid (E334), sodium benzoate (E211), macrogol/polyethylene glycol 6000, sucralose, ascorbic acid (E300) and disodium edetate dihydrate.

The product is available in an amber glass bottle with a tamper-evident, child-resistant cap which is accompanied by 1 press-in bottle adapter, two 6 mL reusable amber oral syringes and two 12 mL reusable amber oral syringes, as described in section 6.5 of the SmPC. Each bottle contains 2 g of powder containing 60 mg of risdiplam.

2.2.2. Active Substance

General information

The chemical name of risdiplam is 7-(4,7-diazaspiro[2.5]octan-7-yl)-2-(2,8-dimethylimidazo[1,2-*b*]pyridazin-6-yl)-*4H*-pyrido[1,2-*a*]pyrimidin-4-one) corresponding to the molecular formula $C_{22}H_{23}N_7O$. It has a relative molecular mass of 401.46 g/mol and the following structure:

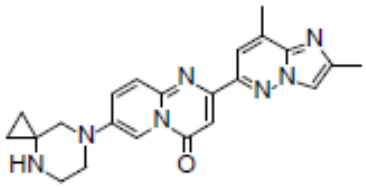


Figure 1: active substance structure

The chemical structure of risdiplam is inferred from the route of synthesis and further elucidated by a combination of elemental analysis, infrared spectroscopy, ultraviolet spectroscopy, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectrometry and crystal structure analysis by X-ray diffraction. Risdiplam is achiral. The solid-state properties of the active substance were measured by differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), X-ray powder diffraction (XRPD), infrared (IR) spectroscopy, Raman spectroscopy, and dynamic vapor sorption (DVS).

The active substance is a non-hygroscopic, light yellow or yellow or greyish yellow or greenish yellow crystalline powder which may contain lumps. It exhibits pH-dependent solubility across the physiological pH range, being soluble at pH 1 dropping off to being practically insoluble at neutral pH.

Polymorphism has been observed for risdiplam following extensive screening experiments. Form A is the crystalline solid form of risdiplam selected for clinical development and has been used in all clinical trials and the proposed commercial finished product. Stability studies have confirmed the stability of Form A.

Manufacture, characterisation and process controls

Risdiplam is synthesised in 10 main steps using starting materials with acceptable specifications defined in line with ICH Q11 and previous CHMP scientific advice.

The process is designed to minimise formation of organic impurities and sufficient isolation steps are

included to allow their purge. The fate and purge of potentially genotoxic impurities have been investigated extensively. Different impurities are controlled according to ICH M7 options 2, 3 or 4 depending on the extent of demonstrated process knowledge. The control options are also in line with previous CHMP scientific advice. Elemental impurities are controlled in relevant intermediates and in the active substance specification by a residue on ignition test. The final crystallisation step ensures form A which is then milled to reduce particle size which improves processability during formulation.

The manufacturing process has been developed following quality by design (QbD) principles, including risk assessment to identify factors influencing the critical quality attributes (CQAs) of risdiplam. These were then prioritised and investigated using a combination of univariate and multivariate studies. The critical material attributes (CMAs) of the starting materials and intermediates were identified and limits for various properties were set and justified based on fate of impurities studies and the demonstrated understanding of the manufacturing process. Critical process parameters (CPPs) were defined through experimentation with those having a likely significant impact on a CMA or CQA considered to be critical. Proven acceptable ranges (PARs) have been defined for critical parameters for the synthetic steps. It has been stated that for each step, only 1 parameter will be changed from its set-point or normal operating range (NOR) at any one time. For the last steps (crystallisation and milling), design spaces are claimed. For both steps, suitable ranges have been defined for quantities of input materials, and process parameters such as times and temperatures for individual unit operations as appropriate. The level of claimed flexibility for each step is fully justified based on the results and analysis of the multivariate studies carried out.

Adequate in-process controls (IPCs) are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development programme. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in a clear and colourless double low-density polyethylene (LDPE) plastic bag and tied. The packaged risdiplam is placed in a suitable metal drum. The LDPE bags comply with Ph. Eur. 3.1.3 Polyolefines and with Commission Regulation (EU) No 10/2011 on plastic materials and articles intended to come into contact with food, including subsequent amendments.

Specification

The active substance specification includes tests for description (appearance and colour), identity (IR, HPLC), polymorphic form (XRPD), assay (HPLC), impurities (HPLC), water content (KF), residual solvents (GC), residue on ignition (Ph. Eur.), elemental impurities (XRF) and particle size distribution (laser diffraction).

Limits for organic, solvent, elemental and genotoxic impurities have been set in line with ICH Q3A, ICH Q3C, ICH Q3D and ICH M7 and are considered adequate considering available batch data.

The absence of microbiological control of the active substance was satisfactorily justified and is considered acceptable on the basis that the finished product is routinely tested.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data were provided from 23 batches of the active substance manufactured on scales up to full production scale throughout development. The results were within the specifications in place at the time of testing. The results from recent production scale batches are consistent from batch to batch.

Stability

Stability data from five pilot to production scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 18 months (4 batches) and 24 months (1 batch) under long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: description, identification of polymorphic form, assay, organic impurities, water content, particle size distribution and microbial contamination. The analytical methods used were the same as for release and are stability indicating as demonstrated in forced degradation studies. No significant changes or trends were observed to any of the tested parameters under long term or accelerated conditions on primary stability batches stored up to 18 months (four batches) and 24 months (one batch).

Photostability testing following the ICH guideline Q1B was performed on one batch. Risdiplam is not photosensitive in the solid state. Risdiplam in the solid state is also stable to higher temperatures and humidity.

The degradation profile of risdiplam was investigated in aqueous solution when exposed to neutral, basic, acidic and oxidative conditions at elevated temperature. Further investigations were carried out in the presence of metal ions, a radical initiator (AIBN) and a photosensitizer (Rose Bengal + O_2). Risdiplam is stable under basic conditions but significant degradation was observed under all other conditions. These studies demonstrated the stability indicating nature of the relevant analytical methods.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

Risdiplam powder for oral solution 0.75 mg/mL is a powder for constitution. Each bottle filled with 2.0 g of powder contains 60 mg of risdiplam. The powder must be constituted with purified water to yield an 80 mL clear oral solution with a concentration of 0.75 mg/mL. The product is available in an amber glass bottle with a tamper-evident, child-resistant cap which is accompanied by 1 press-in bottle adapter, two 6 mL reusable amber oral syringes and two 12 mL reusable amber oral syringes which allow sufficient flexibility and accuracy for the age and weight based posology for patients from 2 months old up to adults.

The aim of development was to provide a once-a-day orally available dosage form for treatment of spinal muscular atrophy suitable for use in both paediatric and adult patients, potentially with swallowing difficulties. The posology is both age and weight dependent and the medicine is intended to be given in a home setting by both caregivers and patients. An oral liquid was selected since, in

combination with the accompanying reusable syringes, this allows sufficient flexibility and ease of administration for the intended population and setting. Accordingly, a quality target product profile (QTPP) was established, setting the main goals of development.

The active substance is a stable crystalline solid routinely isolated as form A. It is milled to reduce particle size which ensures content uniformity during formulation. It exhibits pH-dependent solubility in aqueous media, being most soluble at acidic pH. In solution, risdiplam is sensitive to light and oxidation.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards except for the strawberry flavour whose qualitative composition was provided. Compatibility with the active substance was demonstrated through stability studies on binary mixtures. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. No overage is included.

Palatability was identified as an important element for the acceptability of risdiplam oral solution given that it is indicated for paediatric patients. This was assessed in healthy volunteers using a simple solution containing no sweetener or flavouring. From the responses, it was concluded that there was no pronounced bitterness of risdiplam in the target concentration range. The acceptable taste results obtained from this study were taken as a basis to develop the commercial formulation in which both a sweetener and strawberry flavour are included.

Following constitution, the oral solution is a multidose formulation. In order to prevent microbial growth and degradation, a preservative (sodium benzoate), an antioxidant (ascorbic acid) and a stabiliser (disodium edetate dihydrate) are included in the formulation. The amber bottle provides the oral solution with adequate protection from light. According to the guideline EMEA/CHMP/QWP/396951/2006 "*Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product*" the inclusion of antimicrobial preservatives or antioxidants should be avoided, particularly in the case of paediatric formulations. If unavoidable, the concentration used should be at the lowest effective level. For preservatives, the concentration should be justified in terms of its safety and efficacy (EMA/CHMP/QWP/805880/2012 Rev. 2).

The concentration of ascorbic acid was demonstrated to be the lowest possible. However, this has not been demonstrated for sodium benzoate. Sodium benzoate is a specific issue for very young children as it can cause hyperbilirubinaemia and acute bilirubin encephalopathy which may evolve into kernicterus (EMA/CHMP/508189/2013). In addition, the combination of benzoate with acid ascorbic can produce benzene, a known carcinogen.

The applicant discussed the balance of using the proposed concentration of sodium benzoate to prevent microbial growth against the safety factors in the paediatric population. It was concluded that there is no safety risk of including sodium benzoate at the current concentration in the commercial finished product formulation, considering the targeted population and the chronic use of the product. However, CHMP judged that a lower concentration would have been feasible based on the results of the conducted preservative efficacy test study (PET) and raised a major objection as a result. In response, the CHMP acknowledged the applicant's argument that the proposed level of sodium benzoate does not pose a safety concern but requested the applicant to commit to conduct a new PET study according to Ph. Eur. 5.1.3. The applicant further committed to pursuing development of a new formulation containing the lowest feasible level of sodium benzoate if this is supported by the new PET study results and to provide information on the resultant development plan if warranted. This commitment is included in the recommendations section 2.2.6.

All risdiplam formulations studied during clinical trials and proposed for commercialisation are solution formulations. Biopharmaceutical studies investigated the absorption behaviour of risdiplam in adults and paediatric subjects with respect to the potential impact of formulation-related factors. Precipitation of risdiplam in the human gastrointestinal tract is very unlikely in the therapeutic dose range for adults and children. Moreover, changes in formulation composition are not expected to affect the absorption behaviour of the compound. Therefore, no bioequivalence studies were conducted between the different formulations used in development.

The development of the risdiplam powder for oral solution followed an enhanced development approach that included elements of quality-by-design (QbD). Process development work was predicated on risk assessment methodology to identify parameters for investigation by DoE. The process consists of conventional pharmaceutical operations such as blending, dry granulation, powder filling, and bottle closing, as well as standard equipment. Based on previous experience with similar products, the equipment used, and the quality risk assessments, different ranges of parameters (such as number of revolutions per blend, roller compaction gap size, force and speed, auger rotation speed) were monitored in the different unit operations. Process parameter ranges are considered satisfactory. Differences in the manufacturing processes of the commercial product and clinical trial formulations were satisfactorily described and discussed.

The primary packaging is an amber glass bottle with a tamper-evident, child-resistant cap as described in section 6.5 of the SmPC. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product. The bottle is accompanied by 1 press-in bottle adapter (PIBA), two 6 mL reusable amber oral syringes and two 12 mL reusable amber oral syringes which allow accurate weight- and age-based dosing.

During the procedure, a low risk of leakage of the reconstituted product was identified which was addressed in the immediate term by inclusion of additional labelling instructions. The applicant committed to a thorough review of the container closure system and to conduct new stability studies and a new PET study should the container be changed. This commitment is included in the recommendations section 2.2.6.

Manufacture of the product and process controls

The manufacturing process of Evrysdi consists of four main steps: pre-blending of risdiplam and excipients in fraction A and roller compaction; pre-blending of excipients in fraction B and roller compaction; blending of fractions A and B along with strawberry flavouring; packaging. The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated on 3 consecutive production scale batches, with additional testing conducted to evaluate the content uniformity of risdiplam, ascorbic acid and sodium benzoate in different granulate fractions. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including description of container, appearance of bottle contents, appearance, colour and pH of reconstituted solution, identification of risdiplam (HPLC, UV), identification of sodium benzoate (HPLC), identification of ascorbic acid (HPLC), content of risdiplam per bottle (HPLC), content of

sodium benzoate per bottle (HPLC), content of ascorbic acid per bottle (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.), water content (Ph. Eur.), uniformity of mass of delivered doses (Ph. Eur.) and microbial limits (Ph. Eur.).

The limits for impurities are set in line with ICH Q3B. The single impurity specified above the qualification threshold has been qualified at the appropriate level in clinical studies. Other parameters including limits for preservative and antioxidant are set in line with batch data and pharmacopoeial requirements. The justification for not including tests for determination of minimum fill, deliverable volume and constitution time in the finished product release and shelf-life specifications is acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data indicated that each relevant elemental impurity was not detected above 30% of the respective PDE. Limits for relevant elemental impurities are included in the active substance and excipient release specifications. Based on the risk assessment, control strategy for excipients and active substance, and batch data it can be concluded that no additional controls in the finished product are needed.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product was performed in response to a major objection raised by the CHMP, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities being present in the finished product and no specific control measures are required.

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 7 pilot to production batches, including the 3 primary stability batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. All tested parameters were within specifications in place at the time. Changes to analytical procedures made during development have been adequately justified. In addition, data from 7 batches of a formulation used during clinical development were also submitted and were consistent from batch to batch.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from three production scale batches of finished product stored for up to 18 months under a range of long term conditions (5ºC, 25ºC / 60% RH, 30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The batches were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for the stability indicating parameters as defined in the shelf-life specification. The analytical procedures used are stability indicating. Data from an additional two supportive batches (1 pilot scale – 24 months, 1 production scale – 12 months) were also provided. The majority of measured parameters remained unchanged throughout the study period under all conditions. There was a decrease in risdiplam content and an increase in the specified and total impurities, more so at higher temperature and humidity. A downward trend for ascorbic acid content

was also observed, more so at higher temperature. Finally, an increase in water was observed at higher humidity. Data was extrapolated accordingly to ICH Q3E in order to define an acceptable shelf life and suitable storage conditions. Observed physical and chemical changes are not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

A further study investigated the stability of the reconstituted solution. Samples were pulled from the primary stability study (samples stored at 5ºC, 25 ºC / 60% RH, 30ºC / 75% RH) at 3-month intervals, reconstituted, and stored under refrigerated conditions (5ºC) for up to 64 days. Data is available on samples stored for up to 12 months prior to reconstitution. Other than a downward trend in ascorbic acid content, no significant trends to any measured parameters relative to the age of powder before reconstitution were observed.

A further study was conducted to evaluate the in-use stability of the reconstituted solution under the intended conditions of use. Samples were pulled from the primary stability study (samples stored at 5ºC, 25ºC / 60% RH, 30ºC / 75% RH) after 6 and 12 months, reconstituted, and stored under refrigerated conditions (5ºC) for up to 64 days. Samples were discarded after testing and syringes cleaned as per the SmPC instructions. No significant trends to any of the measured parameters were observed other than a slight decrease in ascorbic acid content.

Photostability was assessed on the powder in bottle, the reconstituted solution and the solution in the provided amber oral syringes. The samples were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No changes to the powder and reconstituted solution were observed indicating that the amber bottle provides adequate protection from light. It is recommended that the solution, once withdrawn from the bottle, is administered to the patient within 5 minutes.

Based on available stability data, the proposed shelf-life of 24 months without special storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable. The reconstituted oral solution is stable for up to 64 days in a refrigerator.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use. The applicant resolved the major objection on sodium benzoate context with arguments that the current concentration presents no safety risk and committed to conducting a new PET study according to Ph. Eur. 5.1.3 and to pursuing the development of a new formulation containing the lowest feasible level of sodium benzoate if this is supported by the new PET study results and to provide information on the resultant development plan if warranted. The major objection in relation to potential nitrosamine contamination was resolved by submission of a satisfactory risk evaluation.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing process. Design spaces have been proposed for several steps in the manufacture of the active substance. The design spaces have been adequately verified.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The MAH should conduct a new PET study according to Ph. Eur. 5.1.3 in order to re-evaluate the antimicrobial efficacy of sodium benzoate. The applicant should pursue the development of a new formulation containing the lowest feasible level of sodium benzoate if this is supported by the new PET study results and to provide information on the resultant development plan if warranted.
- The MAH should undertake a thorough review of the container closure system and conduct new stability studies and a new PET study should the container be changed.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Risdiplam (RO7034067) is an orally administered small molecule SMN2 splicing modifier developed for the treatment of SMA. Risdiplam modulates SMN2 splicing to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, thereby increasing the production of full-length (FL) SMN protein from the SMN2 gene. The resulting increase in functional SMN protein is deemed to compensate for the deficit of this protein in SMA patients.

Primary Pharmacodynamics

The pharmacological activity of risdiplam to modify *SMN2* exon 7 splicing and to increase SMN protein levels was assessed in a variety of *in vitro*, *ex vivo* and *in vivo* model systems. Since humans are the only species known to have the SMN2 gene besides the SMN1 gene, the pre-clinical pharmacological effects of risdiplam could only have been studied in human cells from SMA patients and in genetically modified animal models. *In vitro* studies on human cells from healthy subjects were also performed in order to check for risdiplam selectivity towards SMN2 gene.

At clinically relevant concentrations (Cmax of 37 nM unbound risdiplam in infants with type 1 SMA aged 1-7 months at enrolment), risdiplam efficiently corrected the dysfunctional splicing of the human SMN2 pre-mRNA by shifting the alternative splicing reaction towards the inclusion of SMN2 exon 7 and by inducing gene expression of FL SMN2 mRNA, in cultured Type 1 SMA patient-derived cells (EC50 11-12 nM and 24-19 nM, respectively); this in turns led to the production of the FL mRNA which translated into increased SMN protein levels (EC50 12 nM).

The effect of risdiplam on cultured Type 1 SMA patient-derived cells was approximately 2-fold less potent than in human blood cells from healthy donors, in terms of both gene expression of FL SMN2 mRNA (EC50 8.25-14.2 nM) and reduced Δ7 mRNA (EC50 6.6-6.7 nM), values normalised for human plasma protein binding fraction 11% unbound.

At clinical Cmax, no effect on FL SMN protein level in motor neurons derived by type 1 SMA patient induced pluripotent stem cells (iPSC), was achieved (EC50 182 nM). The applicant justified this result stating that iPSC motor neuron model would represent an immature neuronal cell type that does not

fully recapitulate *in vivo* motor neuron physiology. Notwithstanding the limitations of this *in vitro* model, iPSCs-differentiated motor neurons still represent a valuable tool for drug screening for SMA reflecting the genetic alteration in human SMA. The lack of activity of risdiplam in Type 1 human iPSC-derived motor neuron should be weighted in the context of overall non-clinical and clinical results.

Two different SMA mouse models carrying a varying number of the human SMN2 gene copies, were used to study the effect of risdiplam on SMN2 pre-mRNA. At clinically relevant plasma concentrations (Cmax of 37 nM unbound risdiplam in infants with type 1 SMA aged 1-7 months at enrolment), risdiplam was able to restore SMN protein levels in the severe phenotype of the SMA disease model (SMNΔ7 young mice reflecting Type 1 SMA-like phenotype) more markedly in brain than in quadriceps in terms of ED50 values (brain: 0.172 mg/kg corresponding to unbound plasma level=1.7 nM vs quadriceps: approximately 0.3 mg/kg corresponding to unbound plasma level=42 nM, at postnatal day 7). Risdiplam was able to induce in both brain and quadriceps greater than 2-fold increase of SMN protein respect knock out control animals. When compared to the level of SMN protein in HET mice, the fold increase of SMN protein was much lower being approx. 50% in brain and quadriceps. Although the ideal outcome of a therapy is the complete correction of SMN2 splicing, partial correction can still reduce the severity of the disease with a significant significative impact on quality of life of patients and caregivers.

In the milder mice model phenotype (adult C/C mice reflecting a Type 2/3 SMA-like phenotype), risdiplam lost potency in increasing FL SMN protein in both brain and quadriceps reaching ED50 values (brain: 5.77 mg/kg corresponding to unbound plasma level=149 nM; quadriceps: 10 mg/kg corresponding to unbound plasma level = 262 nM) corresponding to plasma levels 3 to 5-fold higher the clinical Cmax of 50 nM (unbound risdiplam in patients with Type 2/3 SMA phenotype aged 2-25 years at enrolment). No adequate discussion was provided by the applicant for this result that remains a significantly relevant non-clinical result that informs the clinical data in particular, given that no clinical study has included SMA type 4 (adult onset) SMA.

The applicant stated that the clinical risdiplam target exposure/dose was selected on the basis of *in vitro* and *in vivo* studies. At least 2-fold increase of plasma SMN protein level versus baseline was the clinical benchmark predicted to lead to significant clinical benefit. Since the applicant did not provide the baseline SMN levels in the two transgenic SMA mouse models, it is not possible to verify such clinical target, However, it is agreed that data from the two mouse SMA models suggest a positive correlation between FL SMN protein increases and increase in the brain and quadriceps.

The resulting increase in SMN protein levels translated into significant efficacy in rescuing disease phenotype of Type 1 SMA-like SMNΔ7 mice. While vehicle-treated mice developed a severe neuromuscular phenotype with a life expectancy of less than 3 weeks, treatment with the most efficacious dose of risdiplam from PND3 onwards largely protected both central and peripheral phenotypes related to neuromuscular denervation, reduced muscle atrophy, rescued motor function and caused a profound prolongation of animal survival beyond 6 months of age.

Metabolite M1 was identified as a major human metabolite of risdiplam. When tested in fibroblasts, M1 was less potent, with an EC50 for inducing the generation of FL SMN2 transcript and an IC50 for inducing the decrease of exon 7-lacking SMN2 transcript levels, approximately 34 and 28 times higher than those for risdiplam, respectively. In whole blood samples from healthy volunteers, no activity was observed for M1 up to a concentration of 3 µM.

Secondary Pharmacology

At therapeutically relevant concentrations, risdiplam modifies alternative splicing rather than gene expression *in vitro* with high specificity for SMN2 and with a few secondary splice targets only, namely STRN3 and SLC25A17. At a concentration 5-fold higher than its EC90 (605 nM versus 121 nM), risdiplam was shown to significantly influence alternative splicing of only 11 additional genes.

Of those 13 off-target genes in total, FOXM1 and MADD were identified as likely contributors to toxicities seen in studies with animals and *in vitro* systems, while STRN3, SLC25A17, and APLP2 were not considered of relevance for the safety of risdiplam. The applicant referred to insufficient data to characterize the function of different splice variants of STRN3. It is known that STRN3 codes for the protein striatin-3, which is involved in several biological processes, including the negative regulation of intracellular oestrogen receptor signalling pathway. The same applies for the SLC25A17 gene, which codes for Peroxisomal membrane protein PMP34, involved in several biological processes, including ATP and fatty acid transport, and in fatty acid oxidation but the roles of different splice variants of this gene are not known. Thus, the applicant acknowledges that the biological functions of splice variants of STRN3 and SLC25A17 as potentially emerging from treatment with risdiplam are not fully characterised. In animal studies, no apparent associations with pathophysiological outcomes were found. On the other hand, clinical studies conducted with risdiplam no imbalance in adverse events (in particular reproductive system and breast disorders, endocrine disorders) or safety laboratory assessments (including cholesterol, triglycerides) was observed.

Risdiplam and its major human metabolite M1 were tested for off-target activity (including targets considered of importance for abuse potential) at a single test concentration of 10 µM in radioligand binding and enzymatic assays looking at 101 different binding sites or enzyme targets (radioligand binding: 69 human and 13 rat sites; 19 human enzymatic sites).

Both risdiplam and M1 inhibited cyclooxygenase 1 (COX1) and 2 (COX2) by >84% (IC_{50}~2 µM) and acetylcholinesterase by >77% (IC_{50}~0.6 µM for risdiplam, and ~2 µM for M1) at 10 µM. 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. Risdiplam inhibited radioligand binding at histamine H3 (78%, K_i=1.01 µM, IC_{50}=4.2 µM) and muscarinic M1 (54%, K_i=5.6 µM, IC_{50}=6.4 µM) receptors. Risdiplam inhibited the δ-opioid receptor by 62% in the primary screening assay, whilst a follow-up assay identified only 35% inhibition at 10 µM. Hence, no IC_{50} was determined at delta opioid receptors. The free maximal plasma concentration at the therapeutic dose / exposure are below 55 ng/mL (assuming ~15% free concentration with the maximum observed value of 364 ng/mL total). This is equivalent to approximately 0.1 ⌈M (the molecular weight of risdiplam is 401) exposure in the circulation. Hence, this free drug level in the circulation is approximately 6-fold lower than the lowest 50% inhibitory concentration (IC50), i.e. that achieved in the acetylcholinesterase assay. Hence, it is unlikely that the off targets reported are meaningful in terms of clinical exposure to risdiplam and its metabolite M1.

Interaction with COX1/COX2 activity is the basis for the primary pharmacological effect of various approved drugs and inhibition of COX1/COX2 is not associated with any known or reported abuse liability signals. The *in vivo* toxicity studies carried out with risdiplam in mice, rats, rabbits and monkeys have not shown any evidence for effects associated with abuse liabilities.

The applicant mentioned that functional properties, i.e. agonist or antagonist, were not explored due to solubility constraints. Nevertheless, the concentration used in the CRO standard cell-based assays was in excess of 10-fold over the clinically relevant exposure conditions.

Pharmacodynamic drug-drug interactions

Pharmacodynamic drug-drug interaction studies have not been performed with risdiplam, which is considered acceptable.

Safety Pharmacology

The *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.

2.3.2. Pharmacokinetics

Nonclinical studies on the absorption, distribution, metabolism, and excretion of risdiplam (RO7034067) were conducted in mice, rats, rabbits and monkeys using primarily the same formulation, species and strain as in the nonclinical toxicity studies. *In vivo* nonclinical pharmacokinetic (PK) evaluations were performed following both single administration (intravenous and oral) and repeat oral doses of risdiplam mainly in rats and monkeys. A panel of *in vitro* studies was completed to assess plasma protein binding, distribution in blood cells, metabolism, and potential drug-drug interactions (DDIs) mediated through cytochromes P450 (CYPs) or transport proteins.

In vitro results indicated that risdiplam is a highly permeable molecule with no significant active efflux by human transport proteins and a low turnover in intestine microsomes. In line with these *in vitro* results, risdiplam is well-absorbed from the GI tract with moderate to high bioavailability in animals. Risdiplam half-life is short (~5 h), clearance is low (5-10 mL/min/kg) and volume of distribution of risdiplam is moderate (2–3 L/kg) in monkeys and rats. Oral bioavailability was moderate in monkeys (mean 42.6%), while in rats it was greater than 100% (mean 116.9%). The applicant justified these data above 100% as a consequence of the usual 20% of variation observed in rodent pharmacokinetics, taking into consideration the high solubility and permeability observed in PK studies and in PBPK modelling for human. No significant sex difference or accumulation over time was observed after multiple oral administrations across all nonclinical species and daily doses tested; the exposure increased roughly dose proportionally. The pharmacokinetic profile of risdiplam was explored in pre- and post-weaning rats from PND4 and compared to adults in single dose PK and toxicity studies. Total risdiplam exposure increased relevantly (from PND4 until PND14), likely due to accumulation caused by a slower elimination (t½ of 15 and 20 h on PND4 and PND12) and decreased thereafter on PND 31 to total AUCs similar to those observed at PND4. Total exposures on PND31 were consistent with the exposure from other adult rats. Plasma protein binding of risdiplam is moderate (89%) with no significant species differences in adults.

Age-dependent differences in plasma protein binding and half-life were observed in juvenile rats: pre-weaning pups showed a higher free fraction and longer half-life of risdiplam in plasma compared to post-weaning and adult rats. The observed longer half-life might be due to a not yet fully mature clearance mechanism. The lower clearance in the early days of life in rats resulted in a several fold higher total exposure and roughly twofold higher unbound total exposure on PND12 compared to PND4. The total exposure after further repeated doses on PND31 was similar to PND4, but represented only half the unbound exposure on PND4. Risdiplam plasma free fraction in rats showed a strong age dependency and high inter-individual variability in juvenile plasma with up to 90% free fraction in PND4 rats (versus 16% in adult). In contrast to juvenile animals, the plasma protein binding of risdiplam is similar in human blood taken from newborns (cord blood) and from children of various ages up to adulthood.

Risdiplam has been developed to target SMN2 alternative splicing selectively in both the peripheral organs and CNS by penetrating the blood-brain barrier. As expected from *in vitro* data, risdiplam freely distributes from the blood into the CNS and multiple tissues in animals and tissue elimination generally

follows elimination from plasma. Risdiplam showed high passive permeability, which is important for GI absorption and tissue uptake. In rat, the CSF to free plasma partitioning (Kp,uu) was predicted at 0.33 on the basis of *in vitro* efflux ratio data from cells expressing rodent Mdr1a. This prediction is in line with the observed *in vivo* Kp,uu of 0.28, confirming Mdr1a as the principal mechanism that lowers rodent CSF levels. Still, this property did not limit SMN protein increase in mouse brain. Risdiplam is also a strong rodent Bcrp substrate *in vitro*, but this interaction was not apparent *in vivo* since rodent CSF levels were successfully predicted based on the weak Mdr1a interaction alone. This apparent disconnect for brain penetration of rodent Bcrp substrates has also been observed with other molecules. These findings are also in alignment with risdiplam high passive permeability (350 nm/s). In contrast to rat proteins, risdiplam is not a substrate of human MDR1 and a weak substrate of human BCRP. In each of the 3 species studied (mice, rats and monkeys) risdiplam showed elimination kinetics from the CNS comparable to that from plasma. Several weeks after the end of treatment risdiplam was fully eliminated, with drug levels being below lower limit of quantification in brain, CSF and plasma.

The free drug hypothesis applies to all tissues and unbound drug in plasma is also expected to be in equilibrium with free drug in the muscles. Data have shown that risdiplam distribution to and elimination from muscle tissue correlates with plasma levels in mice, rats and monkeys.

In line with the estimated volume of distribution values in rat and monkey (2–3 L/kg), both the rat QWBA and the monkey tissue distribution studies confirmed a wide distribution of risdiplam with tissue elimination parallel to elimination from plasma. Risdiplam levels equivalent or higher than the total plasma levels in bone, mucosa of the GI tract, pancreas, liver, lung, heart, kidney and spleen were therefore confirmed in rodents and non-human primates. Highest risdiplam concentrations in monkeys treated orally 3 mg/kg/day for 7 days were reported in duodenum and liver with ca. 33-fold higher concentrations compared to plasma, while skin/ and spleen/plasma ratios were 5.51 and 5.21 respectively. Skin and spleen high distribution was also detected in rats treated with 3 mg/kg/day PO for 4 days, with spleen/plasma ratio above 20 in pigmented rats. On the other hand, skin concentration of risdiplam was higher in Albino rats than pigmented rats; this result is not consistent with the strong melanin-binding of risdiplam observed both *in vitro* both in ocular tissues. The applicant stated to consider these data with caution due to the high inter-individual variability of the skin results. Moreover, following oral administration of 14C-risdiplam to Albino and partially pigmented rats, higher levels of radioactivity were measured in pigmented skin compared to non-pigmented skin.

Distribution into melanin-containing parts of the eye (choroid + RPE, iris, sclera) was significantly higher than in non-pigmented ocular structures (retina, lens, vitreous body) or the rest of the body (muscle, brain, CSF). The higher accumulation in melanin containing tissues is in line with the strong melanin binding observed *in vitro*. The elimination rate in pigmented tissues differed from the rest of the body and drug levels were still considerably high in the eye, especially in melanin-containing parts in both pigmented rats and monkeys after treatment-free periods. However, a clear decline and elimination could be observed. In toxicology studies, retinal degeneration occurred after prolonged dosing and whose mechanism is not fully understood. As the applicant reported, risdiplam is light sensitive, suggesting that risdiplam and/or M1 metabolite photodegradation products could be toxic to eye tissues. Risdiplam was subjected to *in vitro* phototoxicity evaluation in 3T3 fibroblasts utilizing the neutral red uptake assay, showing no phototoxicity. This study implicitly included the evaluation of any photodegradation products that were possibly generated from risdiplam under UV exposure conditions in the *in vitro* test. The existing *in vitro* study for phototoxicity as conducted in compliance with [ICH S10] is sufficient to conclude that there is no phototoxicity risk from risdiplam in clinical use. The location of the toxicity in the retina periphery is inconsistent with any UV related breakdown of risdiplam or its M1 metabolite, as the relevant spectrum of light does not reach the retina, in particular not the periphery of the retina. Therefore, the systemic distribution of risdiplam into the retina and its action at this site on the retinal pigment epithelium and photoreceptors is not envisaged to be

dependent on UV exposure, and is considered to be associated with risdiplam itself (including any M1) but not related to photodegradation. In accordance, in clinical studies with risdiplam, comprehensive ophthalmological evaluations, which included examination of all melanin containing eyes structures (choroid, retinal pigment epithelium, iris, and sclera), as well as retinal imaging by optical coherence tomography (OCT), confirmed the absence of any findings suggestive of phototoxicity reactions in eye structures in 465 patients with spinal muscular atrophy (SMA) treated with risdiplam for up to 3 years [Sergott et al. 2020].

Risdiplam is relatively metabolically stable *in vitro* and *in vivo*. The major drug related species *in vitro* and *in vivo* in rat, monkeys and human is the parent molecule. The N hydroxy metabolite M1 was identified in liver microsomes and hepatocyte samples of all species. M1 was identified as human major metabolite in healthy volunteers and patients (median M1/parent ratio is 0.287 = ~0.3 in SMA patients). Human exposure to M1 was qualified in all key toxicology studies (repeat dose toxicity, juvenile toxicity, genotoxicity, carcinogenicity, reproductive toxicity) at the respective NOAELs and at doses with adverse toxicities in these study types.

The major excretion pathway in rats is through the faeces while renal excretion does not contribute significantly to the clearance of the compound in nonclinical species. The parent molecule constitutes most of the drug-related material in plasma and excreta. The most abundant metabolite in plasma, M1, is excreted in urine.

In vitro data have shown that liver is expected to be the main organ of risdiplam metabolic clearance and both FMO enzymes and multiple CYP enzymes (mainly CYP3A4) contribute to risdiplam metabolism, mainly generating M1.

In vitro studies showed that risdiplam and its metabolite M1 did not inhibit (reversible or TDI) any of the CYP enzymes tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6) with the exception of CYP3A4. Risdiplam and its major metabolite M1 did not induce any of the CYP enzymes tested (1A2, 2B6, 2C8, 2C9, 2C19, and 3A4). Risdiplam and its metabolite M1 did not inhibit any of the transport protein tested *in vitro* (MDR1, OATP1B1, OATP1B3, OAT1, and OAT3) with the exceptions of BCRP, OCT2, MATE1 and MATE2-K. Based on systemic and local concentrations of risdiplam and M1, the only potentially clinically relevant transporters-DDI risks expected are linked to MATE1 and MATE2-K inhibition by risdiplam. These potential DDIs are reflected in the SmPC.

Risdiplam human exposure after PO administration in healthy volunteers was originally predicted through physiologically based pharmacokinetic (PBPK) modelling using Gastro Plus v8.6 software. Both PBPK prediction and *in vitro* efficacy data for risdiplam were used in the PKPD model to predict the full-length mRNA time course at the intended doses during the Phase I clinical trial.

2.3.3. Toxicology

The nonclinical safety profile of risdiplam was assessed in a comprehensive toxicology programme. The relevance of the animal models was mainly judged on the basis of secondary mRNA splice targets occurring in animals and humans.

The monkey was considered to be a suitable and translational species for the safety assessment of risdiplam for use in humans due to the similar changes in splicing in secondary target genes upon treatment with risdiplam, as observed in SMA patient derived fibroblasts, in stimulated monkey and human monocytes and iPSCs, and in monkey spleen tissue *in vivo*. For at least one of the secondary splice targets identified for monkey and human cells, FOXM1, species differences exist between the primate (monkey and human) and the rat.

Single dose toxicity

No dedicated single dose toxicity studies were performed. Instead, reference is made to the results of studies with short-term treatment duration. This is aligned with the current guidelines. Based on the results of studies with a treatment duration of up to 8 days, acute effects of risdiplam may potentially include bone marrow toxicity and histological changes in gastrointestinal epithelia, skin, tongue and larynx epithelia and germ cell degeneration in testes. However, considering systemic exposures, these acute effects observed in the animal studies do not appear to represent a risk to patients at the intended therapeutic dose levels.

Repeated dose toxicity

Repeated dose toxicity studies included studies in Wistar Hannover rats (adults) and cynomolgus monkeys (sexually immature), with administration of risdiplam, by daily oral gavage, during up to 26 and 39 weeks, respectively. The choice of the animal species was justified based on secondary mRNA splice targets and on metabolism. The SMN2 gene is human-specific.

Studies were also conducted in sexually immature/juvenile rats, in Brown Norway rats, mice and rabbits. These are mostly addressed in other sections, as, as applicable, juvenile animal studies, dose range-finding studies to carcinogenicity or embryo-foetal developmental studies or other toxicity studies.

Risdiplam-related adverse findings were detected in all repeat dose toxicity studies in mice, rats and monkeys. All adverse effects were reversible or partially reversible in nature (depending on the chosen reversibility period and cell turnover in the respective organs) excretion given for retinal degeneration seen in the 39-week study in monkeys.

Effects observed in the chronic toxicity study in Wistar Hannover rats, at the maximum tested dose, included clinical signs of toxicity such as decreased activity, decrease in body weight gain and in the weight of the thymus, testis, epididymis and uterus, and increase in the weight of the adrenal gland. There were histopathological changes in the epithelium of the GI tract and hard palate, and acinar cells of the pancreas, with single cell necrosis; changes in the testes and epididymis, with degeneration/atrophy of seminiferous tubules in the testis and decrease in sperm and minimal degeneration/necrosis of ductular epithelium in the epididymis; vaginal changes indicative of a shift toward an oestrous cycle arrest; presence of cortical pigmentation and minimal to mild haemorrhage in adrenal gland; and thymus with minimal to moderate decreases lymphoid cellularity; and, in males, atrophy of mammary gland. A slight reduction of group mean scotopic b-wave amplitudes in females was observed at electroretinography, which, however, was considered unlikely to be related to treatment. Mortality was observed at the high dose and this was attributed to the risdiplam-related marked decreased cellularity of the bone marrow in combination with intestinal tract findings. Findings fully and partially recovered after an 8-week recovery period. Based on clinical effects and mortality seen at the maximum tested dose (7.5 mg/kg/day) and on the testis findings, the NOAEL for males and females were considered to be 1 and 3 mg/kg/day, respectively. At these respective NOAELs, systemic exposure ($AUC_{0\text{-}24h}$) to risdiplam in males was identical to the targeted exposure in patients; in females, it was approximately 4 times higher. At the maximum tested dose (7.5 mg/kg/day), systemic exposure in animals of both sexes was approximately 8 times higher than the targeted human exposure.

Effects observed in the chronic toxicity study in cynomolgus monkeys included clinical signs of toxicity (shedding/peeling skin at various locations and reddening of the face), decrease in thymus weight, retinal degeneration, mainly in the mid to peripheral layer, epidermal hyperplasia in the skin, and atrophy in the thymus. Depression of electroretinography amplitudes was also observed. At the end of the 22-week recovery phase, retinal degeneration was still observed in animals given the maximum

dose. There were no test item-related findings in the skin and thymus. Based on the findings in the eye of animals administered 3 or 7.5/5 mg/kg/day, the NOAEL was considered to be 1.5 mg/kg/day. At the NOAEL, systemic exposure (AUC_{0-24h}) to risdiplam in males and females was identical to the targeted exposure in patients. At the maximum tested dose (7.5/5 mg/kg/day), systemic exposure was approximately 3 times higher than the targeted human exposure.

Both in rats and monkeys, systemic exposures (AUC_{0-24h}) to risdiplam were generally proportional to dose and with no major gender differences. None of the samples from the control groups contained quantifiable plasma concentrations of risdiplam.

Effects of risdiplam on proliferating cells and tissue, such as effects in male germ cells and skin/mucosa, were attributed to alternative splicing of RNA other than SMN2, namely FOXM1, a major cell cycle regulating factor, and MADD, a gene with various splice variants involved in apoptosis. All these effects were considered of human relevance.

The mechanism of risdiplam-induced retinal changes, observed in the 39-weeks study in cynomolgus monkey was considered to be unknown. No such changes were observed in the 26-weeks study in Wistar Hannover (albino) nor in a further 26-week (non-GLP) study in Brown Norway (pigmented) rats, despite high tissue accumulation and tissue retention of risdiplam in pigmented rat RPE/retina; only minor changes in secondary splice targets, compared to other tissues, were seen in the retina. On the other side, a mechanistic study showed impairment of lysosomal function/autophagosomal accumulation in human retinal pigment epithelium (RPE) cells *in vitro*, with no identical studies conducted using rat and monkey RPE cells. In the absence of findings during on-treatment ophthalmological monitoring conducted in 386 patients with SMA for up to 3 years, it was considered there is evidence of an absence of retinal toxicity associated with risdiplam.

Discussed in more detail and encompassing results from the different duration toxicological studies, the identified target organs were the following:

Retina

Multifocal peripheral retina degeneration in the photoreceptor layer with hypertrophic retinal pigment epithelium (RPE) and microcystoid spaces in the inner retinal layers was seen after 39-week administration of risdiplam ≥3 mg/kg/day to monkeys. Association was found between structural abnormalities in sdOCT, histopathology findings and functional abnormalities in ERG, as animals showing the greatest effects by sdOCT grading also had the greatest ERG depression. Progression of depressed ERG and microcystoid spaces in the inner nuclear layer (INL) were only seen in animals at the high dose (5 mg/kg/day) with an exposure of 5880/6470 ng·h/mL (AUC0-24 in M/F). The only effect which did not recovered was the peripheral photoreceptor loss. The presence of flash-evoked VEP even at the highest dose, led to the applicant suggestion that risdiplam administration did not significantly compromise retinal ganglion cells or their axonal projections to the visual cortex even in animals with affected retinal responses. The NOAEL was set at 1.5 mg/kg/day (AUC 1870/2060 ng-h/mL for males and females, respectively).

Retinal effects were not seen in the dedicated retinopathy study in pigmented rats treated for up to 26 weeks with a high dose of either risdiplam or RO6885247.No consistent effect on the ERG was seen, albeit on the basis of a high variability in some parameters in the ERG between animals. As pointed out by the applicant, systemic exposure in these studies was higher than the exposure that led to retinal toxicity in the monkey (AUC0-24 16100/15700 ng·h/mL [M/F] in albino rats, up to 18000 ng·h/mL in pigmented rats versus 1870/2060 ng·h/mL [M/F] at NOEL in monkey).

The data suggest that retinal effects are seen only in monkeys, the exact mechanism for the delayed type of retinal toxicity being at present unknown; secondary splice targets are unlikely involved, thus indicating a specific biological process in the monkey that leads to retinal damage upon risdiplam treatment. These effects have been identified also for another *SMN2* splicing modifier, RO6885247 in a

chronic 39-week toxicity study in the same species, at exposures in excess of those investigated in patients (Ratni et al. 2018). That's the reason why ophthalmology monitoring was implemented in the 39-week monkey toxicity study with risdiplam as well.

As explained by the applicant no retinal changes were observed in rats (both albino and pigmented rats) despite of high exposure and pronounced melanin binding (see PK section).

In light of these data, is presently unclear whether the retinal degeneration process translates into human risk. Impairment of autophagosomal function has been observed *in vitro* in human RPEs and, as explained by the applicant, this *in vitro* property of risdiplam is possibly related to the retinal effects seen in monkeys. Moreover, no ocular findings have been seen in the clinic (See Clinical AR).

Male germ cells

Degeneration of germ cells was observed in monkey and rat testes after treatment with risdiplam.

In the rat 4-week toxicity study, a minor and reversible increase in the incidence of degenerated spermatocytes in the testis was present in males given 9 mg/kg/day (AUC 0-24h 15300/17700 ng.h/mL).

In adult albino rats administered for 26 weeks, testis effects were noted as well. They consisted of tubular degeneration/atrophy in testis at 3 and 7.5 mg/kg/day and secondary decreased sperm in the epididymis. In addition, one male at the high dose of 7.5 mg/kg/day degeneration/necrosis of the ductular epithelium in the epididymis was seen in one male at the high dose of 7.5 mg/kg/day. The NOAEL was set at 1 mg/kg/day (AUC0-24 of 2200 ng·h/mL).

This finding was seen also in juvenile animals (see respective section). Decreases in testis and epididymis weights were found at ≥1.5 mg/kg/day, which persisted following off-drug period, and reversible adverse testicular microscopic changes at 2.5 mg/kg/day. The NOAEL for microscopic changes in the testis was 1.5 mg/kg/day (AUC0-24 1570 ng·h/mL). Male germ cell degeneration was also observed in older rats with longer durations of treatment but with higher NOAELs, and in monkeys at high exposures (≥12000 ng·h/mL AUC0-24). The difference between younger and older rats in terms of total AUC is potentially associated with differences in the plasma free fraction and clearance of risdiplam, which result in a higher free plasma exposure in younger as compared to older rats.

Bone marrow

In the 26-week repeat-dose toxicity studies in both albino and pigmented rat, a reversible decreased cellularity of the bone marrow was recorded at high doses (7.5 mg/kg in albino and pigmented rats, albino rats: AUC0-24 16100/15700 ng·h/mL M/F; pigmented rats: AUC0-24 14200 ng·h/mL, M). Pronounced decrease in cellularity, in combination with intestinal tract findings, were likely contributing to unscheduled deaths and sacrifices. The NOAEL was 1 and 3 mg/kg/day in M and F albino rats, respectively (AUC0-24: 2200 ng·h/mL for M; 2400 ng·h/mL for F). The bone marrow was identified as a target for toxicity in the bone marrow micronucleus (MN) tests (See Genotoxicity Section).

GI tract

Histopathological changes in the GI tract were seen in the non GLP studies in mice, rats and monkeys subsequent to oral gavage treatment with risdiplam. These changes included increased apoptosis/single cell necrosis in GI, lamina propria vacuolation and single cell necrosis in exocrine pancreas epithelia. The changes were fully reversible.

Skin and larynx

Skin and larynx were identified as targets for risdiplam toxicity in the repeat dose toxicity studies at both 2 and 39 weeks in the monkey, at 6 and 7.5/5 mg/kg/day, respectively. This is consistent with similar studies conducted with the *SMN2* splice modifier RO6885247 (Ratni et al., 2018). Exposures of 5880/6470 ng·h/mL (AUC0-24, M/F) at 5 mg/kg/day, were associated with minor changes during the

in-life phase of the study and microscopically. The NOAELs at 2 and 39 weeks were set at 2 and 1.5 mg/kg/day (AUC0-24 ng.h/mL 2650/2460 and 5880/6470 M/F). Skin changes fully recovered within the 22-week recovery phase in monkeys treated for 39 weeks with the high dose of risdiplam.

No adverse changes were observed in the skin and larynx of mice, rats and rabbits treated with risdiplam.

Thymus

Non-adverse changes in thymus were seen in rats (decreased lymphoid cellularity, reduction of thymus weight) and monkeys (atrophy, decreased lymphocyte count) after chronic daily oral treatment with risdiplam. These effects were fully reversible.

Adrenocortical pigmentation

Risdiplam-related adrenocortical pigmentation was observed with chronic dosing in the rat and was still present after the recovery period. No changes to the adrenals were noted in the monkey studies. It is assumed that the findings represent age-related changes specific for rat.

Non-adverse and reversible findings were observed in uterus of female rats after 26 weeks of risdiplam treatment, which corresponded to a shift toward dioestrus consistent with an oestrous cycle arrest.

Mammary gland

Microscopic changes in the mammary gland were observed in male albino rats at the high dose of 7.5 mg/kg/day after 26 weeks of treatment. These changes were not observed in pigmented rats in the 26-week study with similar exposure. Moreover, no effects on the Leydig cells were seen. In light of these data and on the reversibility of the effect, reversible, this finding was considered non-adverse. No changes in the mammary gland were observed in the monkey chronic toxicity study.

Safety margins

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) to the mean exposure guidance used in clinical trials with SMA patients is provided in a table at the end of this section.

It has been claimed by the applicant that the identified risks and respective low safety margins may be accepted based on the severity of the disease, limited alternative treatment options and lack of an increased sensitivity of patients towards the observed animal toxicities. Moreover, key toxicities observed in animals were declared to be either monitorable (epithelia, haematology) or could be mitigated with imposed contraception requirements (male germ cells, embryofoetal effects) in clinical studies.

Concerning information on repeated dose toxicity studies in the SmPC, the applicant was asked to consider to shorten information in section 5.3 and, on the other side, given its onset, irreversibility and unclear mechanism, to add a special warning in relation to the retinal findings in monkeys in section 4.4 of the SmPC. In response, the applicant considered that inclusion of a warning in relation to the retinal findings in section 4.4 is not needed because of the already available clinical data, but has introduced revisions into section 5.3, mostly, with deletion of some information. In relation to the lack of information on retinal changes in section 4.4, the applicant's argumentation suggests that the lack of an observation of retinal toxicity in patients may have been merely due to a relatively low exposure in patients, with effects in monkeys occurring at only slightly higher exposures. From the non-clinical point of view, the lack of the mentioned warning is not convincingly justified. This issue is not pursued, however, considering that the risk has already been addressed at the clinical level, during the clinical trials.

Genotoxicity

The genotoxic potential of risdiplam was investigated including *in vitro* studies, a short-term *in vivo* study with additional evaluation of primary DNA-damage by the Comet assay and incorporation of *in vivo* MN tests into repeat dose rat toxicity studies to precisely determine a potential no-effect level for systemic exposure.

Table 1: Pivotal (GLP) Genotoxicity Studies with Risdiplam

Study	Species	Dose [mg/kg]/ Concentration
Bacterial mutagenicity *in vitro*	*Salmonella typhimurium*	up to 5000 µg/plate
Micronucleus test, 48 h	Rat, adult	0.75–25 3 times in 48 h
Micronucleus test, 4 weeks[a]	Rat, adult	1, 3, 9
Micronucleus test, 13 weeks[b]	Rat, juvenile	1, 3, 7.5

[a] Integrated in the 4-week repeat dose study.
[b] Integrated in the 13-week repeat dose study.

Risdiplam treatment led to micronuclei induction *in vitro* in mouse and human cell lines and *in vivo* in rat bone marrow erythroblasts. Risdiplam was not mutagenic in bacterial tests. Beyond induction of micronuclei, there was no evidence for primary DNA damage *in vivo* (in liver or jejunum) following treatment with risdiplam, even at doses that clearly raised the frequency of micronucleated cells in the bone marrow. The studies consistently supported the statistical assignment of a lower confidence level no-genotoxic effect level (NOGEL) for MN induction for risdiplam equivalent to an AUC0-24 of at least ~3000 ng·h/mL. The NOGEL appeared to increase with duration of dosing; juvenile animals were not more sensitive than adult animals.

Table 2: *In vivo* Micronucleus Studies and Exposure at the NOEL

Study	NOEL [mg/kg]	Mean AUC_{0-24} (M/F) [ng·h/mL]	Mean C_{max} (M/F) [ng/mL]
Rat, adult (M), 48 h, GLP	3	3800	260
Rat, adult (M/F), 4 weeks, GLP	1	1540/1650	217/200
Rat, juvenile (M/F), 13 weeks, GLP	3	7160/7830	759/725

NOGEL (lower confidence interval) for MN induction ~3000 ng·h/mL .

An indirect mechanism was reasonably suspected to have caused the increases in micronucleated erythrocytes. The additional data from the mechanistic investigation indicated a non-DNA target of risdiplam and an involvement of apoptosis in the induction of micronuclei in a human cell line (a massive increase of PARP upon risdiplam treatment ≥25 µM and suppression of MN induction after pretreatment with a pan caspase inhibitor). The mechanism for this not directly DNA targeting effect is currently unknown but assumed to be associated with secondary splice targets that interfere with the cell cycle control and/or induce apoptotic pathways. Interference of risdiplam with secondary splice targets such as *FOXM1* and *MADD*, which interfere with the cell cycle control or induce apoptotic pathways, can possibly cause such effects (Costa 2005, Laoukili et al. 2005).

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 could be 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 in principle monitored in SMA patients with haematology investigation.

Carcinogenicity

A carcinogenicity study using rasH2 transgenic mice with 6 months duration of treatment did not generate any evidence for a tumorigenic potential of risdiplam; there were also no other adverse findings in this study . Risdiplam AUC_{0-24} at the highest dose (9 mg/kg/day) on day 179 was 15600/11800 ng·h/mL (in M/F), i.e. well in excess of the exposures at which micronucleus induction was observed in bone marrow of juvenile and adult rat. The applicant informed that a two-year carcinogenicity study in rats is planned to be conducted as a post-approval commitment, in agreement with feedback received from CHMP and PDCO. The applicant provided the details of the study and proposed timelines for this study that will have to be submitted as a post-approval commitment that will need to be fulfilled- this was agreed**.** Furthermore, it is recommended that lack of complete non-clinical data on carcinogenicity is considered in the RMP, and that the reference to the ongoing carcinogenicity study in rats is clearly presented in SmPC section 5.3.

Reproductive and developmental toxicity

Reproductive and developmental toxicity studies comprised studies on embryo-foetal development, pre-postnatal development and toxicity upon direct dosing to the offspring (juvenile animal studies). No stand-alone fertility studies were conducted. Assessment of potential effects on male and female fertility was incorporated in two of the juvenile animal studies, with mating after a recovery period or, in the case of a 13-week study in juvenile animals, immediately after the end of the treatment period. Reproductive and developmental toxicity studies were conducted in Wistar Hannover rats and, in the case of embryo-foetal development, also in New Zealand White rabbits. In all studies, risdiplam was administered daily by oral gavage.

Except for 3 non-pivotal studies, all the others were GLP compliant. However, unlike for other GLP-compliant studies, for the pivotal embryo-foetal development studies in rats and rabbits), no information could be located in the "Non-clinical studies GLP compliance" annex to the application cover letter included in the initial marketing authorisation application dossier. In response to a request for clarification, the applicant has submitted a revised Non-clinical studies GLP compliance" annex. According to this, the test facility/test site where the two studies were conducted was part of an EU or an OECD Mutual Acceptance of Data (MAD) accepted GLP Monitoring programme in the period in which the test facility/test site was used.

No adverse effects were observed in male or female fertility. However, it is noted that no studies were conducted with concomitant exposure to risdiplam during mating and early embryonic development. In response to requests for clarification, the applicant has justified the lack of fertility studies with concomitant exposure to risdiplam during mating and early embryonic development because of the observation of adverse effects on male sperm cells in rats and monkeys and of teratogenicity in rabbits. The justification is accepted. Information on fertility in sections 4.6 and 5.3 of the SmPC has also been revised.

Furthermore, concerning reversibility of effects on male germ cells, the applicant has revised the text of section 5.3 of the SmPC, as requested, and, additionally, also the text of section 4.6. The current text proposals are considered adequate.

Concerning embryo-foetal development, the pivotal study in rats showed reduction in foetal weight (−15%) accompanied by an increased incidence of foetuses with morphological variations indicative of delayed development. This occurred at a dose level which induced only slight non-adverse maternal toxicity. Maternal systemic exposure (AUC_{0-24h}) to risdiplam at the NOAEL for embryofoetal development in the rats (3 mg/kg/day [Cmax 319 ng/mL and AUC0-24 4630 ng·h/mL on GD15]) was approximately 4.4-times higher than the targeted human exposure of 2000 ng·h/mL. There was no

evidence of teratogenicity neither in the pivotal study nor in the dose-range finding study. The pivotal study in rabbits showed, at the maximum tested dose (12 mg/kg/day), severe maternal toxicity, abortions, increased in incidence of late resorptions, and in fetuses with hydrocephaly, absent accessory lung lobes or small gallbladder. Maternal systemic exposure ($AUC_{0\text{-}24h}$) to risdiplam at the NOAEL for the mothers and embryo-fetal development (4 mg/kg/day [Cmax 1500 ng/mL, AUC0-24 7990 ng·h/mL on GD15]) was approximately 4.1-times higher than the targeted human exposure. Fetal malformations were also observed in the dose-range finding study in pregnant rabbits with 0, 4, 1 and 5 malformed fetuses in the 0, 3, 6 and 12 mg/kg/day dose groups, respectively.

No adverse maternal or pre-postnatal development effects were observed in the pivotal pre-postnatal development study, where maternal systemic exposure at the maximum tested dose (3.0 mg/kg/day) was, on average, approximately, 2.7-times higher than the targeted exposure in patients. Dose-related increase in the length of gestation and lower live birth index were however observed at ≥ 3 mg/kg/day in the dose range finding study. It was considered that this effect could be possibly attributed to an inhibition of COX-1 and -2, two potential secondary targets of risdiplam. There were no adverse findings on the survival, growth, and development of the offspring (including behavioural tests and mating performance). There were no effects on female germ cells, as assessed by primordial follicle counts and ovarian histopathology.

Juvenile animal studies were conducted with administration of risdiplam during up to 4 weeks starting at PND4 or during up 13 weeks starting at PND22.

The dose range finding study in juvenile rats revealed an increased sensitivity to risdiplam treatment in pre-weaning rats in comparison to older rats, resulting in high mortality rates observed at doses at or above 3.5 mg/kg/day (AUCs around 3000 ng·h/mL or above) within 2 to 7 days of initiation of treatment. This were declared by the applicant to be correlated with increased free plasma exposure, with pre-weaning pups showing a much higher plasma free fraction and longer half-life of risdiplam in plasma than that of post-weaning and adult rats. However, it is unclear if also the toxicity profile of risdiplam is different in pre-weaning rats. The mortalities observed in pre-weaning rats in a study were considered to be a concern and the applicant was asked to further discuss the cause of the early death of pups and the clinical relevance of these findings for the youngest patient population. In response, to explain the increased sensitivity to risdiplam treatment in pre-weaning rats in comparison to older rats, the applicant referred to the relatively slower elimination and markedly higher free fraction in pre-weaning rats, and argued that is not aware of any other possible reason. As for the clinical relevance of the higher sensitivity in pre-weaning rats, the applicant referred to results from *in vitro* studies with human plasma and to pharmacokinetics and safety data from clinical trials. According to these, risdiplam showed similar plasma protein binding in human from birth to adulthood, and risdiplam was safe and well tolerated in patients across all age groups. According to the clarifications provided by the applicant, the causes of the deaths observed in the DRF finding study were not identified, as no or only very limited histopathology could be performed on the decedent neonates. Nevertheless, results from the limited histopathology revealed findings (toxicity profile) consistent with findings in the toxicity studies in older rats. The increased sensitivity of the neonate rats versus older rats can reasonably be attributed to a higher free fraction and longer half-life of risdiplam in pre-weaning rats compared to that in older animals. Such higher exposure levels are not relevant for the clinical use of risdiplam in the paediatric patient population, where the free fraction is comparable across all ages. The issue is considered without relevance to paediatric patients.

Due to the different sensitivities, pivotal studies in juvenile rats were divided into two parts: pre-weaning and post weaning.

In the first one (4-week one), treatment with the high dose of 2.5 mg/kg/day resulted in decreased food consumption and lower body weight gain, which was correlated with reduced long bone growth

and delayed preputial separation in males. In the second one (13-week study), no effects on specific parameters of juvenile development were observed up to the highest dose of 7.5 mg/kg/day. Of concern. in the 4-week juvenile rat study , minimal to mild nephroblastomatosis (a pre-neoplastic lesion) was observed in all test-item treated groups; one male at 0.75 mg/kg/day (low dose) and one male and one female at 1.5 mg/kg/day (intermediate dose), and two females at 2.5 mg/kg/day (high dose). After the 8-week recovery period, malignant nephroblastoma were present in the kidney of one female each at 1.5 mg/kg/day and 2.5 mg/kg/day. In the 13-week study , a malignant nephroblastoma was observed in one male at 7.5 mg/kg/day (high dose). The study reports concluded these findings as spontaneous in origin. However, as rat kidney neoplasms are uncommon and given the high risdiplam distribution to kidney and that the findings were only observed in risdiplam-treated animals, the applicant was asked to provide a further discussion on the relation to treatment and clinical relevance of these findings.

In response, the applicant has claimed that the cause of the observed increased incidence of nephroblastomatosis and nephroblastoma in the two studies is a genetic predisposition in the breeding generation used to breed the animals included in these studies. Based on the location of the lesions, indicating an embryonal origin, and their low incidence, the lesions were interpreted to be spontaneous in origin. Furthermore, risdiplam does not display properties that could induce mutations or genetic changes in genes driving the development of nephroblastomatosis.

Nevertheless, the provided historical control data from the Contract Research Organisation shows a relatively low incidence of nephroblastomatosis and nephroblastoma: among males, one out of 457 animals with malignant nephroblastoma and, among females, 3 out of 335 animals with nephroblastomatosis. In this respect, the applicant argues that information from breeders, which is not available, would be more relevant than historical controls from the respective CRO.

As for the lack of properties that could induce mutations in genes driving the development of nephroblastomatosis, there is reference to 3 key genes highly associated with nephroblastoma (WT1, CTNNB1, and WTX) and to the results of the genotoxicity assays.

The applicant has provided further clarifications on the significance of the nephroblastomatosis and nephroblastoma observed in two juvenile rat studies ([a 4-week study with treatment during PND4-31 and a 13-week study with treatment during PND22-112, respectively]).

According to the response, the 13-week study showed no evidence of effect, based on incidence. This study showed no nephroblastomatosis and the incidence of nephroblastoma (one male at 7.5 mg/kg/day) was in line with the historical control data.

As for the 4-week study, this showed incidences of nephroblastomatosis and nephroblastoma above the historical control data provided by the CRO. However, the same was not observed in a previous 4-week study with a comparable study design (only 2 dose groups instead of 3, but same size of groups) using similar dosage in Wistar rats dosed from PND4 to 31. Furthermore, there is no indication for that risdiplam could affect genes mentioned as important in the context of nephroblastoma.

The applicant considers that there is no need for further amendments to section 5.3 of the SmPC and this is accepted. It may be concluded that the increased incidence of nephroblastomatosis and nephroblastoma observed in a 4-week study in juvenile rats does not represent a risk to patients. This finding was not reproduced in another study with identical study design. Furthermore, knowledge on the development of nephroblastomatosis and nephroblastoma, key genes known to be associated with development of nephroblastoma and evidence for lack of effects of risdiplam on these genes does not indicate that exposure to risdiplam may lead to the development of nephroblastomatosis and/or nephroblastoma.

As for adult animals, margins of exposures at the respective NOAEL were low to null.

Other toxicity studies

Risdiplam and RO6885247 have been tested on a human retinal pigment epithelial cell line (ARPE19) for functional impairment . Treatment of cells for 24 h and longer revealed an increase in lysosomal mass at non-cytotoxic concentrations (with maximal effects at 3.13 and 6.25 µg/mL) indicative of impairment of lysosomal function. The phototoxic potential of risdiplam is considered by the applicant to be low. The UV absorption spectrum for the major human metabolite M1 is almost identical with the spectrum of risdiplam. Thus, M1 was not tested for phototoxicity because no change in a risk for phototoxicity would be expected from human exposure to M1 as compared to risdiplam itself. No impact of the UV absorption potential on the retinal toxicity of risdiplam is expected, because the retina is not exposed to wavelengths shorter than ~400 nm. No phototoxic potential of risdiplam is expected in the visible range above 400 nm. Risdiplam did not elicit any irritative or sensitisation effect in an LLNA assay. Nevertheless, the phototoxic properties of risdiplam should be further discussed. Risdiplam absorbs light between 240 and 400 nM with an absorbance maximum at 290 nm with a MEC value of 13417.8 Lmol-1/cm which is greater than the threshold of 1000 Lmol-1/cm. Further, risdiplam binds melanin with high affinity and distributes to and accumulates in melanin-containing parts of the eye (choroid and RPE, iris, sclera) of pigmented rats and monkeys with a slow elimination (up to 65 days). In the 3T3 test using an UVA light source (315-690 nm), risdiplam was concluded as non-phototoxic up to the limit of solubility (9 µg/mL). However, in human-derived epidermal keratinocytes, UVA irradiation ("artificial sunlight") affected cell viability and triggered release of IL-1, IL-8 and TNFα in risdiplam-treated cells at lower concentrations than that tested in the 3T3 study (0.1 to 3 µg/mL) and risdiplam was concluded as phototoxic.

Risdiplam and RO6885247 have been tested on a human retinal pigment epithelial cell line (ARPE19) for functional impairment. Treatment of cells for 24 h and longer revealed an increase in lysosomal mass at non-cytotoxic concentrations (with maximal effects at 3.13 and 6.25 µg/mL) indicative of impairment of lysosomal function, whereas phagocytosis and oxidative stress levels of ARPE19 cells remained unchanged at this time point. Accumulation of autophagosomes involved in clearing damaged organelles was also shown for both compounds with 48 h of treatment. It remains unclear how these *in vitro* short-term changes relate to delayed retinal toxicity seen *in vivo* mechanistically.

As part of an interspecies safety assessment, four *SMN2* splicing modifiers including risdiplam were tested *in vitro* for their concentration-effect relation on RNA markers (*FOXM1B/C* transcript variants) for off-target splicing effects (i.e., secondary pharmacology) in human and Cynomolgus monkey iPSCs . As these markers translate into the FOXM1 transcription factor, all four compounds were also tested for their impact on cell cycle progression. Treatment with the test items for 24 h from 0.64 nM to 10 µM revealed comparable IC_{50} values between human and Cynomolgus monkey cells with respect to the down-regulation of *FOXM1B/C* transcript variants . In this regard, RO6885241 (the metabolite M1 of RO6885247) and risdiplam were more potent than RO6885247, whereas the major metabolite of risdiplam, M1 did not appear to affect the expression levels of the *FOXM1B/C* transcript variants. Furthermore, a concentration-dependent effect to induce mitotic arrest in Cynomolgus monkey and human iPSCs was detected for RO6885247, RO6885241 and risdiplam, but not for risdiplam M1.

In vitro studies that were conducted with a series of *SMN2* splicing modifiers, which included risdiplam, suggested that a distinct number of gene transcripts could be affected by alternative splicing (see also Palacino et al. 2015). To contribute to mechanistic understanding of toxicities provoked by treatment with risdiplam, RNA sequencing analyses followed by detailed analysis of spliced genes were integrated into the 2-week dose-range finding repeat dose toxicity studies conducted in the rat and monkey.

Gene expression analysis was performed in spleen, duodenum, and testis in rats treated for 2 weeks with a focus on the genes, the splicing of which were most affected *in vitro* and with previously tested

compounds, i.e. *Madd*, *Strn3*, *Aplp2*, *Smn1* and *Foxm1* genes [Ratni et al. 2018]. Gene expression analysis of risdiplam-treated animals revealed a splicing response at the highest dose of 7.5 mg/kg/day for *Madd* and *Strn3* gene transcripts and to lower extent for the *Aplp2* gene transcript in spleen, duodenum, and testis. *Aplp2* was not seen as a major secondary splice target in the *in vitro* pharmacology studies but surfaced as more affected in these *in vivo* studies in rats and monkeys at the high doses at which these were conducted. Transcripts of the *Smn1* and *Foxm1* genes remained unchanged in alternative splicing. Similar investigations were integrated into the 2-week dose-range finding toxicity study conducted in the Cynomolgus monkey with risdiplam. Spleen, duodenum, and testis were analyzed from the animals treated with 0.75, 1.5, 3 and 6 mg/kg/day. The analysis with mRNA isoform specific qPCR assays revealed a secondary pharmacological response to risdiplam treatment at the highest dose for the transcripts of the *MADD* and *STRN3* genes, and to a lower extent for the *APLP2* gene transcript in all three organs. The transcript variants *FOXM1B/C* of the *FoxM1* gene showed a down-regulation in testis in one animal at the highest dose. Transcripts of the *SMN1* genes remained unchanged in alternative splicing in response to treatments. Since secondary pharmacological response was detected in spleen, this organ was further analyzed for transcriptome-wide mRNA splicing or expression changes by RNA-sequencing. This analysis revealed that, except for the above-mentioned spliced transcripts, the vast majority of mRNAs exhibited either no change in alternative splicing or no dose-dependent trend in such changes upon treatment with risdiplam. Furthermore, a dose-dependent trend for pathway expression changes was not detected in the RNA sequence and pathway analyses.

Splicing analyses for the retina and choroid/RPE were also integrated into a monkey multiple dose PK study with risdiplam and another *SMN2* splice modifier, RO6885247 administered at 3 mg/kg/day over 7 days. Splice variants of the main secondary splice targets *FOXM1*, *STRN3*, *APLP2*, and *MADD* were examined. In contrast to spleen and skin samples, splice variant changes were detected in the retina and choroid/RPE only for *APLP2* and *STRN3* and these changes were clearly weaker than in spleen and skin. Both compounds showed consistent results in this analysis. Splicing changes have returned to control conditions when measured after 6 weeks of recovery. Similar observations were made in a study conducted with albino and pigmented rats.

A local lymph node assay was conducted in the mouse to assess skin irritation (erythema) and sensitisation after epidermal (to the ears) or oral induction exposures. In this study, risdiplam did not elicit any irritative or sensitisation effect.

Exposure ratios and key toxicities

A NOAEL was established for risdiplam in all pivotal toxicity studies for genotoxicity, repeat dose toxicity, juvenile toxicity, reproductive toxicity and carcinogenicity.

Table 3: 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
Haematology 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 Embryofetal (lethality and teratogenic) effects in rabbits with maternal toxicity	 >2 ~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)

2.3.4. Ecotoxicity/environmental risk assessment

EVRYSDI was submitted as an orphan medicinal product - Article 3 (1) of Regulation (EC) No 726/2004, being the active substance risdiplam.

An experimental log Kow value for the PBT screening has not been provided. The PBT assessment cannot be finalised and the applicant should experimentally determine the log Kow as a function of pH covering an environmentally relevant pH-range and calculate the ion-corrected log Dow.

The applicant highlighted that the logDOW values obtained by the HPLC method were confirmed with the pH-metric method as well as QSAR. Nevertheless, the shake-flask test according to OECD 107 is commissioned to Arcadis (Schweiz) Ltd, to perform logDOW values at pH 5, 7, and 9 in compliance with GLP. The results will be available by the end of April 2021.

The assessor acknowledges the accomplishment of the shake-flask test according to OECD 107 that will be available by the end of April 2021. However, the results of such test must be shared with the CHMP since they should be assessed and the EPAR updated. Therefore, the applicant must commit to submitting the results of the shake-flask test by the end of April 2021.

Phase I calculations result in a refined PECsw of 0.0009 µg/l based on a prevalence study from Italy and can be accepted.

Phase II has been included as complementary data to estimate the environmental risks. The provided acute-based surface water PNECs are not acceptable. Despite these weaknesses, it is considered that due to the calculated low environmental exposure risdiplam unlikely represents a risk. However, the log Kow values were calculated using the HPLC method that covers log Kow(s) in the range of 0-6 and may not reliable enough for risdiplam, therefore the applicant should confirm /discuss if both results calculated by HPLC method and experimentally determined by the Shake-Flask method will be similar.

Risdiplam is not readily biodegradable.

2.3.5. Discussion on non-clinical aspects

Spinal muscular atrophy (SMA) is an autosomal recessive disorder secondary to loss-of-function mutations in both alleles of the survival of 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 ribonucleic acid (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.

Risdiplam is an orally administered small molecule SMN2 splicing modifier developed for the treatment of SMA. Risdiplam modulates SMN2 splicing to shift the balance from exon 7 exclusion to exon 7 inclusion into the mRNA transcript, thereby increasing the expression of full-length SMN protein from the SMN2 gene in a dose dependent manner. The resulting increase in functional SMN protein is deemed to compensate for the deficit of this protein in SMA patients

A comprehensive nonclinical testing programme, consistent with ICH guidelines and performed in relevant *in vitro* and animal models, was designed to characterize the pharmacology, pharmacokinetics / toxicokinetics, and toxicology of risdiplam. In the toxicity studies, risdiplam was administered orally as per the intended clinical route of administration (except for the dermal local lymph node assay [LLNA] assay). However, in the transgenic mouse model to study efficacy of risdiplam, the intraperitoneal route of dosing was used for very young mice due to their susceptibility to the stress of oral dosing. Intravenous administration was used in some pharmacokinetics studies (e.g., to judge absolute bioavailability).

The **pharmacological effects** and specificity of risdiplam were investigated in pharmacology studies conducted *in vitro*, *ex vivo* and *in vivo*.

The *in vitro* and *ex vivo* pharmacological studies evaluated the efficacy of risdiplam to induce SMN2 exon 7 inclusion to produce the full-length SMN2 transcript and the resulting translation into increased SMN protein levels. These analyses were conducted with Type 1 SMA patient fibroblasts, in cultured motor neurons derived from Type 1 SMA patient-induced pluripotent stem cells (iPSCs) and in whole blood from healthy volunteers. The effect of risdiplam major human metabolite M1 on SMN2 transcript splicing was assessed in Type 1 SMA patient-derived fibroblasts and whole blood from healthy volunteers.

In Type 1 SMA patient fibroblasts, risdiplam resulted 2-fold more active in correcting alternative splicing (i.e., reducing Δ7 mRNA) than in increasing functional gene expression (i.e., increasing FL mRNA). EC50 values (target effect) for both endpoints were below the clinical Cmax of 37 nM unbound risdiplam in infants with Type 1 SMA aged 1-7 months at enrolment, while EC100 was 3-fold higher the same clinical Cmax. It appears that in terms of EC50 values the ability of risdiplam to increase FL SMN protein production (EC50 12 nM), correlates better with reduction of SMN2 Δ7 mRNA (EC50 11-12 nM) rather than with the increase of FL SMN2 mRNA (EC50 24-29 nM). This is in line with data from clinical PD.

On the contrary, no effect on SMN protein level in motor neurons derived by Type 1 SMA patient induced pluripotent stem cells, was achieved at clinical Cmax of 37 nM unbound risdiplam in infants with Type 1 SMA (EC50 182 nM). Traditionally, it is unfeasible to obtain patient-originated and SMA-related motor neuron samples, therefore motor neurons derived by Type 1 SMA patient induced pluripotent stem cells still represent a valuable tool for drug screening for SMA reflecting the genetic alteration in human SMA. The lack of activity of risdiplam in Type 1 human iPSC-derived motor neuron should be weighted in the context of overall non-clinical and clinical results.

In whole blood from healthy donors, risdiplam was equally able to reduce Δ7 mRNA and increase FL SMN2 mRNA expression, however, it was approximately 2-fold more potent than in Type 1 SMA patient fibroblasts in increasing FL SMN2 mRNA (EC50 8.25-14.2 nM) and reducing Δ7 mRNA (EC50 6.6-6.7 nM) (EC50 values normalised for human plasma protein binding fraction, 11% unbound).

Metabolite M1 (RO7112063) was approx. 30-fold less potent than risdiplam in Type 1 SMA patient fibroblasts for reducing Δ7 mRNA and increasing FL mRNA, and approx. 15 to 30-fold less potent than risdiplam in whole blood from healthy donors for both endpoints, with EC50 values exceeding the clinical Cmax. In whole blood from healthy donors neither risdiplam or metabolite M1 did change the SMN1 splicing, showing selectivity towards the SMN2 gene.

Overall, in severe SMA phenotype with transgenic **animal models** knock-out for SMN1 gene and possessing two copies of the human SMN2 gene, risdiplam showed to correct dysfunctional splicing of SMN2 gene being able to restore (doubled) SMN protein level respect control animals, in brain and quadriceps, although this increase did not reach the SMN level expressed in healthy animals. Risdiplam was more potent in increasing SMN protein level in brain than in quadriceps. The effects were observed at clinically relevant Cmax of 37 nM.

On the contrary, risdiplam lacked activity (in terms of ED50 for increase FL SMA protein in brain and quadriceps) in the milder phenotype mouse model (adult C/C mice reflecting a mild phenotype) achieving mouse plasma levels 3 to 5-fold higher the clinical Cmax of 50 nM (Firefish clinical study). This non-clinical result remains a significantly relevant nonclinical aspect in particular given that no clinical study has included SMA type 4 (adult onset) SMA (see clinical efficacy).

Based on the low potency observed in *in vitro* studies, no effect of the M1 metabolite was tested *in vivo*.

Although it was not possible to determine whether the clinical risdiplam benchmark exposure/dose to predict significant clinical benefit (e.g. at least 2-fold increase of plasma SMN protein level versus baseline) was achieved in non-clinical models, data from the two mouse SMA models suggest a positive correlation between FL SMN protein increases in blood and increase in the brain and quadriceps. Nevertheless, it is noted that although in clinical PD studies risdiplam increases 2-2.5 fold the SMN protein plasma level, no evidence of correlation between PD biomarker and clinical effect has been observed.

At the highest effective dose of 1 mg/kg (plasma level 21 nM) administered from postnatal day (PND) 3 to PND24 followed by 3 mg/kg (plasma level 56 nM) up to day 220, the percent survivals at PND60 and 220, were 82% and 36% vs 0 in vehicle treated mice (all vehicle-treated mice died before day 21). In this treatment group, the median survival time day was 201 vs 10.5 vehicle treated mice. However, the major contribution to overall survival in this treatment group, comes from the higher supratherapeutic dose of 3 mg/kg administered from post-natal day 24 onwards.

Improvements in secondary phenotypes such as motor behaviour (righting reflex) in young mice at PND16, or tissue necrosis (tail and eye) in adult mice at PND220 was observed from the dose range 1 mg/kg IP → 3 mg/kg PO. In this treatment group treatment with risdiplam:

- reduced the loss of vGLUT1 synapses in L3-5 motoneurons in adult mice; the effect was nearly normalised to heterozygous;
- reduced the loss of the number of L4 ventral root axons even if the effect was not normalised to HET;
- reduced the loss of weight of extensor digitorum longus muscle reaching normalisation to HET;
- fully restored the denervation of neuromuscular junction in longissimus muscle reaching normalisation to HET.

The **secondary pharmacodynamic studies** evaluated the effects of risdiplam on off-target receptors, enzymes and channels and on potential splice targets other than SMN2 in the global transcriptome of Type 1 SMA patient-derived fibroblasts. A global transcriptome analysis of alternative splice sites and specific splice site analysis of identified secondary splice target genes after treatment with risdiplam (and with other SMN2 splice modifiers as discussed in Ratni et al. 2018) was also studied in other cell types and in tissue material from toxicity studies in animals. Of those 13 off-target genes in total, FOXM1 and MADD were identified as likely contributors to toxicities seen in studies with animals and *in vitro* systems, while STRN3, SLC25A17, and APLP2 were not considered of relevance for the safety of risdiplam The applicant referred to insufficient data to characterize the function of different splice variants of STRN3. It is known that STRN3 codes for the protein striatin-3, which is involved in several biological processes, including the negative regulation of intracellular oestrogen receptor signalling pathway. The same applies for the SLC25A17 gene, which codes for Peroxisomal membrane protein PMP34, involved in several biological processes, including ATP and fatty acid transport, and in fatty acid oxidation but the roles of different splice variants of this gene are not known. Thus, the applicant acknowledges that the biological functions of splice variants of STRN3 and SLC25A17 as potentially emerging from treatment with risdiplam are not fully characterised. In animal studies, no apparent associations with pathophysiological outcomes were found... On the other hand, clinical studies conducted with risdiplam no imbalance in adverse events (in particular reproductive system and breast disorders, endocrine disorders) or safety laboratory assessments (including cholesterol, triglycerides) was observed.

The *in vivo* toxicity studies carried out with risdiplam in mice, rats, rabbits and monkeys have not shown any evidence for effects associated with abuse liabilities. The applicant mentioned that functional properties, i.e., agonist or antagonist, were not explored due to solubility constraints. Nevertheless, the concentration used in the CRO standard cell-based assays was in excess of 10-fold over the clinically relevant exposure conditions.

Safety Pharmacology

The *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.

Pharmacokinetics

Nonclinical studies on the absorption, distribution, metabolism, and excretion of risdiplam were conducted in mice, rats, rabbits and monkeys using primarily the same formulation, species and strain as in the nonclinical toxicity studies. *In vivo* nonclinical pharmacokinetic evaluations were performed following both single administration (intravenous and oral) and repeat oral doses of risdiplam mainly in rats and monkeys. A panel of *in vitro* studies was completed to assess plasma protein binding, distribution in blood cells, metabolism, and potential drug-drug interactions (DDIs) mediated through cytochromes P450 or transport proteins.

Risdiplam and its metabolite M1 concentrations in plasma and tissue samples from nonclinical species

(mouse, rabbit, rat, Cynomolgus monkey) and in samples from *in vitro* studies (including human matrices) were quantified by liquid chromatography tandem mass spectrometry (LC-MS/MS). For TK measurements, LC-MS/MS methods used for the determination of risdiplam concentrations in mouse, rat, rabbit, and Cynomolgus monkey plasma and in Cynomolgus monkey CSF were adequately validated. Acceptable linearity, precision, accuracy and specificity of test items were observed over a range of 0.5 to 2500 ng/mL in plasma or 0.100 to 100 ng/mL in monkey CSF.

Absorption

Absorption parameters were determined both *in vitro* and *in vivo* in mice, rats, rabbits and monkeys.

In vitro studies have been performed in LLC-PK1 and MDCKII cells.

Even if, according with ICH M9 guideline and Q&A, permeability should be assessed by validated and standardised *in vitro* methods using Caco-2 cells, the method used is considered acceptable. Those methods are also endorsed by FDA guidance "In Vitro Metabolism- and Transporter- Mediated Drug-Drug Interaction Studies".

Both risdiplam and M1 were found to be highly permeable compounds, with an average passive permeability in parental LLC-PK1 and MDCKII cells above 300 nm/s.

After IV administration of risdiplam to adult rats and monkeys, half-life was short (up to 5 h), clearance was low (up to 9 mL/min/kg) and volume of distribution of risdiplam was moderate (3 and 2 L/Kg in rats and monkeys, respectively).

After single PO administration risdiplam was rapidly absorbed, with tmax values ranged from 1 to 3 hours in all adult animal species. Half-life was longer and tmax delayed in young pups (PND4 and PND12 rats) compared to older rats. Oral bioavailability was moderate in monkeys (mean 42.6%), while in rats it was greater than 100% (mean 116.9%). The applicant justified these data above 100% as a consequence of the usual 20% of variation observed in rodent pharmacokinetics, taking into consideration the high solubility and permeability observed in PK studies and in PKPD.

Distribution

Plasma protein binding was moderate for both risdiplam and M1 with average fraction unbound values of 11% and 7.4 % in human, 10% and 13.4% in mouse, 16% and 8.9% in rat, 15% and 11.2% in monkey and 10% and 7.5% in rabbit, respectively.

Risdiplam free fraction showed a markedly age dependency and inter-individual variability in juvenile rats while age dependency was less pronounced in mice and monkeys and no differences in plasma protein binding were observed for human from birth to adulthood.

In isolated human plasma proteins, albumin resulted to be the main binding protein for risdiplam, which showed a fraction unbound of 12%, while the blood plasma partitioning ratio was close to 1 in human, monkey and rat.

Risdiplam melanin binding was very strong, with average fraction unbound values lower than 0.1% at 1 µM and 0.2% at 10 µM. On the contrary, risdiplam did not show interaction with human OATP transporters; therefore, hepatic uptake should likely to be driven predominantly by passive diffusion, which is consistent with the high passive permeability observed in LLC-PK1 and MDCKII cells (Papp>300 nm/s).

Highest risdiplam concentrations in monkeys treated orally 3 mg/kg/day for 7 days were reported in duodenum and liver with ca. 33-fold higher concentrations compared to plasma, while skin/ and spleen/plasma ratios were 5.51 and 5.21 respectively. Skin and spleen high distribution was also detected in rats treated with 3 mg/kg/day PO for 4 days, with spleen/plasma ratio above 20 in pigmented rats. On the other hand, skin concentration of risdiplam was higher in Albino rats than pigmented rats; this result is not consistent with the strong melanin-binding of risdiplam observed both *in vitro* both in ocular tissues. The applicant stated to consider these data with caution due to the high inter-individual variability of the skin results. Moreover, following oral administration of 14C-risdiplam to Albino and partially pigmented rats, higher levels of radioactivity were measured in pigmented skin compared to non-pigmented skin. Although the applicant did not adequately justify these inconsistent results, no skin findings have been observed in toxicology studies in rats.

In line with melanin binding *in vitro* data, risdiplam distribution into melanin-containing parts of the eye of pigmented rats and monkeys was significantly higher than in non-pigmented ocular structures or the rest of the body (muscle, brain, CSF). Moreover, as expected, risdiplam distributed better in ocular tissues of pigmented rats than in Albino rats: Choroid+RPE/plasma ratio was 5220 and 0.80 in pigmented and Albino rats respectively. In addition, risdiplam decrease was very slow in those tissues, up to 65 days for Choroid+RPE.

In monkeys, mean tissue concentrations from 2h to 6 weeks post last dose (1008h) generally decreased, less pronounced in iris, lens, cornea, choroid+RPE, sclera and retina (up to 5-fold decrease) and more pronounced in vitreous humour/body (ca. 30-fold decrease) and aqueous humour (concentration <0.500 ng/g at 6 weeks post-last dose).

Risdiplam penetrates into the CNS, with the maximum concentration reached within 1 hour in mice and rats. Risdiplam concentration in brain tissue reflected approximately those of total plasma level: brain-to-plasma AUC ratio was 0.75 in mice following single oral dose of 10 mg/kg risdiplam, 1 in monkeys treated orally with 3 mg/kg/day for 7 days, and 1.02 and 1.52 following 4-days 3 mg/kg/day PO administration to Albino and Pigmented rats respectively. These results are consistent with high permeability and lack of interaction of risdiplam with MDR1 protein. However, risdiplam concentration was found to be below in CSF (Cynomolgus monkeys) and in muscle (rats and monkeys) than in plasma.

Drug levels decreased rapidly after the end of treatment in all animals studied, confirming the lack tissue accumulation, except for melanin-containing tissues (e.g., up to 65 days in Choroid+RPE tissues in rats).

14C- risdiplam crossed the placental barrier in pregnant rat, with radioactivity levels below the limit of quantification in the foetus within 72 h.

Metabolism

Risdiplam was relatively stable in incubations with human liver microsomes and hepatocytes, with ≥89% and ≥98% of parent drug recovered unchanged after incubation, respectively; same results have been seen in animals, with unchanged drug accounting for 73% and 86% (rat), 71% and 88% (monkey), 82% and 84% (mouse) and 73% and 80% (rabbit) of the drug-related material after incubation in liver microsomes and hepatocytes, respectively.

The main organ of biotransformation for risdiplam is represented by liver, but also kidney and intestine can metabolize ^{14}C-risdiplam: drug's turnover was greatest in liver (24%) then kidney (9%), then intestine (2%) after incubation with human hepatic, renal and intestinal microsomes.

The N-hydroxy metabolite M1 was identified as the main one, since it was retrieved in liver microsomes and hepatocyte of all species and represents the major circulating metabolite in both human and animal plasma.

The enzymes involved in human metabolism of risdiplam are FMO1 and FMO3 and multiple members of the cytochrome P450 superfamily (CYP). Incubation of unlabelled and 14C-risdiplam with solutions containing CYPs and FMO enzymes showed that multiple oxidative metabolism products were generated by each of the enzymes. In particular, M1 can be generated by both FMO1 and FMO3 as well as CYPs, mainly 3A4/5: the turnover produced by the recombinantly expressed FMO enzymes was considerably higher (>60%) than that of the CYP enzymes (<10%). This result was also confirmed by incubation of risdiplam with FMOs and CYPs in presence and absence of the respective inhibitors: the most effect was obtained with the CYP3A4/5 inhibitor ketoconazole and with the FMO inhibitor methimazole, that caused 62% and 46% inhibition when incubated with risdiplam 1 µM, respectively.

Risdiplam was identified as the major drug-related component (≥88%) in adult and juvenile rat plasma collected following multiple oral administration at 2.5 mg/kg and 10 mg/kg respectively. Also in monkeys, parent drug accounted for ≥ 84% of the identified drug-related material in plasma samples following multiple oral administration of risdiplam at 6 mg/kg.

Single oral (5 mg/kg) and IV (2 mg/kg) administration of 14C-risdiplam to naïve rats confirmed the higher concentration of unchanged drug than the other metabolites.

In line with *in vitro* results, M1 metabolite has been identified as the major one in all the studies previously reported. However, as stated by the applicant, these data could not be used to assess M1 levels due to oxidative degradation under the plasma sample storage and analysis conditions used initially for risdiplam. Therefore, dedicated bioanalytical methods, which involved an addition of a stabilizer (L-ascorbic acid) to the plasma samples and handling of the samples under cold conditions (nominal 4°C), were developed to overcome the instability of M1. These methods were used throughout the bioanalytical workflows in studies started after February 2017.

Therefore, in order to better characterize risdiplam PK and the formation of M1 metabolite, the applicant performed pharmacokinetics bridging studies with a single administration in rats and 3 days repeat-dosing in monkeys, in which plasma samples were correctly stabilised. M1 has also been monitored in the animal toxicity studies conducted after February 2017 in rats (embryofoetal and pre- and postnatal development, juvenile toxicity), mice (carcinogenicity) and rabbit (embryofoetal development). Those studies confirm M1 as the main metabolite.

Following single oral administration of 3 mg/kg risdiplam to Wistar rats, all rats were exposed to parent drug and its metabolite M1 over the whole sampling interval (24h). In terms of AUC(0-last), the metabolite M1 exposure in plasma represented on average 36.3% (range: 34.2% to 37.6%) of parent compound exposure, reaching the maximum concentration of 132 ng/mL at 2 hours post-dose. Same results have been seen in monkeys administered with 3 mg/kg/day risdiplam over 3 days: M1 exposure accounted for an average 12.4% and 15.2% of parent compound on day 1 and day 3 respectively. The higher exposure to both analytes was observed on Day 3: AUC(0-last) Day3/Day1 ratios were 2.32 and 2.81 for risdiplam and M1 respectively.

Excretion

Elimination studies performed in rats and monkeys confirmed faeces as the main route of excretion, while excretion via urine accounted for a much lower amount.

Following single oral (5 mg/kg) and intravenous (2 mg/kg) administration of 14C-risdiplam to naïve rats there was nearly complete excretion, with approximately 87% and 83% of the radioactivity recovered in faeces within 72 hours, while urine accounted for 7% and 9% of dose, respectively.

For metabolite identification, pool samples (0 to 48 hours) were investigated: unchanged risdiplam was identified as the major drug-related component in excreta, accounting for 50% and 44% of the dose in naïve rats following oral and intravenous administration respectively, while metabolite M5 was the most abundant metabolite identified (6.8 and 5.7% of the dose following oral and IV administration respectively).

In BDC rats following 5 mg/kg oral administration and 2 mg/kg IV, 11%, 70% and 8% (oral) and 17%, 50% and 19% (IV) of the dose was recovered within 72 hours in the urine, faeces and bile respectively.

In line with previous results, analysis of urine and faeces collected over 7 days after single dosing (5 mg/kg oral and 2 mg/kg IV) of 14C-risdiplam to Albino and partially pigmented rats showed faecal excretion as the main route of elimination, with the total amount of the radioactivity excreted via faeces

accounting for up to 87% of the dose following oral administration and ~ 79% of the dose following IV administration. Urine excretion was between 12 and 7% of the dose following both route of administration.

Faecal elimination has been confirmed as the main route in human mass balance study, in which most of 14C-risdiplam-related radioactivity was found in faeces (53.2%) followed by urine (28%).

Risdiplam has also been found to be excreted in milk of lactating female rats treated. Mean milk:plasma concentration ratios were between 1.21 and 3.50.

Pharmacokinetic drug interactions

In human hepatocytes, risdiplam or M1 did not exhibit significant ability to induce mRNA of cytochrome P450 isoforms. Similarly, risdiplam demonstrated low potential to cause direct inhibition of all CYPs isoforms. At the highest concentration tested, no significant reversible inhibition was detected for both risdiplam and M1, except for CYP3A4/5. Risdiplam tested up to 12.5 µM demonstrated low potential to cause direct inhibition of CYP3A4/5 and exhibited a maximal 28% and 55% inhibition for midazolam and testosterone as a substrate, respectively. An IC50 of 11 µM was estimated for inhibition of testosterone metabolism.

Risdiplam did not inhibit MDR1, OATP1B1, OATP1B3, OAT1 nor OAT3 when tested up to 50 µM, while displayed significant inhibition against OCT2, MATE1 and MATE2-K, with IC50 values of 8.72, 0.15 and 0.09 µM, respectively.

M1 did not displayed inhibition potential of human OATP1B1 or OATP1B3 when dosed at 50 µM, while at 2 µM M1 did not inhibit OAT1 and OCT2 but moderately inhibited MATE1 and MATE2-K by 26% and 47%, respectively. At 20 µM, RO7112063 inhibited the OAT1-, OCT2-, MATE1 and MATE2-K-mediated transport by 34, 45, 77 and 54%, respectively.

Regarding OCT2, MATE1 and MATE2-K, a 7-concentration follow-up inhibition assay was performed resulting in 34, 66 and 45% maximum inhibition at 20 µM, respectively. For the interaction with MATE1 an IC50 value of 14.8 µM was calculated.

In line with EMA guideline on DDI (2012) and according to the applicant, these results reveal a potential clinical perpetrator drug-drug-interaction risk involving MATE1 and MATE2-K for risdiplam. Therefore, the applicant is requested to amend section 4.5 of the SmPC in order to highlight that caution is advised in case of co-administration with substrates of these transporters, providing also examples of MATE1 and MATE2-k substrates potentially co-administered with risdiplam.

Distribution into melanin-containing parts of the eye (choroid + RPE, iris, sclera) was significantly

higher than in non-pigmented ocular structures (retina, lens, vitreous body) or the rest of the body (muscle, brain, CSF). The higher accumulation in melanin containing tissues is in line with the strong melanin binding observed *in vitro*. The elimination rate in pigmented tissues differed from the rest of the body and drug levels were still considerably high in the eye, especially in melanin-containing parts in both pigmented rats and monkeys after treatment-free periods. However, a clear decline and elimination could be observed. In toxicology studies, retinal degeneration occurred after prolonged dosing and whose mechanism is not fully understood. As the applicant reported, risdiplam is light sensitive, suggesting that risdiplam and/or M1 metabolite photodegradation products could be toxic to eye tissues. Risdiplam was subjected to *in vitro* phototoxicity evaluation in 3T3 fibroblasts utilizing the neutral red uptake assay, showing no phototoxicity. This study implicitly included the evaluation of any photodegradation products that were possibly generated from risdiplam under UV exposure conditions in the *in vitro* test. The existing *in vitro* study for phototoxicity as conducted in compliance with [ICH S10] is sufficient to conclude that there is no phototoxicity risk from risdiplam in clinical use. The location of the toxicity in the retina periphery is inconsistent with any UV related breakdown of risdiplam or its M1 metabolite, as the relevant spectrum of light does not reach the retina, in particular not the periphery of the retina. Therefore, the systemic distribution of risdiplam into the retina and its action at this site on the retinal pigment epithelium and photoreceptors is not envisaged to be dependent on UV exposure, and is considered to be associated with risdiplam itself (including any M1) but not related to photodegradation. In accordance, in clinical studies with risdiplam, comprehensive ophthalmological evaluations, which included examination of all melanin containing eyes structures (choroid, retinal pigment epithelium, iris, and sclera), as well as retinal imaging by optical coherence tomography (OCT), confirmed the absence of any findings suggestive of phototoxicity reactions in eye structures in 465 patients with spinal muscular atrophy (SMA) treated with risdiplam for up to 3 years [Sergott et al. 2020].

Toxicology

The nonclinical safety profile of risdiplam was assessed in a comprehensive toxicology programme. The intended pharmacological target, the SMN2 gene, exists only in humans, and thus a pharmacological responder species as requested by existing guidelines does not exist unless studies are conducted in transgenic mouse models. However, the use of the available transgenic mouse models of SMA for toxicity testing was not considered appropriate due to lack of availability in sufficiently large numbers, lack of suitable characterisation of relevant physiological parameters, difficulties in handling and treatment and the lack of comprehensive background information about physiology and pathology in these models.

Hence the relevance of the animal models was mainly judged on the basis of secondary mRNA splice targets occurring in animals and humans. FOXM1 and MADD were emerging from toxicity studies on a series of SMN2 splice modifiers as primary candidates for these secondary splice targets with toxicological implications. The monkey was considered to be a suitable and translational species for the safety assessment of risdiplam for use in humans due to the similar changes in splicing in secondary target genes upon treatment with risdiplam, as observed in SMA patient-derived fibroblasts, in stimulated monkey and human monocytes and iPSCs, and in monkey spleen tissue *in vivo*. The secondary splice targets were largely consistent with those published for another series of compounds enhancing the SMN2 exon 7-including variant [Palacino et al. 2015]. For at least one of the secondary splice targets identified for monkey and human cells, FOXM1, species differences exist between the primate (monkey and human) and the rat.

Mouse (carcinogenicity), rat (general toxicity, juvenile toxicity, reproductive toxicity, genotoxicity) and rabbit (reproductive toxicity) were used as well-established toxicology species for respective study types in small molecule drug development. However, its acknowledged that these species are non-

responders for the SMN2 splice modification. In contrast to the monkey, they also may not show off-target splicing events fully resembling those seen in human cells due to differences in exon/intron sequences and splice variants.

Metabolic profiling fully supported the toxicology species selection (Section 4.4).

Since treatment of SMA preferentially aims at babies and children, but also includes adults, the safety of risdiplam was investigated in both juvenile and adult animals.

The toxicology, safety pharmacology and secondary pharmacology programme for risdiplam included:

Results from the repeated dose toxicity identified toxicities with very low safety margins. It has been claimed by the applicant that the identified risks and respective low safety margins may be accepted based on the severity of the disease, limited alternative treatment options and lack of an increased sensitivity of patients towards the observed animal toxicities. Moreover, key toxicities observed in animals were declared to be either monitorable (epithelia, haematology) or could be mitigated with imposed contraception requirements (male germ cells, embryofoetal effects) in clinical studies.

A two-year carcinogenicity study in rats is planned to be conducted post-approval. This is acceptable and in agreement with feedback received from CHMP and PDCO. Reference to the ongoing carcinogenicity study in rats is presented in SmPC section 5.3.

Except for 3 non-pivotal studies, all the others were GLP compliant.

In relation to the data on fertility, further amendments were made to section 5.3 of the SmPC.

The juvenile rat studies reveal an increased sensitivity to risdiplam treatment in pre-weaning rats in comparison to older rats, resulting in high mortality rates observed at doses at or above 3.5 mg/kg/day (AUCs around 3000 ng·h/mL or above) within 2 to 7 days of initiation of treatment. It is proposed that the increased sensitivity is correlated to a higher free fraction and longer half-life of risdiplam in pre-weaning rats compared to older rats. However, it was unclear if also the toxicity profile of risdiplam is was different in pre-weaning rats. The applicant has provided further clarifications in relation to the observed sensitivity of pre-weaning rats. According to these clarifications, the causes of the deaths observed in the DRF finding study were not identified, as no or only very limited histopathology could be performed on the decedent neonates. Nevertheless, results from the limited histopathology revealed findings (toxicity profile) consistent with findings in the toxicity studies in older rats. The increased sensitivity of the neonate rats versus older rats can reasonably be attributed to a higher free fraction and longer half-life of risdiplam in pre-weaning rats compared to that in older animals. Such higher exposure levels are not relevant for the clinical use of risdiplam in the paediatric patient population, where the free fraction is comparable across all ages.

In the 4-week juvenile rat study , it is noted that minimal to mild nephroblastomatosis (a pre-neoplastic lesion) was observed in all test-item treated groups; one male at 0.75 mg/kg/day (low dose) and one male and one female at 1.5 mg/kg/day (intermediate dose), and two females at 2.5 mg/kg/day (high dose). After the 8-week recovery period, malignant nephroblastoma were present in the kidney of one female each at 1.5 mg/kg/day and 2.5 mg/kg/day. In the 13-week study, a malignant nephroblastoma was observed in one male at 7.5 mg/kg/day (high dose). The study reports concluded these findings as spontaneous in origin. As rat kidney neoplasms are uncommon and given the high risdiplam distribution to kidney and that the findings were only observed in risdiplam-treated animals, a further discussion on the relation to treatment and clinical relevance was requested.

After the applicant's response, it was still considered that it is not clear whether risdiplam could have had an impact on the maturation of spontaneously occurring nephroblastomatosis. The applicant has provided further clarifications on the significance of the nephroblastomatosis and nephroblastoma

observed in two juvenile rat studies [a 4-week study with treatment during PND4-31 and a 13-week study with treatment during PND22-112, respectively]).

According to the response, the 13-week study showed no evidence of effect, based on incidence. This study showed no nephroblastomatosis and the incidence of nephroblastoma (one male at 7.5 mg/kg/day) was in line with the historical control data.

As for the 4-week study, this showed incidences of nephroblastomatosis and nephroblastoma above the historical control data provided by the CRO. However, the same was not observed in a previous 4-week study with a comparable study design (only 2 dose groups instead of 3, but same size of groups) using similar dosage in Wistar rats dosed from PND4 to 31. Furthermore, there is no indication that risdiplam could affect genes mentioned as important in the context of nephroblastoma.

The CHMP considers that there is no need for further amendments to section 5.3 of the SmPC.

It may be concluded that the increased incidence of nephroblastomatosis and nephroblastoma observed in a 4-week study in juvenile rats does not represent a risk to patients. This finding was not reproduced in another study with identical study design. Furthermore, knowledge on the development of nephroblastomatosis and nephroblastoma, key genes known to be associated with development of nephroblastoma and evidence for lack of effects of risdiplam on these genes does not indicate that exposure to risdiplam may lead to the development of nephroblastomatosis and/or nephroblastoma.

The phototoxic properties of risdiplam were discussed in detail. In the 3T3 test using an UVA light source (315-690 nm), risdiplam was concluded as non-phototoxic up to the limit of solubility (9 µg/mL). It's agreed that risdiplam absorbs in the UV range and was not phototoxic *in vitro*. The study implicitly included the evaluation of any photodegradation products that were possibly generated from risdiplam under UV exposure conditions in the *in vitro* test. The existing *in vitro* study for phototoxicity as conducted in compliance with [ICH S10] could provide sufficient evidence to conclude that there is no phototoxicity risk arising from risdiplam.

2.3.6. Conclusion on the non-clinical aspects

The results of the nonclinical pharmacology, pharmacokinetic, and toxicology studies seem to support in general the use of risdiplam in clinical practice in patients with SMA. Exposure levels at the no observed adverse effect levels (NOAELs) of most nonclinical safety findings might be considered sufficient to elicit pharmacodynamic effects by increasing SMN protein levels. This has formed the basis for studying the efficacy of risdiplam at the doses used in pivotal clinical studies in SMA patients of all ages and severity types of the disease.

Risdiplam unlikely represents a risk for the environment. However, the log Kow values were calculated using the HPLC method that covers log Kow(s) in the range of 0-6 and may not be reliable enough for risdiplam. The applicant must commit to submitting the results of the shake-flask test by the end of April 2021.

The CHMP considers the following measures necessary to address the identified non-clinical issues:

- a two-year carcinogenicity study in rats is planned to be conducted as a post-approval commitment.
- accomplishment of the shake-flask test according to OECD 107 that should be available by the end of April 2021

2.4. Clinical aspects

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- ***Tabular overview of clinical studies***

The PK characteristics of risdiplam were assessed in 5 studies in healthy adult subjects by non-compartmental analysis (NCA), and via the Population Pharmacokinetic (PPK) approach in infantile-onset (Type 1) SMA infants aged 2.2-6.9 months at study enrolment) in Study BP39056 (FIREFISH), in later-onset (Type 2 and 3) SMA patients aged 2-25 years in BP39055 (SUNFISH), and in non-naïve SMA patients 1-60 years old in Study BP39054. An overview of all clinical studies conducted with risdiplam in healthy subjects and in patients with SMA are provided in the Tables below.

Table 4: Overview of Clinical Studies with Risdiplam in Healthy Subjects

Study No.	Objectives	Study Design	Population	No. Subjects	Dose, Route, Regimen
BP29840 (completed)	Entry-into-Human study Part 1: Safety, tolerability, PK and PD of single ascending doses of risdiplam Part 2: Food effect Part 3: Itraconazole interaction	Part 1: Single-centre, randomised, double-blind, placebo-controlled, single ascending dose study Part 2: Food effect (not conducted; food effect investigated in Part 1) Part 3: Single-centre, open-label, one-sequence, two-period crossover study	Healthy male subjects, age 18-45 years	Part 1: 25 (18 active, 7 placebo) Part 3: 8	Part 1: single oral doses of 0.6, 2, 6, 18 mg risdiplam or placebo Part 3: single oral doses of 6 mg risdiplam alone or in combination with 200 mg bid itraconazole (Day 1 to Day 8)
BP39122 (completed)	Mass balance study (absorption, distribution, metabolism, excretion)	Single centre, open-label, non-randomised	Healthy male subjects, age 35-65 years	6	Single oral dose of 18 mg [^{14}C]-labelled risdiplam
NP39625 (completed)	Safety, tolerability, PK and PD of risdiplam in Japanese subjects	Double-blind, randomised, placebo-controlled, single ascending dose study	Healthy Japanese subjects, age 18-60 years	24 (18 active, 6 placebo)	Single oral dose of 2, 6, 12 mg risdiplam or placebo
BP40995 (completed)	Effect of hepatic impairment on the PK and safety of risdiplam	Multicentre, open-label, non-randomised, parallel-group study	Healthy adult subjects; mild and moderately hepatic impaired subjects	10 healthy subjects; 16 hepatic impaired subjects (8 mild, 8 moderate)	Single oral dose of risdiplam 5 mg
BP41361 (completed)	Drug-drug interaction study with CYP3A substrate midazolam	Open-label, non-randomised, 2-part study	Healthy adult subjects, age 18-55 years	35	5 mg risdiplam (first part) and 8 mg risdiplam (second part) once daily for 2 weeks; midazolam 2 mg single dose on 2 occasions

Table 5: **Overview of Clinical Studies with Risdiplam in Patients with SMA**

Study No.	Objectives	Study Design	Population	No. Patients	Dose, Route, Regimen
BP39056 FIREFISH (ongoing) pivotal Phase 2/3 study	Part 1: Safety, tolerability, PK, PD, dose selection for Part 2 Part 2: Efficacy, safety and tolerability, PK, PD	Seamless [1], multicentre, two-part study Part 1: Open-label dose-escalation phase with a 24-month treatment period, followed by an open-label extension (OLE) Part 2: Open-label single-arm study with a 24-month treatment period, followed by an OLE	Infants with Type 1 SMA; age 1-7 months at enrolment	Part 1: 21 patients Part 2: 41 patients	Once daily oral administration Part 1: 0.00106 mg/kg single dose; 0.0106, 0.04, 0.08, 0.2, 0.25 mg/kg once daily. Part 2 starting dose at enrolment: 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.
BP39055 SUNFISH (ongoing) pivotal Phase 2/3 study	Part 1: Safety, tolerability, PK, PD, dose selection for Part 2 Part 2: Efficacy, safety and tolerability, PK, PD	Seamless [1], two-part randomised, multicentre, placebo-controlled, double-blind study Part 1: double-blind, randomised (2:1), placebo controlled, exploratory dose finding phase, followed by open label phase up to 24 months, and an OLE Part 2: double-blind, randomised (2:1), placebo controlled, parallel group treatment period, followed by an OLE	Part 1: Type 2 and Type 3 SMA (ambulant and non-ambulant) Part 2: Type 2 and non-ambulant Type 3 SMA patients; age 2–25 years	Part 1: 51 patients in 2 age groups, 2–11 years (n = 31) and 12–25 years (n = 20) Part 2: 180 patients age 2–25 years	Once daily oral administration Part 1: placebo; 3 and 5 mg; 0.02, 0.05, 0.15 and 0.25 mg/kg; Part 2: 0.25 mg/kg for patients with BW <20 kg, 5 mg for patients with BW ≥20 kg; placebo
BP39054 JEWELFISH, (ongoing)	Safety, tolerability, PK, PD	Multicentre, open-label, non-comparative; patients previously enrolled in BP29420 or treated with nusinersen, AVXS-101 or olesoxime	Type 1, 2 or 3 SMA patients age 6 months to 60 years	174 patients	Once daily oral administration age 2–60 years: 5 mg for patients with BW ≥20 kg and 0.25 mg/kg for patients with BW<20 kg; age 6 months to <2 years: 0.2 mg/kg

- **Table 5: Overview of Clinical Studies with Risdiplam in Patients with SMA (cont.)**

Study No.	Objectives	Study Design	Population	No. Patients	Dose, Route, Regimen
BN40703 RAINBOWFISH (ongoing) supportive Phase 2 study	Efficacy, safety and tolerability, PK, PD	Open-label, single-arm, multicentre 24-month treatment period plus extension phase	Asymptomatic infants (age from birth to 6 weeks), genetically diagnosed with SMA (10 patients with 2 copies of *SMN2* gene and CMAP ≥1.5 mV)	Up to 25 infants planned (12 enrolled by 25 Feb 21t)	Once daily oral administration at a dose selected to achieve the target exposure of mean $AUC_{0\text{-}24h,ss}$ ≤2000 ng.h/mL; all infants receive currently a dose of 0.2 mg/kg

$AUC_{0\text{-}24h,ss}$ = area under the concentration-time curve from time zero to 24 h at steady state; BW=body weight; CMAP=compound muscle action potential; OLE=open-label extension; PD=pharmacodynamics; PK=pharmacokinetics; SMA=spinal muscular atrophy.

[1] Operationally seamless in some countries.

The risdiplam clinical development programme is a comprehensive series of studies, designed to confirm the clinical benefit of risdiplam for patients with both infantile- and later-onset SMA. According to the Clinical Overview, at the time of submission, the risdiplam clinical programme is the largest clinical development programme conducted for SMA. The breadth and scope of the overall population included in these trials support the proposed broad indication for risdiplam for the treatment of SMA.

- ***Analytical methods***

Risdiplam and its main M1 metabolite's concentrations were determined both alone) and all together in human plasma through validated LC MS/MS methods. Risdiplam alone was also determined in urine samples through a LC MS/MS method . For both plasma and urine analytical methods, preventive measures described in the Validation Report and in the mentioned Bioanalytical Reports were correctly applied to mitigate the impact of carry-over for RO7034067.

Since different methods were used to determine the same analytes and different laboratories were involved in the analyses, a cross-validation was consequently performed . As risdiplam is sensitive to light and M1 is sensitive both to light and oxidation in solution, ascorbic acid was added as a stabilizer and the sample analysis was handled under light protection and cold conditions.

Fully validated LC MS/MS methods were also used to determine risdiplam together with diazepam , diazepam + M1 and quinidine . Same methodology was used to determine itraconazole + its metabolites) and midazolam + its metabolites).

Four liquid scintillation counting (LSC) methods were developed to quantify 14C radioactivity in human plasma, whole blood, urine and faeces samples.

Protein binding was investigated in human plasma using the equilibrium dialysis method with diazepam or quinidine as control compound. Diazepam, quinidine and risdiplam were determined using validated LC-MS/MS methods .

Clinical genotyping for the determination of SMN1 and SMN2 copy numbers was determined either by digital polymerase chain reaction (PCR) or by the SMA Plus test .

Expression of SMN1, SMN2 full length, and SMNΔ7 (SMN2 mRNA with exon 7 missing) mRNA was measured using a quantitative reverse transcription multiplex PCR method, To determine SMN protein in human whole blood, a prototype assay was developed and validated.

Evaluation and Qualification of Models

Population Pharmacokinetics Model

A PopPK model was initially developed on a total of 3,478 PK observations from venous and capillary blood samples from 151 SMA patients and healthy volunteers available, from the four clinical studies BP29840, BP39054 (JEWELFISH), BP39055 (SUNFISH) Part 1, and BP39056 (FIREFISH) Part 1 and Part 2.The initial population PK model was then applied to the new data set pooled from 5 clinical studies, i.e. BP29840, BP39054, BP39055, BP39056 and BP41361. Upon evaluation and confirmation of the reference model as the base model to the new dataset, covariate analysis was performed.

The final selected PopPK model is based on a structural model consisting of three transit-compartments absorption connected to a systemic linear two-compartmental PK model. The model included as covariates the time-varying body weight effect described by allometry model on CL/F and Q/F with a shared estimated exponent, and on Vc/F and Vp/F with a shared estimated exponent; a time-varying age effect as a maturation function with sigmoidal model structure on CL/F and Vc/F, and the effect of healthy subject on CL/F. The model incorporated IIV on CL/F, Vc/F, and ktr as independent random effects and separate proportional residual errors on plasma and capillary blood samples.

The parameter estimates summarised in the Table below show that the parameters were estimated with good precision indicated by the relative standard error being less than20% except for Vp/F and Age50-Vc/F (25.9% and 21.1%, respectively). The 95% CIs were comparable between the estimates by the covariance matrix and the bootstrap analysis, and the intervals of each parameter estimates were considered reasonable.

Degree of η-shrinkage were 5.43, 22.9 and 10.1% for CL/F, ktr and Vc/F, respectively, indicating that the analyses with post-hoc parameters and estimation of individual secondary PK parameters such as AUC and C_{av} could be reliably performed. The shrinkage for residual errors were 5.58 and 2.46% for venous and capillary blood samples, respectively. The condition number was low (40.4) and none of the parameters estimated showed high correlations (>0.9) with the others.

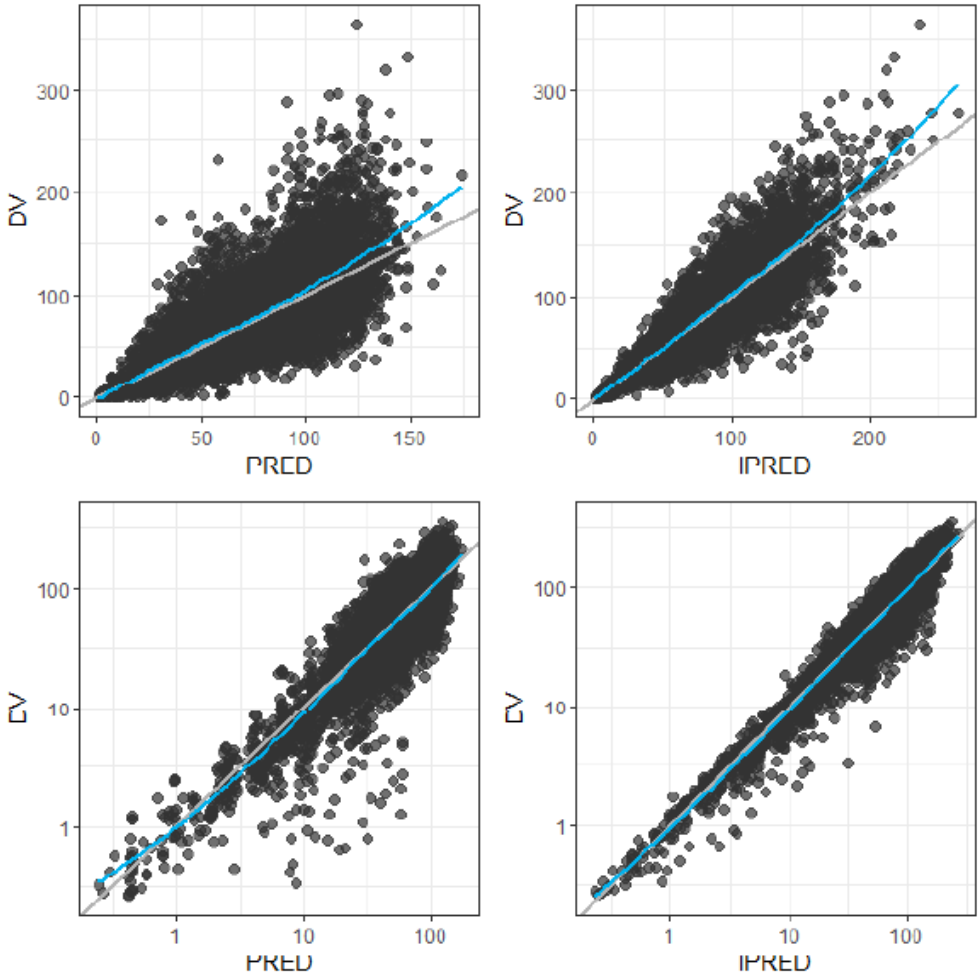
Table 6: Summary of the Final PopPK Model Parameters

Parameter	Unit	Estimate	RSE (%)	95% CI	95% CI (bootstrap)*
Fixed Effects					
CL/F	L/h	2.64	2.13	2.53-2.75	2.52 – 2.76
ktr	/h	5.18	2.74	4.9-5.45	4.84 – 5.52
Vc/F	L	98.0	1.80	94.5-101	93.8 – 103
Q/F	L/h	0.682	10.5	0.541-0.822	0.589 – 1.50
Vp/F	L	92.9	25.8	45.8-140	49.6 – 133
Covariate Effects					
Effect of WT on CL/F and Q/F		0.276	11.8	0.212-0.34	0.167 – 0.341
Effect of WT on Vc/F and Vp/F		0.860	3.34	0.803-0.916	0.792 – 0.915
Age_{50} – CL/F	y	0.877	17.1	0.583-1.17	0.640 – 1.26
Age_{50} – Vc/F	y	0.322	21.1	0.189-0.455	0.226 – 0.653
Healthy subjects on CL/F	fraction	0.524	13.1	0.389-0.659	0.392 – 0.751
Random Effects					
CL/F (CV)		0.0678 (26.0%)	8.21	0.0568-0.0787	0.0574 – 0.0810
ktr (CV)		0.272 (52.2%)	11.4	0.211-0.333	0.211 – 0.329
Vc/F (CV)		0.0651 (25.5%)	8.85	0.0538-0.0764	0.0535 – 0.0790
Error Model					
σ_1 proportional - venous (CV)		0.0546 (23.4%)	3.17	0.0512-0.058	0.0512 – 0.0575
σ_2 proportional – capillary (CV)		0.117 (34.2%)	15.7	0.0808-0.153	0.0842 – 0.167
OFV = 64499					

OFV = objective function, RSE = relative standard error of estimate; CV = coefficient of variation; WT = body weight. *derived by a bootstrap with 200 estimations (87.5% converged)

The GOFs in the Figure below show good consistency between DV and PRED, as well as IPRED which mostly displayed a homogenous distribution of data points around the identity line.

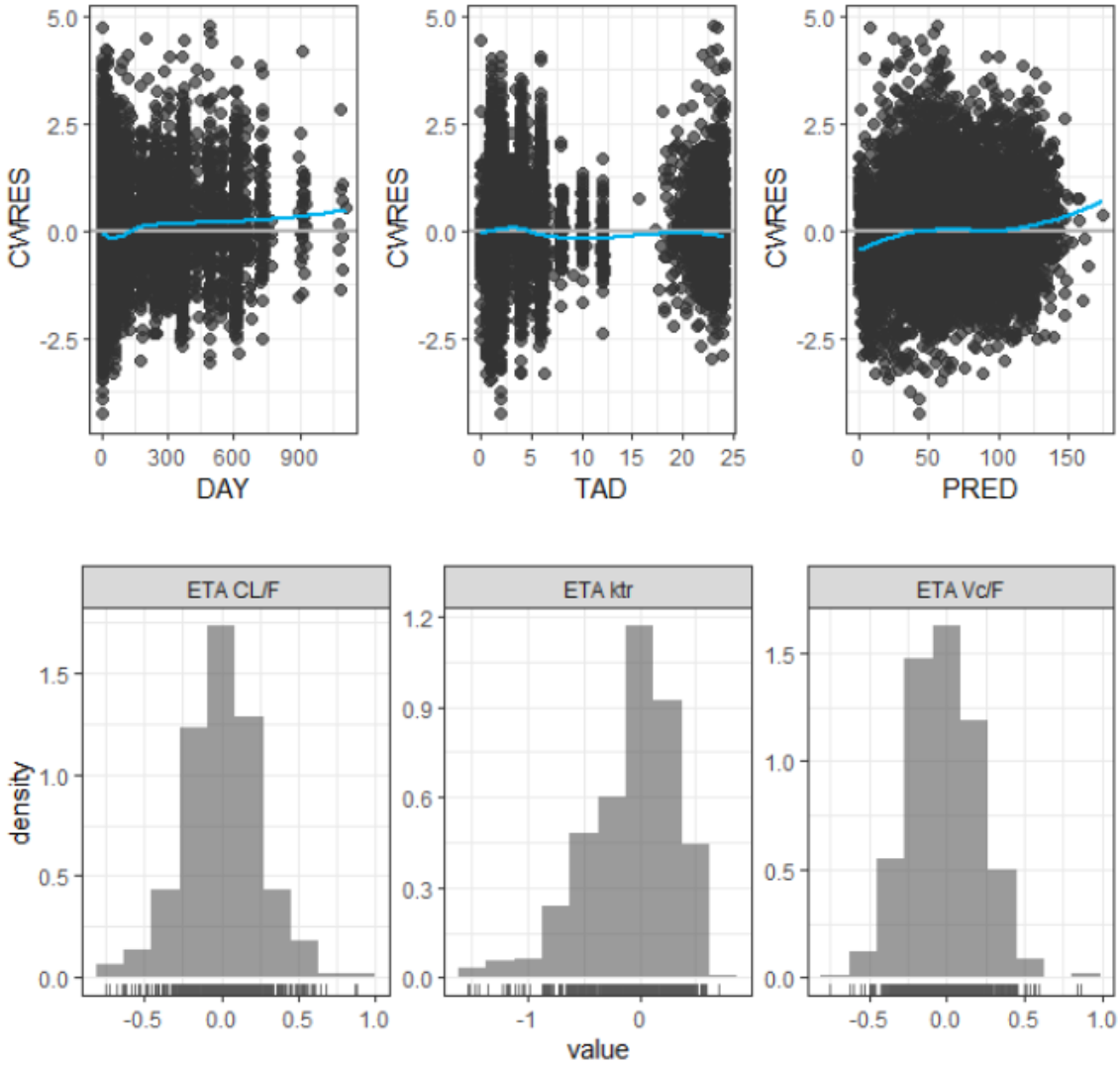
Figure 2- Goodness-of-Fit Plots for the Final PK model of Risdiplam



DV – Observed risdiplam concentrations [ng/mL], PRED (IPRED) – NONMEM predicted risdiplam concentrations [ng/mL] based on population (individual) PK parameters. Grey and blue lines indicate identity line and smooth, respectively

The distribution of CWRES shown in the Figure below were randomly scattered around the zero line with the majority of data between -2.5 and +2.5 standard deviations against time or population predictions. The inter-individual variability (IIV) of CL/F, ktr and Vc/F were generally normally distributed.

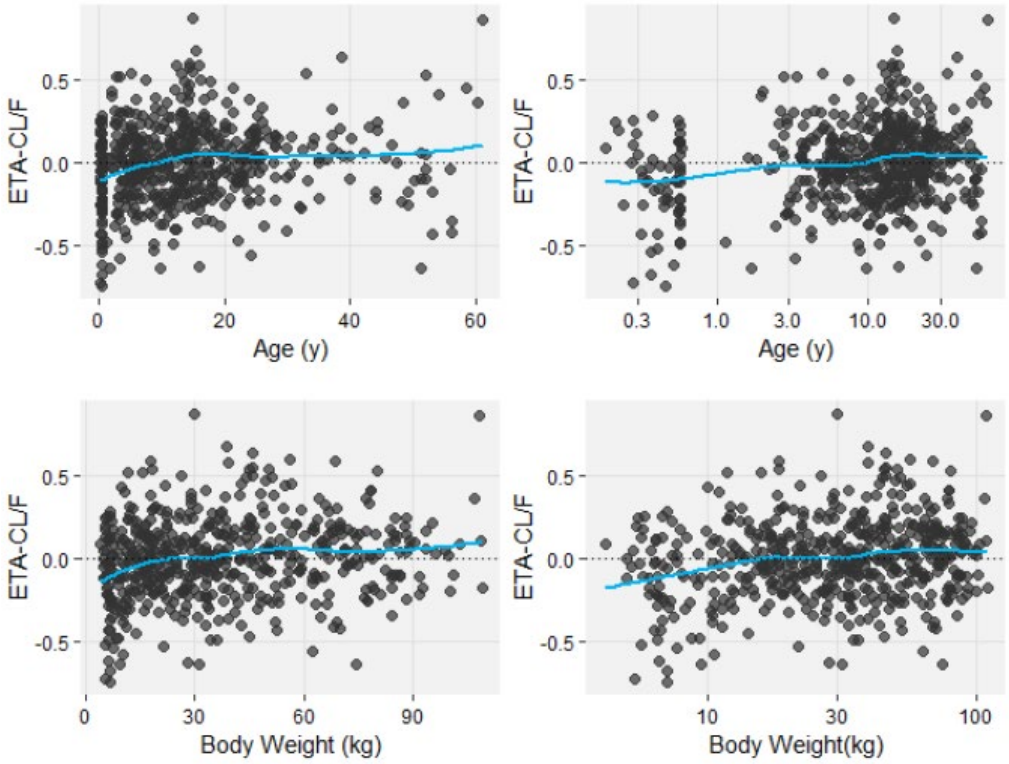
Figure 3 - Goodness-of-Fit Plots for the Final PK model of Risdiplam – II



DAY – days after the first drug intake, TAD – time after the last drug intake (h), CWRES – Conditional weighted residual values. Blue lines indicate smooth.

The role of allometric and maturation functions in description of risdiplam CL/F of the final model is illustrated in the Figure below. Both allometric and maturation functions are required to capture risdiplam CL/F across the age and body weight range. The distribution of ETA-CL/F against age and body weight (Figure below) showed slightly lower values in children < 1 y or with body weight < 10 kg.

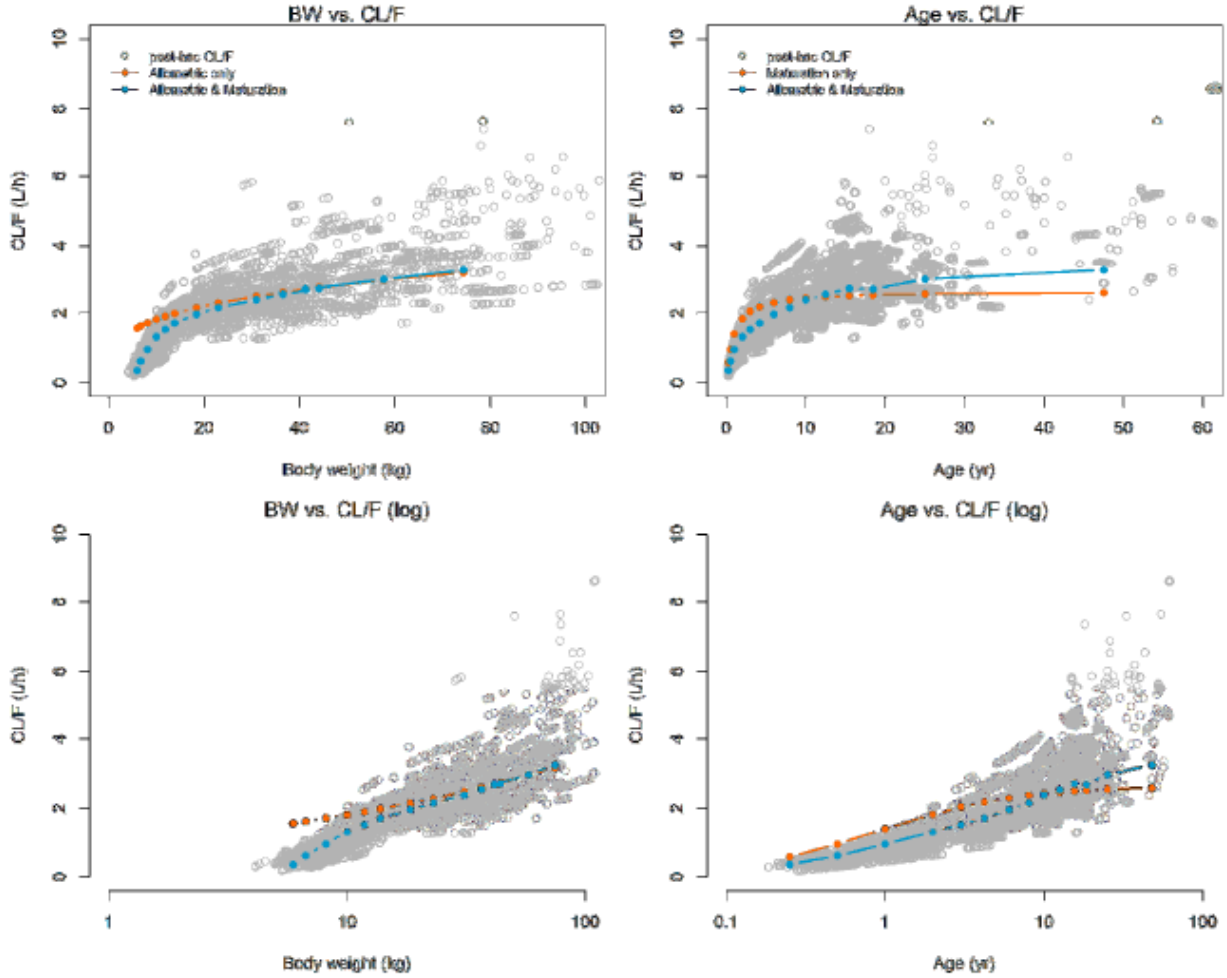
Figure 4 - Distribution of ETA-CL/F against Age and Body Weight



Blue lines indicate smooth

Additional investigations with estimations of separate CL/F for these children < 1 y or with body weight <10 kg however, did not show improvement.

Figure 5- The Role of Time-Varying Age (Maturation Function) and -Body Weight (Allometric Function) as Covariate on Description of Risdiplam CL/F



The pc-VPC with time after the first and the last doses are shown in Figures below, respectively. Although slight under prediction of 2.5th percentile was shown, the median and 97.5th percentile were in a good agreement with the observations.

Figure 6- Prediction Corrected Visual Predictive Check (All Populations) of the Final PK Model of Risdiplam

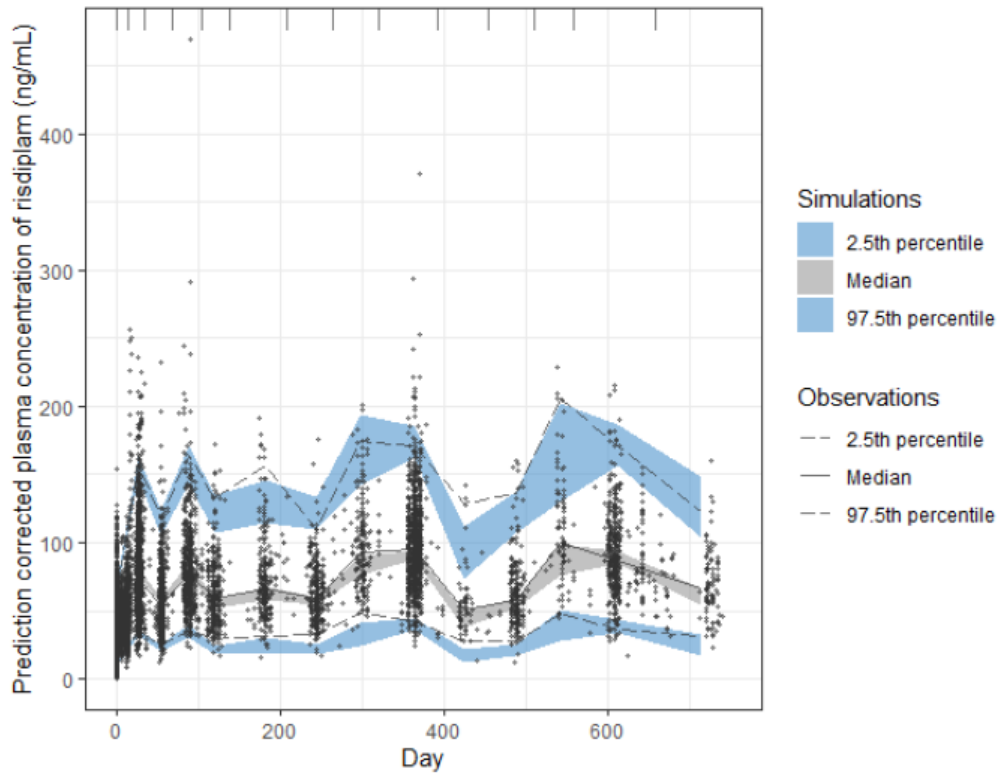
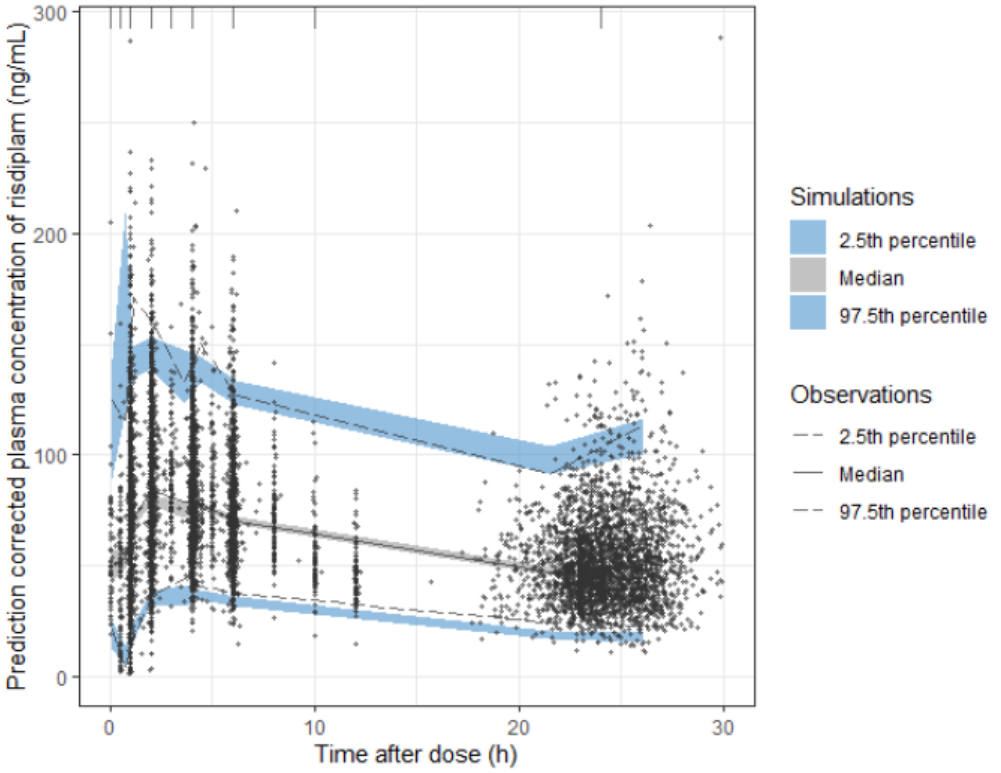


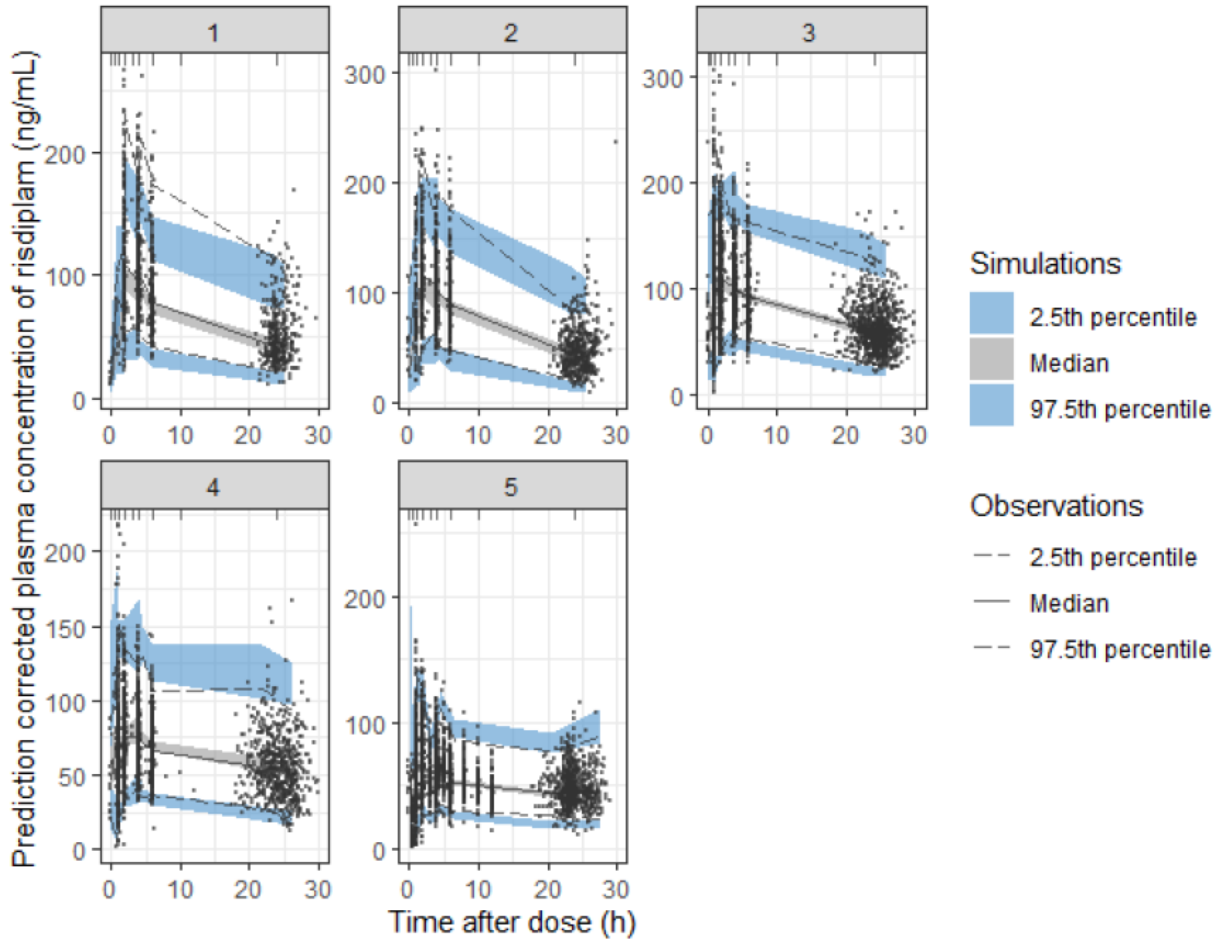
Figure 7- Prediction Corrected Visual Predictive Check (All Populations) of the Final PK Model of Risdiplam with Time After Dose



The pc-VPC with time after the last dose stratified by age (Figure below) showed consistent median between the predictions and observations in all age groups. Although minor deviations were seen in 2.5th or 97.5th percentiles in some of the time points, the observations were mostly within the respective confidence interval and prediction of central tendency and variability was considered acceptable.

Based on the pc-VPCs, the predictive performance of the final PK model of risdiplam was considered satisfactory.

Figure 8- Prediction Corrected Visual Predictive Check (All Populations) of the Final PK Model of Risdiplam with Time After Dose (by Age Groups)



The age groups are 1 (infants): Age < 1 y, 2 (toddlers): 1 y ≤Age<4 y, 3 (children): 4 y ≤Age< 12 y, 4 (adolescents):12 y ≤Age≤18 y, 5 (adults): Age> 18 y

2.4.1. Pharmacokinetics

Absorption

Study BP29840 enabled to characterize appropriately the absorption and disposition of risdiplam after single ascending oral doses, from 0.6 mg to 18 mg, in healthy subjects, based on the pharmacokinetic profiles derived from 19 venous blood samples, collected at pre-dose and at 0.50, 1.00, 2.00, 3.00, 4.00, 4.50, 5.00, 6.00, 8.00, 10.00, 12.00, 24.00, 36.00, 48.00, 72.00, 96.00, 144.00 and 216.00 h post dose. Urine samples were also collected at pre-dose and for the following intervals: 0-6h, 6-12h, 12-24h, 24-48h and 48-72h.

The ascending doses were stopped at 18 mg, with a mean exposure of 1310 h.ng/mL derived for AUC_{0-24h}. None of the 6 subjects dosed with 18 mg (cohorts 4 and 6) showed AUC_{0-24h} values above 1500 h.ng/mL (the range was 1210 to 1470 h.ng/mL), as the pre-specified individual exposure cap for the parameter based on the findings in the animal toxicology studies.

Risdiplam showed to be rapidly absorbed, as first quantifiable concentrations observed for all subjects occurred between 0.5 and 1.0 hour post-dose, and for all administered doses. Median Tmax values were derived as between 2.0 and 3.0 hours (ranging from 1.0 to 4.50 hours) post-dose. In a closer observation of the mean pharmacokinetic profiles until 24h, double peaks are seen at 4h and 10h, corresponding to the time of meals.

A linear and dose proportional increase in Cmax and AUC was observed.

The performed mass balance study also showed a rapid absorption of [14C/12C]-RO7034067, with measurable radioactivity in plasma in all subjects at the first sampling time point at 0.5 hour post-dose (and at 1 hour post-dose for all subjects in blood). The mean Cmax and AUC0-inf obtained for [14C/12C]-RO7034067 radioactivity were similar to the mean values obtained in SAD study BP29840. However, the variability (CV%) was higher.

Characterisation of risdiplam pharmacokinetics on the mass balance study was achieved by the collection of venous blood samples during the study for the quantification of radioactivity in plasma at the following time points: pre-dose and at 0.5, 1, 2, 3, 4, 4.5, 5, 5.5, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 288, 312, 336, 360, 384, 408, 432, 456, 480, and 504 h post dose, corresponding to 22 days of blood sampling. Urine and faeces were also quantitatively collected at the following time intervals: 0-24h, 24-48h, 48-72h, 72-96h, 96-120h, 120-144h, 144-168h, 168-192h, 192-216h, 216-240h, 240-264h, 264-288h, 288-312h, 312-336h, 336-360h, 360-384h, 384-408h, 408-432h, 432-456h, 456-480h, 480-504h, and then every 24h from day 22 to day 36.

The performed study NP39625 also showed for the Japanese population a rapid absorption of risdiplam and similar dose normalised exposure to the Caucasian population selected in study BP29840.

The proposed wording for Section 5.2 (Absorption) of the SmPC is in line with the observed PK data. Moreover, the SmPC proposes patients do drink water after taking Evrysdi, to ensure the drug has been completely swallowed.

No relative or absolute bioavailability studies have been conducted. However, the applicant expects a close to complete absorption of risdiplam from the oral dose. Based on mass balance data, *in vitro* metabolism data and PBPK and popPK modelling, the bioavailability of risdiplam is expected to be high (>0.8).

Risdiplam is to be administered as an oral solution. The to-be-marketed formulation is identical to the formulation used in the pivotal clinical studies, and therefore no bioequivalence study is required. The formulations used in the exploratory Part 1 and pivotal Part 2 of the Phase II clinical studies are almost identical solutions (except for isomalt), and therefore no comparative bioavailability study was necessary during the drug development phases.

Based on the summary of results obtained for the investigation of a potential food effect on study BP29840 (Part I) performed with healthy subjects, intake of a high-calorie, high-fat breakfast had no relevant effect on the PK of risdiplam at a dose of 6 mg (F01 formulation). However, conclusion is made by comparing two cohorts with a limited number of subjects (n=3). No other dedicated food effect study was performed.

In studies with SMA patients (BP39056 (FIREFISH), BP39055 (SUNFISH) and BP39054 (JEWELFISH)), study medication was taken once daily in the morning with the patient's regular morning meal, except when site visits were planned and study medication was administered at the clinical site.

Only a limited available data for a food effect conclusion (derived from Study BP29840) is available. The clinical studies in SMA patients were conducted with the recommendation to take risdiplam with the morning meal. Therefore, the applicant proposes to update the SmPC to indicate that risdiplam shall be taken with a meal, as done during the clinical studies.

Distribution

From *in vitro* studies, it was concluded for risdiplam an average fraction unbound value of 11% in human, with the drug being predominantly bound to serum albumin. Moreover, no age dependency on protein binding was detected. An *in vitro* blood-to-plasma ratio of 1.3 was also derived. From the mass balance study, the blood-to-plasma ratio ranged between 0.691 to 0.925, over all time points for which this blood-to-plasma ratio could be calculated (1 hour to 120 hours post-dose), with a mean of 0.822. By individual, the blood-to-plasma ratio showed a mean range of 0.808 to 0.910 along time. Differences found between *in vitro* and *in vivo* data for Blood-to-Plasma partitioning were justified by the applicant by the use of different methods. B/P ratio is mostly between 0.8 and 1.0 (0.87±0.07).

The apparent volume of distribution (V/F) was derived from SAD study (BP29840) for the different doses (0.6 to 18 mg). The volume of distribution showed to increase with dose, from 247 L (0.6 mg) to 542 L (18 mg). The mean elimination half-life has also increased with the dose, from 25h (0.6 mg) to 69h (18 mg).

The differences in estimates for the apparent volume of distribution (V/F) and for the mean elimination half-life derived for the 0.6 mg and 18 mg dose administered in SAD study were justified to be related to the low number of subjects per dose cohort. Consequently, these results should be seen with caution.

The proposed wording for Section 5.2 (Distribution) of the SmPC is in line with estimates from *in vitro* and population pharmacokinetics modelling.

Elimination

Based on results of metabolic characterisation, approximately 8% of risdiplam dose is renally excreted as unchanged form. A low renal excretion is in accordance to the results from SAD study, where a mean of approximately 4% was derived for the fraction excreted parameter, for all doses (0.6 to 18 mg). Renal clearance was approximately estimated as 325 mL/h for all doses (range 316 to 333 mL/h) (see table below). In the SAD study, the apparent terminal elimination half-life of RO7034067 was 40.1 to 68.7 hours from 2 to 18 mg.

Assuming a free fraction in human plasma 10.7% for risdiplam the expected filtration clearance is approximately 13.4 mL/min (assuming GFR=125 mL/min). For a renal clearance of 5.42 mL/min (or 325 mL/h), risdiplam could be, apparently, renally reabsorbed. Nevertheless, no data from in-vitro or in animals experiments indicate a renal reabsorption of risdiplam:

- As risdiplam molecule (pKa1 = 3.78 (base), pKa2 = 6.62 (base)) is expected to be ionised in urine, it makes its resorption unlikely.
- *In vitro* (transport) and animals data did not indicate renal reabsorption of risdiplam. In the multiple dose study performed with healthy subjects (Study BP41361, the mean elimination half-life derived on steady state for the 5 mg QD regimen was 37.1h (CV 17.2%, range 28.9h to 46.6h) and for the 8 mg QD regimen was 41.1h (CV 15.9%, range 30.5h to 53.8h).

Population PK analyses estimated in the final model an apparent clearance (CL/F) of 2.61 L/h for risdiplam. Based on study BP39055 (SUNFISH) PopPK analysis, for the total of 117 SMA patients (type 2 and type 3), with ages ranging from 3.2 to 26.4 years, the elimination half-life was estimated with a median of 51h (ranging from 25.4 to 107h).

The proposed wording for Section 5.2 (Elimination) of the SmPC is in line with results from the popPK analysis, i.e. «Population PK analyses estimated an apparent clearance (CL/F) of 2.6 L/h for risdiplam. The effective half-life of risdiplam was approximately 50 hours in SMA patients.

Metabolism

Risdiplam was relatively metabolically stable in incubations with human liver microsomes and hepatocytes, with ≥89% and ≥98% of parent drug recovered unchanged after incubation, respectively.

The main site of biotransformation was the piperazine moiety. The N-hydroxy metabolite M1 was identified in liver microsomes and hepatocyte samples of all species. All other metabolites were formed in the liver microsomes and hepatocytes of at least 3 species. No additional major metabolites were observed following incubation with microsomes and hepatocytes from other species.

In *in vitro* metabolism studies with recombinantly expressed human enzymes incubations of unlabelled and 14C-risdiplam with recombinant human CYP and FMO enzymes have shown that risdiplam can be metabolised by both FMO1 and FMO3, and minimally by CYPs 1A1, 2J2, 3A4, and 3A7. Multiple oxidative metabolism products were generated by each of the enzymes, with FMO enzymes favouring the N-oxidation pathway to generate M1. M1 can be generated by both FMO1 and FMO3 as well as CYPs 1A1, 2J2, and 3A enzymes.

The metabolic pathway of risdiplam in humans was proposed on the basis of the results from *in vitro* metabolism studies using human hepatocytes, human liver microsomes, microsomes expressing human CYP isoforms and the results from the mass balance study. Parent drug was the main drug-related component in plasma (accounting for 83% of drug-related material in circulation as percent of AUC0-48h) and excreta (urine and faeces). The main site of biotransformation was the piperazine moiety. M1 (N-hydroxy metabolite) accounted for 14% of total radioactivity (percent AUC0-48) in plasma; it was excreted in urine. Additional low-level metabolites (M2, M7 and M26), all resulting from biotransformation of the piperazine moiety were observed in plasma. M5, M7 (both resulting from biotransformation of the piperazine moiety), M10 (carboxylic acid metabolite) and M18 (sulphate conjugate) were the most abundant metabolites in faeces. M7 was the most abundant metabolite in urine.

The metabolic characterisation is presented in the Table below.

Table 7: Summary of metabolic characterisation. Values are presented as % of radioactive dose

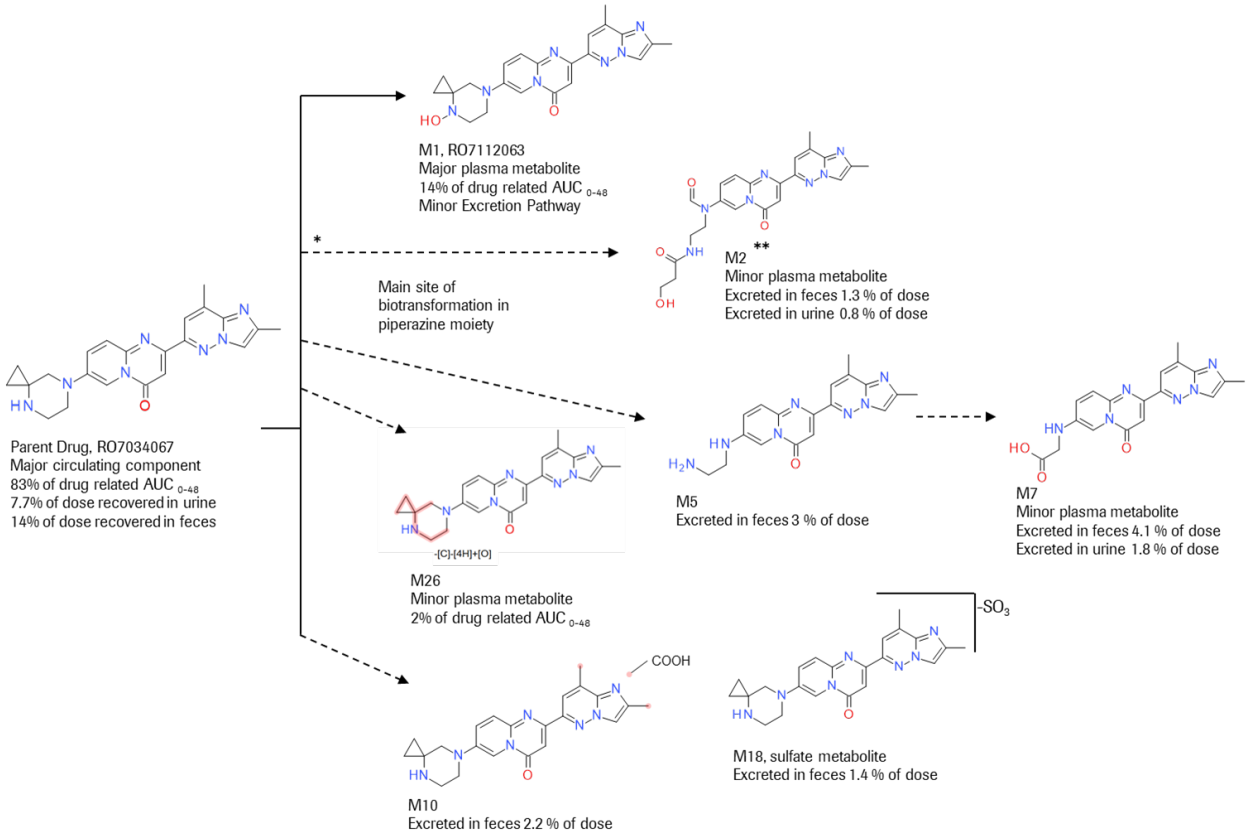
	Parent	M5	M7	M10	M18	Minor Metabolites	Other minor metabolites + Trace levels	Total metabolite
Faeces	14%	3%	4.1%	2.2%	1.4%	9.6%	8%	28.3%
Urine	7.7%	0.4%	1.8%	Not detected	Not detected	4.9%	7.7%	14.8%

A concern on the use truncated AUC_{0-48h} for conclusions instead of AUC_{0-inf} was raised, given the expected risdiplam elimination half-life (approximately 50h). However, based on applicant's analysis, the metabolite identification at the truncated area under the concentration-time curve from Time 0 to 48 hours (AUC_{0-48}) in the human absorption, distribution, metabolism and excretion (hADME) study is considered representative of AUC_{inf}, considering that nonclinical and clinical PK data, as well as safety data, do not suggest a potential different metabolite profile in plasma beyond 48 h post-dose.

Moreover, the applicant has additionally performed an exploratory metabolite identification on selected plasma samples from HVs dosed with a single dose of 18 mg risdiplam (single ascending dose [SAD] study - BP29840) in order to identify the major circulating drug-related material. The exploratory metabolite identification data up to 216 h post dose in the SAD study, from a representative individual, increases the confidence that the metabolite identification at truncated AUC_{0-48} in the hADME study is representative of AUC_{inf}. It was concluded that the gap due to the limited analytical sensitivity of the radio profiling method resulting in remaining unexplained radioactivity is distributed to a number of minor metabolites, as it was indicated by the more sensitive MS-based analysis using plasma samples from the SAD study. Based on this exploratory analysis, it was not identified any persistent metabolite with a significantly longer $t_{1/2}$ than unchanged risdiplam up to 216 h.

The proposed human metabolic pathway is displayed in the Figure below.

Figure 9



The proposed wording for Section 5.2 (Elimination) of the SmPC is in line with data from *in vitro* metabolism studies, mass balance study and pharmacology (PD) study:

« Risdiplam is primarily metabolised by flavin monooxygenase 1 and 3 (FMO1 and FMO3), and also by CYPs 1A1, 2J2, 3A4 and 3A7.

Approximately 53% of the dose (14% unchanged risdiplam) was excreted in the feces and 28% in urine (8% unchanged risdiplam). Parent drug was the major component found in plasma, accounting for 83% of drug related material in circulation. The pharmacologically inactive metabolite M1 was identified as the major circulating metabolite.».

According to the GL on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1), in general, enzymes involved in metabolic pathways estimated to contribute to ≥ 25% of drug elimination should be identified if possible and the *in vivo* contribution quantified. This applies to cytochrome P450 (CYP) enzymes and non-CYP enzymes.

In the mass balance study, the parent drug was the major component found in plasma, accounting for 83% of drug-related material in circulation (percent of AUC_{0-48h}). The pharmacologically inactive metabolite M1 (N-oxidation of risdiplam) was identified as the major circulating metabolite and represented 14% of drug-related AUC_{0-48h}. Four additional low level metabolites (M2, M7, M9 and M26) were observed in plasma. Relative to the AUC of total drug-related material in plasma, no individual metabolite accounted for more than 2.2%.

In the multiple dose study, the applicant has characterised the pharmacokinetic of metabolite M1, showing a metabolite ratio that ranged from 0.188 to 0.303 for AUC_{0-24h} and from 0.160 to 0.233 for C_{max}. The study design enabled to well characterize the pharmacokinetics of metabolite M1, which presents a similar elimination half-life as the parent compound.

Despite a polymorphism is described for FMO enzymes [Hisamuddin et al, Pharmacogenomics, 8(6), 635–643], it will have no impact on the elimination of risdiplam, as M1 presents a low contribution (<25%) for the elimination of the drug.

Dose Proportionality and time-dependency

Based on results from SAD study, the dose proportionality was assessed across risdiplam doses by PK assessor, using the power model as described by Smith et al. [Pharm Res. 2000 Oct;17(10):1278-83] on log-normalised AUC_{0-t} and C_{max} values (Figures below). Peak plasma concentrations (C_{max}) and overall plasma exposure (AUC_{Inf}) increased in a dose-proportional fashion over the investigated dose range of risdiplam, after a single dose administration.

Figure 10– Risdiplam dose proportionality for C_{max} after single dose

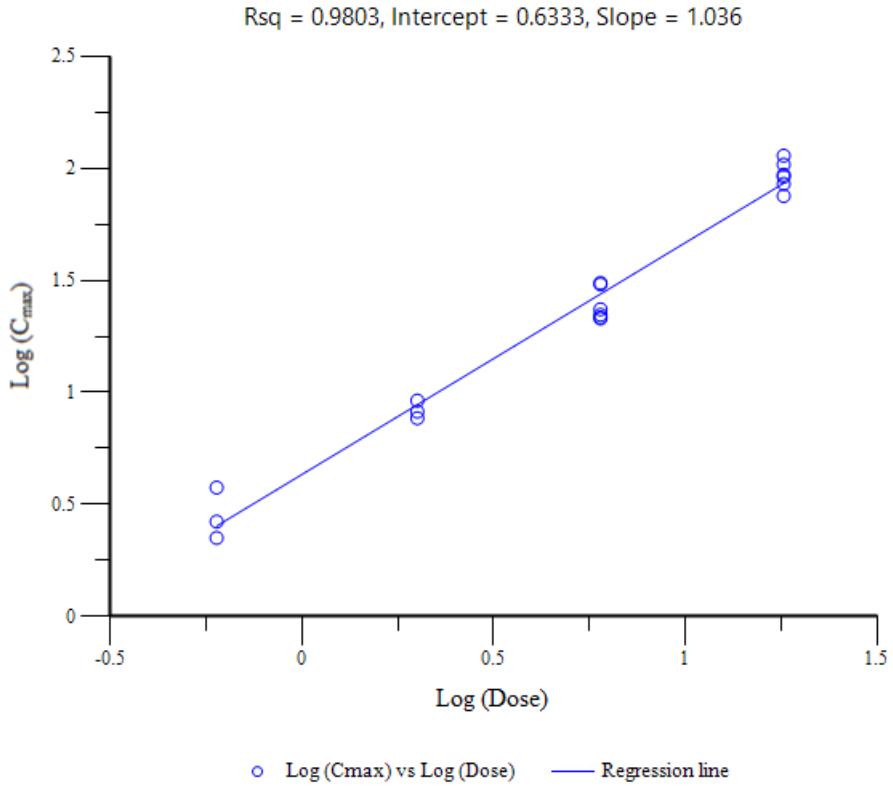
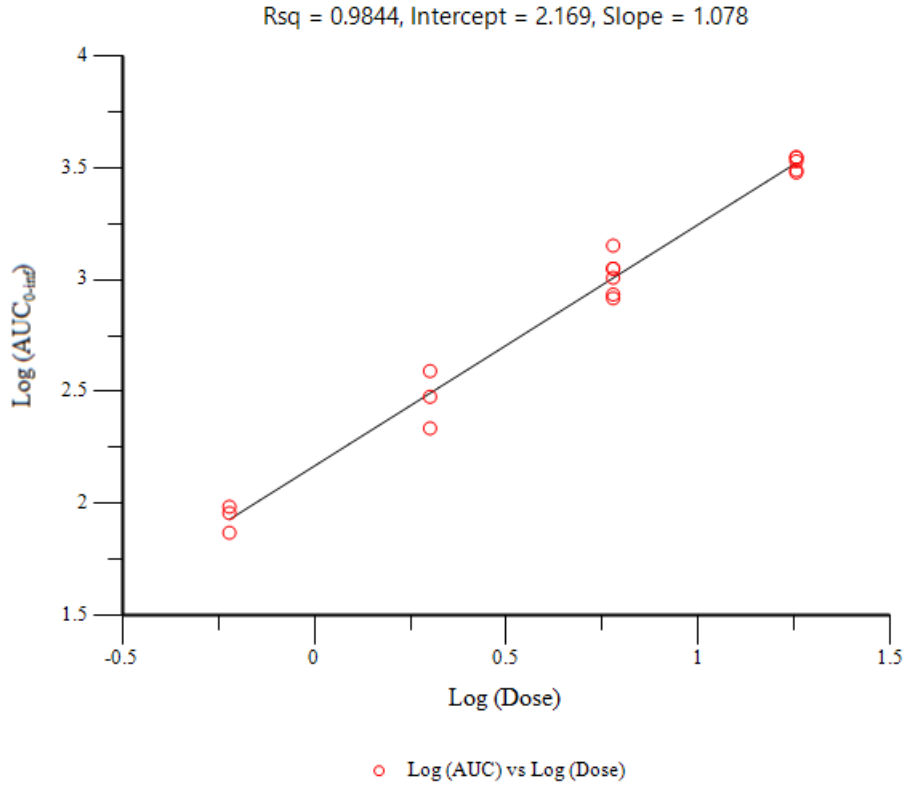


Figure 11 – Risdiplam dose proportionality for AUC_{0-inf} after single dose



Study no. BP41361 was the only study performed with multiple once daily administration of risdiplam in healthy adult subjects. Below it presented a table resuming dose proportionality on steady state:

Table 8 – Risdiplam: Dose proportionality for C_{max} and AUC_{tau} on steady state after 5 mg and 8 mg once a day (performed by PK assessor)

Dose (mg)	Fold Increase in Dose	C_{max} (ng/mL)	AUC_{tau} (ng.h/mL)	Fold Increase in C_{max}	Fold Increase in AUC_{tau}
5 QD	-	78.6	1250	-	-
8 QD	1.6	113	1730	1.44	1.38
Overall	2.67	34.4	480	1.44	1.38
DPF	-	-	-	0.900	0.862

Parameters C_{max} and $AUC_{0-\tau}$ presented as G_{mean}
DPF - Dose Proportionality Factor, defined as the ratio of Fold Increase in Parameter (G_{mean}) divided by Fold Increase in Dose

Risdiplam steady-state peak plasma concentration (C_{max}) and exposure (AUC_{tau}) increased slightly less than proportional to the increase in dose from 5 to 8 mg daily, with a Dose Proportionality Factor of 0.9 and 0.86, respectively.

Based on results presented for study no. BP41361, the actual accumulation of risdiplam after multiple doses, based on AR_{AUC} and AR_{Cmax}, was 3.15 and 3.04, respectively, for the 5 mg QD regimen and 2.76 and 2.58, respectively, for the 8 mg QD regimen. This indicates there was an approximately 3-fold accumulation of risdiplam over the course of the study on both regimens.

On steady state, the elimination half-life ($t_{1/2}$) and Clearance (Cl_{SS}/F) for risdiplam are similar between the 5 mg regimen and the 8 mg regimen, indicating no saturation in the elimination processes (table below).

According to multiple-dose Study BP41361 results, in healthy subjects the steady-state is attained approximately after 7 days of treatment with 5mg of risdiplam administered once daily. Also, in SMA patients (Studies BP39055 and BP39056) the steady state is attained after 7 to 14 days of treatment with risdiplam administered once daily at different dosing schemes. Data have been provided in both graphic and tabular form and confirm that in healthy subjects the steady state is attained in both cases after 7 days and is maintained within day 14 of treatment.

Intra- and inter-individual variability

In the single ascending dose study performed with healthy subjects, variability in plasma PK parameters was low, ranging from 9-27% for C_{max} and from 6-29% for AUC_{Inf}. The variability was therefore less than 30% on both parameters.

In the multiple dose study performed with healthy subjects, variability in plasma PK parameters was also low.

Pharmacokinetics in target population

The following studies contribute to the characterisation of the Pharmacokinetics in target population:

- BP39056 (FIREFISH): a two-part, multicentre, single arm, open-label study to investigate safety, tolerability, PK, PD and efficacy in infants with Type 1 SMA. Plasma PK samples were collected from Type 1 SMA patients. For Part 1, plasma PK samples were collected at: 2, 4, 6h post-dose on Day 1, pre-dose, 2, 4, 6 h post-dose on Weeks 4,12, 52, 78 and 104, while pre-dose samples were drawn on Day 2, pre-dose and 4 h post-dose samples were collected on Weeks 1 (Day 7), 2, 8, 17, 26, 35, 43, 61, 70, 87 and 96. For Part 2, plasma PK samples were collected at: 2, 4, 6 h post-dose on Day 1, pre-dose, 2, 4, 6 h postdose on Weeks 4, 8, 26, 43, 78 and 96, while pre-dose samples were drawn on Weeks 1 (Day 2), 2, 17, 35, 52, 61, 70, 87 and 104.

  A total of 21 patients were enrolled in the dose-finding Part 1 of the study. A total of 41 patients were enrolled in Part 2 of the study which assessed safety and efficacy of risdiplam at the pivotal dose. The open-label extension phase of both parts is ongoing.

- BP39055 (SUNFISH): a two-part, multicentre, randomised, placebo-controlled, double-blind study to investigate safety, tolerability, PK, PD and efficacy in Type 2 and 3 SMA patients. On Part 1, plasma PK samples were collected at: 1, 2, 4, 6 h postdose on Day 1, pre-dose, 1, 2, 4, 6 h post-dose on Weeks 4, 8, 52 and 87, while predose samples were drawn on Weeks 1 (Day 7), 2, 17, 35, 70 and 104. On Part 2, the PK sample collections were at 1, 2, 4, 6 h post-dose on Day 1, pre-dose, 1, 2, 4, 6 h postdose on Weeks 4, 52 and 87, while pre-dose samples were drawn on Weeks 1 (Day 7), 2, 8, 17, 35, 70 and 104

  A total of 51 patients were enrolled in the dose-finding Part 1 of the study, and 180 patients were enrolled into the pivotal Part 2 (120 patients on risdiplam, 60 patients on placebo) which assessed safety and efficacy of risdiplam at the selected dose. The open-label extension phase of both parts is ongoing.

- BP39054 (JEWELFISH): an open-label, non-comparative study to investigate safety, tolerability, PK and PD in adults, children, and infants with SMA who were previously enrolled in Study BP29420 (MOONFISH) with the splicing modifier RO6885247 (RG7800) or previously treated with nusinersen, olesoxime (a Roche development molecule which has since been discontinued), or AVXS-101 (ZOLGENSMA→; a gene therapeutic). Study enrollment has been completed with 174 patients, and the study is ongoing.

Plasma PK samples were collected from Type 1, 2 or 3 SMA patients at 1, 2, 4, 6 h postdose on Day 1, pre-dose, 1, 2, 4, 6 h post-dose on Weeks 4, 8, 52 and 87 while predose samples were drawn on Weeks 1 (Day 7), 2, 17, 26, 35, 43, 70 and 104 according to protocol version 1 (2017). Sampling times were however adjusted on study protocol versions 2 (2018) and 3 (2019) to the following PK sampling points: 1, 2, 4, 6 h post-dose on Day 1, pre-dose, 1, 2, 4, 6 h postdose on Weeks 4, 13, 52 and 91, and pre-dose samples on Weeks 2, 26, 39, 65 and 104 for patients aged 2 – 60 years. For patients aged 6 months to 2 years the PK samples were collected at the following time points: 2, 4, 6 h post-dose on Day 1, predose, 2, 4, 6 h post-dose on Weeks 4, 13, 26, 39, 78, 91, and pre-dose samples on Weeks 2, 52, 65 and 104.

- BN40703 (RAINBOWFISH): a study to assess the efficacy, safety and tolerability, PK and PD of risdiplam in pre-symptomatic infants (from birth to 6 weeks of age at enrollment) who have been genetically diagnosed with SMA. Recruitment is ongoing, and 12 patients have been enrolled by 25 February 21.

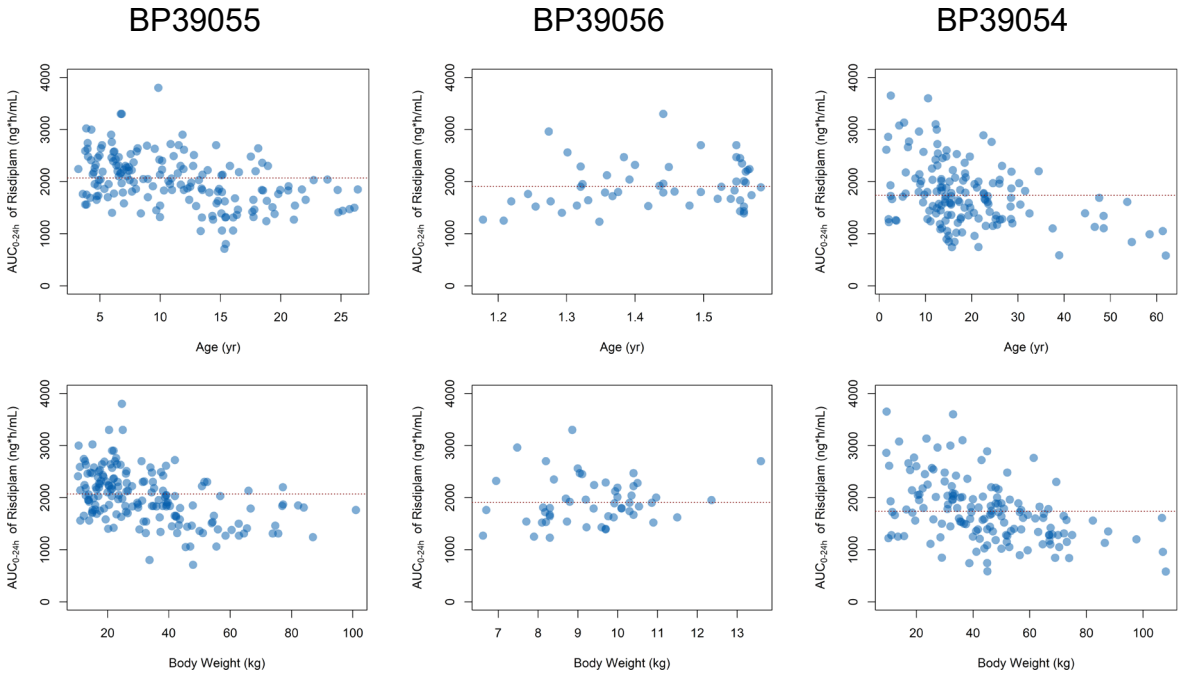
The pharmacokinetic profiles obtained for SMA patients in the three clinical studies (BP39056, BP39055 and BP39054) were analysed through a population pharmacokinetics (PopPK) approach.

The PopPK model was initially developed on a total of 3,478 pharmacokinetics observations from venous and capillary blood samples from 151 SMA patients and healthy volunteers available as of 24 April 2019 from the four clinical studies BP29840, BP39054 (JEWELFISH), BP39055 (SUNFISH) Part 1, and BP39056 (FIREFISH) Part 1 and Part 2. Qualification of PopPK model is described in the respective section of this assessment report.

The primary individual PK parameters estimated for risdiplam for each patient participating in Study BP39054 (JEWELFISH), BP39055 (SUNFISH) and BP39056 (FIREFISH) were used to derive secondary PK parameters such as AUC0-24h and average concentration over the observation period (Cav). These secondary PK parameters are summarised by study and assigned dose. In addition to the predicted Cmax, the highest observed actual concentration is also reported. Due to the dose-escalation design in Parts 1 of BP39055 (SUNFISH) and BP39056 (FIREFISH), most patients had at least one change in the assigned dose during the course of their treatment, which is reflected and depicted in the AUC0-24h time courses. The individual patient's time courses of risdiplam AUC0-24h are shown for each study. The Figure below displays the exposure versus age and body weight, respectively, by study for all patients.

The AUC0-24h at the Month 12 visit (or the last dosing occasion for Study BP39054, as most patients had not reached 12 months of treatment in this study) was estimated using post-hoc PK parameters of the final model and was approximately 2000 ng•h/mL (range: 1740 – 2070 ng•h/mL) across all studies in SMA patients. The selected dosing regimen of 0.2 mg/kg for patients < 2 years, 0.25 mg/kg for patients ≥ 2 years with a body weight of < 20 kg, and 5 mg for patients ≥ 2 years with a body weight of ≥ 20 kg indeed achieved the targeted mean AUC0-24h of approximately 2000 ng•h/mL across all studies.

Figure 12- Risdiplam $AUC_{0\text{-}24h}$ (Last Dose) vs. Age or Body Weight across SMA Studies



$AUC_{0\text{-}24h}$: area under the concentration-time curve from time zero to 24 hours
Note: Dotted lines indicate the median $AUC_{0\text{-}24h}$ of each study.

Box plots of simulated C_{max} and $AUC_{0\text{-}24h}$ at steady-state, stratified by age and body weight were also performed and are presented below:

Figure 13- Simulated $AUC_{0\text{-}24h}$ for SMA Patients in Studies BP39055, BP39056 (Part 2) and BP39054, stratified by Age and Body Weight

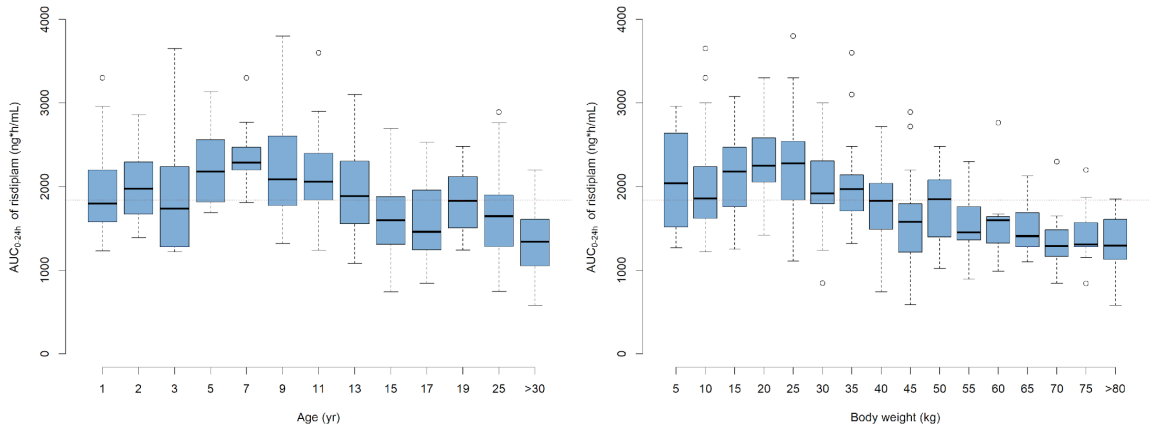
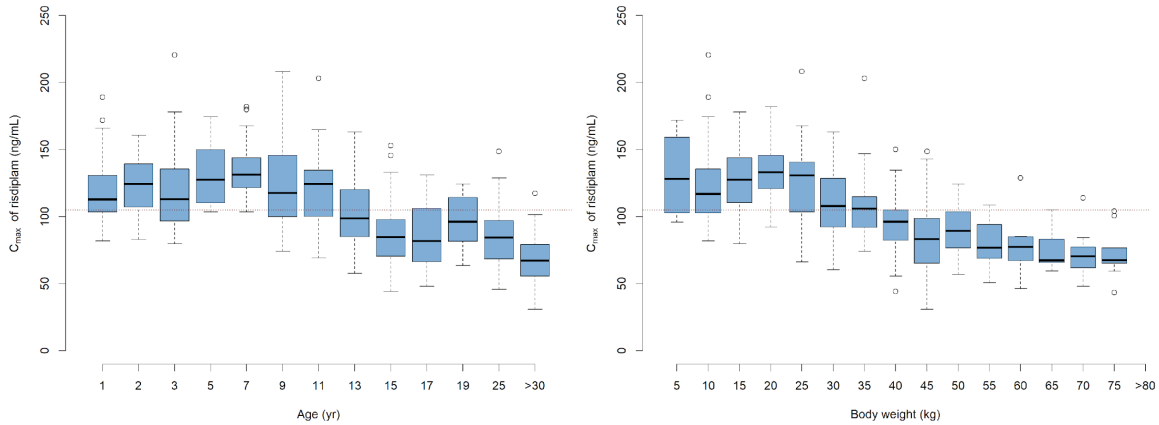


Figure 14 - Simulated C_{max} for SMA Patients in Studies BP39055, BP39056 (Part 2) and BP39054, Stratified by Age and Body Weight



Based on the proposed posology, patients (with a body weight > 50 kg or age < 1.3 years or age >13 years) seem to have a lower exposure whereas other groups of patients have a higher exposure. Nevertheless, the dosing regimen studied in the pivotal clinical trials (resulting on a lower or higher end of exposure) showed no relevant differences in terms of efficacy or safety outcomes.

Below are presented the final results for the PK analysis for each study.

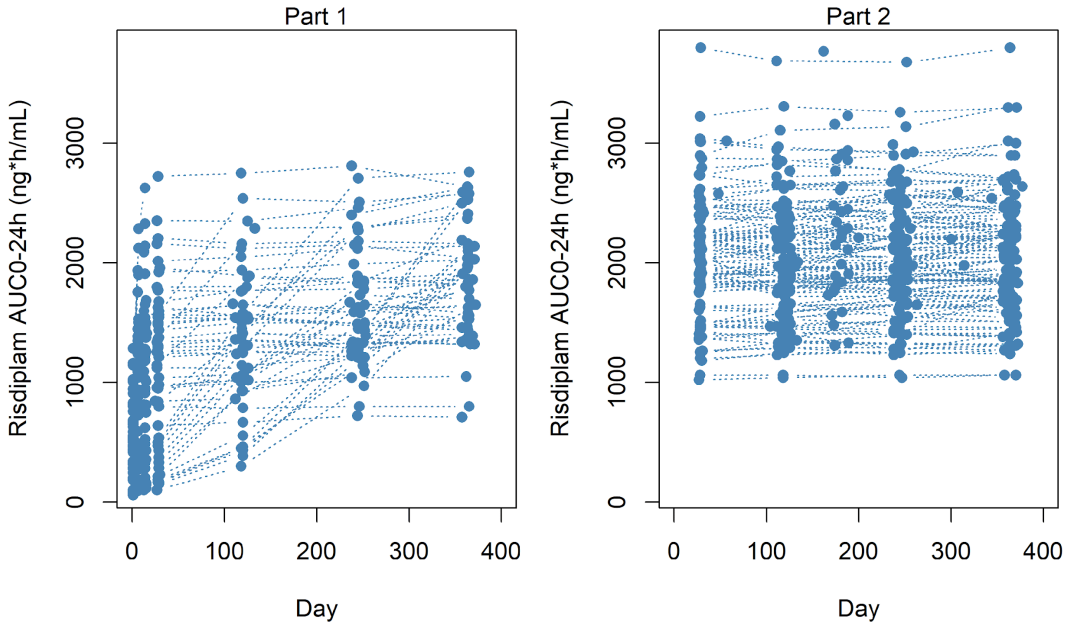
Study BP39055 (SUNFISH)

The individual $AUC_{0\text{-}24h}$ – time course of Type 2 or 3 SMA patients between Day 28 and the 12-month visit are shown for Part 1 and 2 in the Figure below.

Part 1 was the dose finding part of the study, and therefore patients received several different dose levels. All PK parameters for Part 1 patients are reported in the PK-PD report.

For the pivotal Part 2, a summary of AUC0-24h and simulated Cmax at the Month 12 visit, average concentration over the main 12 months treatment period (Cav) during the double-blind phase of the study, and observed Cmax throughout the 12 months treatment period, is presented in the Tables below. Only 4 patients withdrew from the study before the Month 12 visit.

Figure 15- Study BP39055 in Type 2 and 3 SMA Patients: Individual Risdiplam AUC_{0-24h} up to Month 12



AUC_{0-24h}: area under the concentration–time curve from time 0 to 24 hours

Table 9 - Study BP39055 Part 2 in Type 2 and 3 SMA Patients: Secondary PK Parameters at Month 12

Parameters	0.25 mg/kg (n=28)	5 mg (n=89)	All (n=117)
Age[a]			
Mean	5.4	13.5	11.6
median [range]	4.8 [3.2–11.0]	12.8 [4.9–26.4]	11.0 [3.2–26.4]
Body Weight[a]			
mean	15.4	40.2	34.3
median [range]	15.1 [10.6 – 19.0]	36.0 [19.5 – 101]	30.0 [10.6 – 101]
AUC_{0-24h} (ng□h/mL) [b]			
Mean	2250	2010	2070
median [range]	2270 [1560–3020]	1950 [1060–3800]	2050 [1060–3800]
2.5^{th} to 97.5^{th} percentiles	1650–3010	1250–3220	1270–3050
C_{max} (ng/mL)-simulated [b]			
Mean	134	108	114
median [range]	132 [103–178]	106 [58.4–208]	111 [58.4–208]
2.5^{th} to 97.5^{th} percentiles	105–176	63.1–167	63.4–175
C_{av} (ng/mL)			
Mean	88.3	82.6	84.0
median [range]	90.2 [64.0–122]	78.6 [42.5–156]	83.6 [42.5–156]
2.5^{th} to 97.5^{th} percentiles	64.2–117	50.3–125	51.0–123
Effective half-life (h)[a]			
Mean	39.1	57.9	53.4
median [range]	37.9 [25.4–56.6]	56.8 [28.5-107]	51.0 [25.4–107]
2.5^{th} to 97.5^{th} percentiles	27.2-55.3	33.9-99.6	28.9-98.6
Accumulation ratio[c]			
Mean	NA*	2.69	NA*
median [range]	NA*	2.57 [1.74–4.57]	NA*
2.5^{th} to 97.5^{th} percentiles	NA*	1.81–4.10	NA*

AUC_{0-24h}: area under the concentration-time curve from time zero to 24 hours; C_{av}: average concentration over the 12 months double-blind treatment period; C_{max}:maximum concentration

Summarised by dose at 12-month visit. Four patients withdrew from the study before 12-month visit.

[a] at 12-month visit

[b]simulated at the dosing of 12 months visit

[c]derived only for the patients ≥12y and who received risdiplam 5 mg throughout the 12-month treatment duration(n=49). *Not applicable for the patients <12y and received 0.25 mg/kg because of influence of the maturation, growth and changes in doses on the accumulation ratio.

Table 10 - Study BP39055 Part 2 in Type 2 and 3 SMA Patients: Highest Observed Concentration

Parameters	0.25 mg/kg (n=28)	5 mg (n=89)	All (n=117)
C_{max} (ng/mL)-observed [a]			
Mean	137	115	120
median [range]	129 [70.8–196]	110 [50–228]	121 [50–228]
2.5th to 97.5th percentiles	86.8–193	58.5–205	60.9–197

C_{max}: maximum concentration
[a] Highest concentration observed during the 12 months double-blind treatment period for each patient (12 patients in the 5 mg group had previously received 0.25 mg/kg when they achieved the C_{max}).

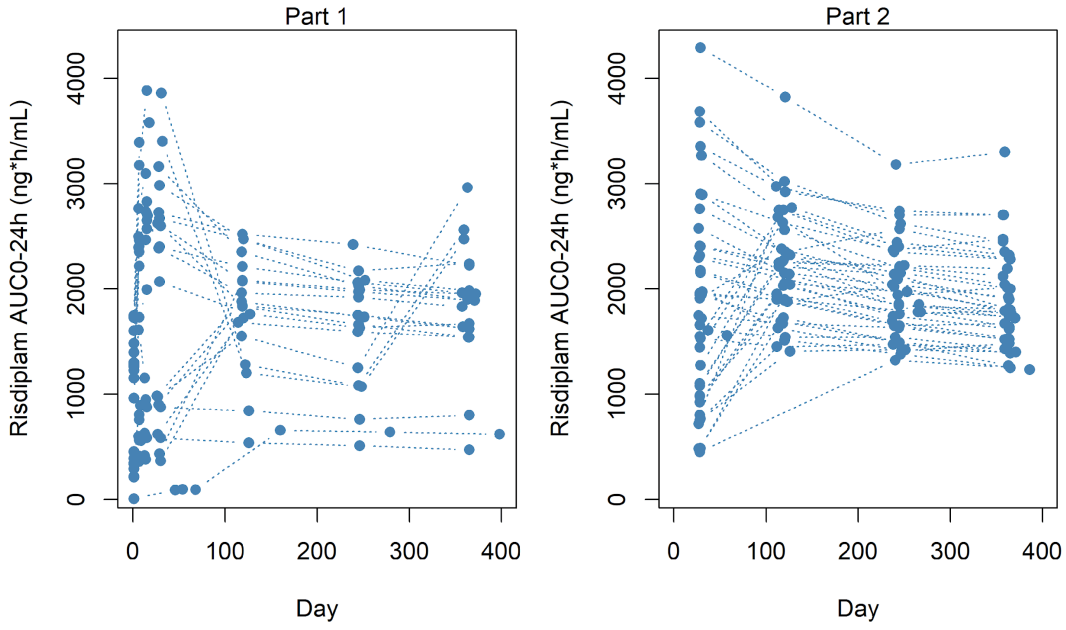
BP39056 (FIREFISH)

The individual AUC0-24h – time course of all Type 1 SMA patients between Day 28 and the Month 12 visit are shown for the dose-finding Part 1 and the pivotal Part 2 in the Figure below. A summary of AUC0-24h and simulated Cmax after the risdiplam administration at the Month 12 visit, average concentration over the main 12 months treatment period (Cav), and observed Cmax throughout the 12 months treatment period, for patients treated with the final selected dosing regimen of 0.2 mg/kg is reported in the Tables below.

The risdiplam exposure was comparable between Parts 1 and 2, and the mean AUC0-24h at the Month 12 visit of 1930 ng.h/mL at the selected dose of 0.2 mg/kg is compliant with the exposure target defined in the study protocol.

A total of 5 patients withdrew from the study before the 12-month visit (Part 1: n=2, Part 2: n=3) and 4 patients received 0.08 mg/kg until the 12 month visit (Part 1: n=3, Part 2: n=1). The individual secondary PK parameters of all Type 1 SMA patients, including these 9 patients, are reported in the PD-PK report.

Figure 16 - Study BP39056 in Type 1 SMA Patients: Individual Risdiplam AUC_{0-24h} up to Month 12



AUC_{0-24h}: area under the concentration-time curve from time zero to 24 hours

Table 11 - Study BP39056 in Type 1 SMA Patients: Secondary PK Parameters at 0.2 mg/kg at Month 12

Parameters	Part 1 (n=16)	Part 2 (n=37)	All (n=53)
Age[a]			
mean	1.5	1.4	1.4
median [range]	1.5 [1.3–1.6]	1.4 [1.2–1.6]	1.4 [1.2–1.6]
Body weight (kg)[a]			
mean	9.6	9.3	9.4
median [range]	9.6 [7.5 –12.4]	9.4 [6.62 – 13.6]	9.4 [6.6 – 13.6]
AUC_{0-24h} (ng□h/mL)[b]			
mean	2000	1900	1930
median [range]	1930 [1540–2960]	1800 [1230–3300]	1830 [1230–3300]
2.5^{th} to 97.5^{th} percentiles	1540–2810	1250–2760	1260–2880
C_{max} (ng/mL)-simulated [b]			
mean	125	118	120
median [range]	121 [94.8–172]	114 [81.9–189]	117 [81.9–189]
2.5^{th} to 97.5^{th} percentiles	98.0–166	82.9–168	84.5–170
C_{av} (ng/mL)			
mean	79.0	81.8	81.0
median [range]	78.2 [58.9–99.9]	78.4 [47.9–149]	78.4 [47.9–149]
2.5^{th} to 97.5^{th} percentiles	59.2–99.0	50.2–124	50.6–120

AUC_{0-24h}: area under the concentration-time curve from time zero to 24 hours; C_{av}: average concentration over the 12 months main treatment period; C_{max}: maximum concentration

[a] At Month 12 visit

[b] Simulated after dosing at Month 12 visit

Table 12 - Study BP39056 in Type 1 SMA Patients: Highest Observed Concentration

Parameters	Part 1 (n=16)	Part 2 (n=37)	All (n=53)
C_{max} (ng/mL)-observed [a]			
mean	217	185	194
median [range]	200 [128–364]	181 [103–296]	181 [103–364]
2.5^{th} to 97.5^{th} percentiles	130–354	108–295	111–329

C_{max}: maximum concentration

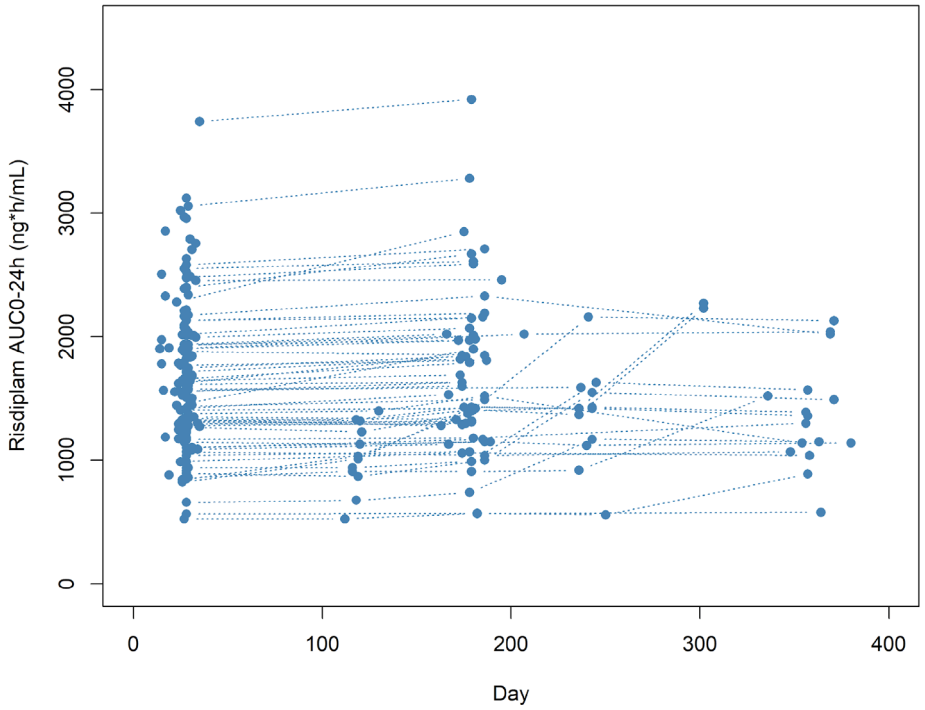
[a] Highest concentration observed during the 12 months main treatment period for each patient (2 patients in Part 1 received 0.25 mg/kg at the time of observed C_{max} and were not included). 4 patients received 0.08 mg/kg (Part 1: n=3, Part 2: n=1), 5 patients withdrew from the study (Part 1: n=2, Part 2: n=3).

BP39054 (JEWELFISH)

Among the 173 patients with Type 1, 2 or 3 SMA who received treatment with risdiplam in Study BP39054, 148 patients had a PK observation period of 28 days or longer, and these patients were included in the PK summary. Two patients were younger than 2 years and received 0.2 mg/kg whereas the others received either 0.25 mg/kg or 5 mg (respectively, initially 3 mg for the first enrolled patients).

The individual AUC0-24h – time courses between Day 28 and the Month 12 visit are shown in the Figure below. A summary of AUC0-24h and simulated Cmax after the latest risdiplam administration, average concentration over the observation period (Cav), and observed Cmax throughout the observation period, for these patients treated with either 0.25 mg/kg or 5 mg are reported in the Tables below. The overall mean $AUC_{0\text{-}24h}$ at the last dosing occasion - including the 2 patients who received 0.2 mg/kg - was 1740 ng.h/mL.

Figure 17- Study BP39054 in Previously Treated Type 1, 2 and 3 SMA Patients: Individual $AUC_{0\text{-}24h}$ up to Month 12 for Risdiplam



$AUC_{0\text{-}24h}$: area under the concentration-time curve from time zero to 24 hours

Table 13 - Study BP39054 in Previously Treated Type 1, 2 and 3 SMA Patients: Secondary PK Parameters at Last Observation

Parameters	0.25 mg/kg (n=13)	5 mg/kg (n=133)	All (n=146)
Age[a]			
Mean	5.1	20.5	19.1
median [range]	3.74 [2.02–16.8]	17.1 [2.5–62.0]	15.8 [2.02–62.0]
Body weight (kg)[a]			
mean	14.5	47.6	44.6
median [range]	13.9 [10.2 – 18.6]	45.1 [9.5 - 108]	43.8 [9.5 - 108]
$AUC_{0\text{-}24h}$ (ng□h/mL)[a]			
Mean	1860	1720	1730
median [range]	1730 [1220–3080]	1640 [580–3650]	1670 [580–3650]
2.5th to 97.5th percentiles	1230–2950	773–3070	804–3090
C_{max} (ng/mL)-simulated [a]			
Mean	115	92.1	94.1
median [range]	108 [79.7–166]	86.2 [30.9–221]	88.5 [30.9–221]
2.5th to 97.5th percentiles	80.8–165	44.7–161	45.2–164
C_{av} (ng/mL)			
Mean	74.7	69.2	69.7
median [range]	74.1 [44.6–117]	65.6 [23.4–157]	67.2 [23.4–157]
2.5th to 97.5th percentiles	46.2–112	35.6–118	35.8–117

$AUC_{0\text{-}24h}$: area under the concentration-time curve from time zero to 24 hours; C_{av}: average concentration over observation period; C_{max}: maximum concentration

[a] At the last dosing occasion

Note: PK parameters for 2 patients (<2y; dose 0.2 mg/kg) and for 25 patients (PK data for <28 days) not included in the summary.

Table 14 - Study BP39054 in Previously Treated Type 1, 2 and 3 SMA Patients: Highest Observed Concentration

Parameters	0.25 mg/kg (n=13)	5 mg/kg (n=133)	All (n=146)
C_{max} (ng/mL)-observed [a]			
Mean	130	111	113
median [range]	114 [86.7–258]	107 [38.1–229]	108 [38.1–258]
2.5th to 97.5th percentiles	89.2–236	51.2–203	51.6–206

C_{max}: maximum concentration

[a] Highest concentration over observation period from first to latest dose; 3 patients included in the 5 mg group received 0.25 mg/kg when they achieved C_{max}; 2 patients (<2y; dose 0.2 mg/kg) and 25 patients (PK data for <28 days) not included,.

Based on a PopPK analysis with a validated model, it was shown that a mean exposure of $AUC_{0\text{-}24h,ss}$ ≤2000 ng•h/mL has been reached with the final selected doses in the efficacy studies. The selected dosing regimen indeed achieved similar exposure across the wide age and body weight range.

Based on study BP39055 (SUNFISH) PopPK analysis, for the total of 117 SMA patients (type 2 and type 3), with ages ranging from 3.2 to 26.4 years, the elimination half-life was estimated with a median of 51h (ranging from 25.4 to 107h).

Special populations

Impaired renal function

Based on results from the SAD study (Study BP29840) and mass balance study (Study no. BP39122), approximately 4% and 8% of risdiplam dose was renally excreted as unchanged form, respectively.

Given that renal route is considered a minor elimination route for risdiplam and that the main metabolite M1 is inactive, no risk of a clinically relevant increase in exposure to risdiplam or its metabolite M1 in patients with renal impairment is expected. Therefore, a pharmacokinetic study in subjects with decreased renal function is not necessary in order to obtain adequate treatment recommendations.

Moreover, and despite risdiplam is being primarily hepatically eliminated, it is also considered that a pharmacokinetic study in subjects with a decreased renal function is not necessary to evaluate the impact on the total elimination of risdiplam, as in the hepatic impairment study, mild and moderate hepatic impairment shown no impact on the PK of risdiplam.

Therefore, studies to investigate the PK of risdiplam in patients with renal impairment were not conducted.

Impaired hepatic function

Given results obtained from the mass balance study, where a total of 43.1% of the dose was excreted on the form of metabolites in faeces and urine, the liver is considered as an important elimination organ for risdiplam.

Considering that liver disease can cause alterations in drug disposition and pharmacokinetics (PK) of risdiplam and its main metabolite M1, a hepatic impairment study (Study BP40995) was conducted to assess whether impaired hepatic function has an impact on the exposure of risdiplam and to provide dosing recommendations for risdiplam in subjects with hepatic impairment.

Study BP40995 investigated the effect of Child-Pugh mild and moderate hepatic impairment on the plasma PK of a single 5mg oral dose of risdiplam compared to matched healthy subjects with normal hepatic function. Severe hepatic impairment was not investigated. In comparison to subjects with normal hepatic function, risdiplam AUCinf and Cmax were approximately 20% and 5% lower in subjects with mild hepatic impairment and 8% and 20% higher in subjects with moderate hepatic impairment. Such differences were deemed not statistically significant. M1 metabolite ratios for AUClast, AUCinf, and Cmax were similar between normal hepatic and mild/moderate hepatic impairment groups. No significant safety concerns related to the treatment have been identified.

The proposed wording for Section 5.2 (Pharmacokinetics in special populations – Hepatic Impairment) of the SmPC is in line with the observed PK data.

Gender

In the population pharmacokinetics modelling, the effect of sex as a covariate was tested on the parameter CL/F, which was 15.2% higher in male than in female subjects). The sex effect as a covariate was considered clinically not relevant. Gender effect is not addressed in the proposed SmPC.

Race

The applicant has performed a Single Ascending Dose study in Japanese subjects (Study no. NP39625).

This study was designed as an Investigator/subject-blinded, randomised, placebo-controlled study investigating the safety, tolerability, PK and PD of single oral doses of RO7034067 in healthy Japanese subjects.

The pharmacokinetics of risdiplam did not differ in Japanese and Caucasian subjects. Moreover, in the covariate analysis performed as part of the PopPK modelling for the prediction of risdiplam pharmacokinetics in SMA patients, Asian race was not found to be a statistically or clinically relevant covariate and was therefore not included in the final PK model of risdiplam.

The proposed wording for Section 5.2 (Pharmacokinetics in special populations – Ethnicity) of the SmPC is in line with the observed PK data.

Children and Weight

In the population pharmacokinetics modelling, the time-varying body weight and age were necessary to describe the variability of the heterogeneous population in terms of age and body weight and therefore used as covariates in the final model. The dose is therefore adjusted based on age (below and above 2 years) and body weight (up to 20 kg) to obtain similar exposure across the age and body weight range. No data are available in patients less than 2 months of age.

Elderly

No dedicated studies have been conducted to investigate PK in patients with SMA above 60 years of age. Patients with SMA up to 60 years of age were included in the JEWELFISH study. Subjects without SMA up to 69 years of age were included in the clinical PK studies, which indicates that no dose adjustment is required for patients up to 69 years of age.

Interactions

In vitro

In vitro studies have showed that risdiplam and its major circulating metabolite M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4 and that risdiplam and M1 did not inhibit (reversible or time dependent inhibition [TDI]) any of the CYP enzymes tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6) with the exception of CYP3A.

In vitro studies have also showed that risdiplam and M1 are not a significant inhibitor of human multidrug resistance protein (MDR) 1, organic anion transporting polypeptide (OATP) 1B1, OATP1B3, organic anion transporter 1 and 3 (OAT 1 and 3). However, it was shown that:

•Risdiplam is an inhibitor of OCT2, MATE1 and MATE2-K *in vitro*

•M1 is an inhibitor of BCRP and MATE1 *in vitro*

In order to assess clinical relevance of *in vitro* inhibition flags, EMA guideline on DDI recommend estimating:

•For intestinal efflux (BCRP): The drug level in the GI tract calculated as the PO dose divided by 250 mL. Despite M1 is a circulating metabolite, it is not detected in faeces in human. Therefore, this approach is not applicable for M1.

•For hepatic efflux (BCRP) and renal uptake (OCT2, MATE1 and MATE2-K): The ratio of unbound plasma Cmax to the *in vitro* IC50 ([I]/IC50).

In vivo inhibition of a transporter at a certain site can be excluded if the ratio [I]/IC50 is lower than 0.02. Based on results shown in Table below, the only potentially clinically relevant DDI risks expected are linked to MATE1 and MATE2-K inhibition by risdiplam, in contrast to, for example, OCT2 inhibition by parent or metabolite M1 or BCRP inhibition by M1. The possible risk is related to the elimination of drugs that are substrates of these renal uptake transporters, and for which renal route is a primary route of elimination.

Table 15: Human Drug-Drug Interaction Risk Assessment for Transport Proteins Inhibition by Risdiplam or M1

Compound / Protein	IC_{50} [µM][a]	Total C_{max} in SMA patients [ng/mL][a]	[I] [µM][b]	[I]/IC_{50}	Threshold[c]
Risdiplam / OCT2	8.7	Median = 194 (0.2 mg/kg, <2 years) Max observed = 364	0.052 0.097	**0.006** **0.011**	**0.02**
Risdiplam / MATE1	0.15	Median = 194 (0.2 mg/kg, <2 years) Max observed = 364	0.052 0.097	**0.34** **0.65**	
Risdiplam / MATE2-K	0.09	Median = 194 (0.2 mg/kg, <2 years) Max observed = 364	0.052 0.097	**0.57** **1.08**	
M1 / MATE1	14.8	Median = 58 (0.2 mg/kg, <2 years) Maximum = 109	0.010 0.019	**0.0007** **0.0013**	
M1 / BCRP	2.3	Median = 58 (0.2 mg/kg, <2 years) Maximum = 109	0.010 0.019	**0.0045** **0.0084**	

Grey shaded areas indicate values above the [I]/IC_{50} threshold.

[a] Risdiplam and M1 plasma concentrations at steady state at pivotal doses (BP39055 "Sunfish" Part 2 study: 0.25 mg/kg (body weight<20 kg) or 5 mg, BP39056 "Firefish" study: 0.2 mg/kg).
The assessment was based on the median and maximum observed C_{max} values in the "Firefish" study; C_{max} values were lower in older patients in the "Sunfish" study . Median M1 percentage vs parent of ~30% (observed ratio 0.287) was assumed for calculating M1 C_{max} values.

[b] [I] is the unbound plasma concentration (assuming free fraction in human plasma 10.7% for risdiplam and 7.4% for M1,).

[c] Most conservative [I]/IC_{50} threshold above which the Sponsor should further investigate the DDI potential by conducting a clinical DDI study.

The proposed wording for Section 4.5 (Interaction with other medicinal products and other forms of interaction - Effects of risdiplam on other medicinal products) of the SmPC is in line with *in vitro* results.

In silico

A PBPK model was used to translate the results of Study BP41361 to the paediatric SMA patient population aged between 2 months to 18 years-old, and to evaluate the CYP3A inactivation risk. The simulations indicated a similar extent of CYP3A inactivation effect in children aged 2 months to 18 years as observed in Study BP41361.

Moreover, the simulations have also indicated that a CYP3A enzyme inhibition in the liver is negligible and the predicted increase in midazolam AUC was mostly due to intestinal CYP3A inhibition. Therefore, the DDI risk for intravenously administered CYP3A substrates is considered negligible. Due to the low degree of enzyme inactivation in the small intestine, a greater DDI risk for CYP3A substrates with lower intestinal availability than midazolam (FG <0.55) is not expected. For drugs with higher intestinal availability than midazolam, the DDI risk is negligible.

There are no requirements to predict this interaction in paediatrics. If information from the PBPK model is included in the SmPC, a full qualification and validation of the paediatric PBPK model, with focus on this interaction is needed which seems to not have been done. Therefore, PBPK simulations are not necessary for this application and consequently the SmPC should not reflect these simulations.

In vivo

Given that *in vitro* studies have shown that risdiplam is primarily metabolised by flavin monooxygenase 1 and 3 (FMO1 and FMO3), and also by CYPs 1A1, 2J2, 3A4 and 3A7, and given that itraconazole is a strong inhibitor of CYP3A activity *in vivo*, the potential inhibitory effect on the metabolism of risdiplam (RO7034067) was studied in an *in vivo* clinical study (Study no. BP29840).

In this study, the potential interaction was assessed in a dedicated Part 3 of the Single Ascending Dose clinical study (Study no. BP29840). In order to minimize the number of subjects required, a within-subject study design was chosen. Moreover, to account for uncertainties in the elimination of

RO7034067 in humans, which may be prolonged by itraconazole, an open-label, one-sequence design was selected.

In the *in vivo* study, it was shown that itraconazole co-administration was associated with a minor effect on the PK of a single oral dose of risdiplam: there was a slight increase in AUC0−120h (geometric mean ratio 1.108) and a slight decrease in Cmax (geometric mean ratio 0.906). These results suggest a limited contribution of the CYP3A pathway to risdiplam metabolism, and hence a small likelihood of clinically significant interaction with inhibitors or inducers of the CYP3A enzymes.

In vitro studies have also showed that risdiplam and M1 did not inhibit (reversible or Time Dependent Inhibition) any of the CYP enzymes tested with the exception of CYP3A4, for which have shown a reversible and time dependent inhibition in a concentration in a concentration between 5 µM and 12.5 µM. Therefore, as a signal for time-dependent inhibition of CYP3A by risdiplam was identified *in vitro*, an *in vivo* study (Study no. BP41361) was performed with a multiple-dose administration of risdiplam for 2 weeks as once daily (QD) dosing, as the assessment of time-dependent inhibition *in vivo* requires multiple dose administration of the perpetrator.

Study no. BP41361 was an open-label, non-randomised, Phase 1, 2-part study to investigate the safety, tolerability, and PK of a QD multiple-dosing regimen of risdiplam (Part 1) and the effect of risdiplam on the PK of midazolam (Part 2) following oral administration in healthy adult male and female participants.is described below regarding the potential interaction on the pharmacokinetics of midazolam.

Based on the results obtained for midazolam, the ratios of the geometric least-squares mean (90% CI) of midazolam co-administered with risdiplam compared to midazolam alone were 1.08 (0.93, 1.26), 1.11 (1.02, 1.20), and 1.16 (1.06, 1.28) for AUCinf, AUClast, and Cmax, respectively, indicating that co-administration of risdiplam may have slightly increased the exposure of midazolam in healthy subjects. The observed magnitude of this effect is however not considered clinically relevant.

The proposed wording for Section 4.5 (Interaction with other medicinal products and other forms of interaction - Effects of risdiplam on other medicinal products) of the SmPC, regarding midazolam is in line with the results obtained in the study no. BP41361. PK assessor agrees with the recommendations in the absence of a need of a dose adjustment for drugs that are CYP3A substrates.

Exposure relevant for safety evaluation

There was no evidence of a relationship between the occurrence of AEs or SAEs and individual exposure (C_{av}) in the pivotal studies BP39055 (SUNFISH) Part 2 and BP39056 (FIREFISH) Part 2. Treatment with risdiplam was well tolerated across the entire exposure range, and the average risdiplam concentration (C_{av}) was comparable in patients experiencing AEs or SAEs versus patients not experiencing these events.

2.4.2. Pharmacodynamics

Mechanism of action

Risdiplam is an oral formulation, centrally and peripherally distributed small molecule SMN2 splicing modifier that increases production of functional SMN protein by promoting the inclusion of exon 7 in SMN2 mRNA.

The applicant proposed mechanism of action (MoA) is based on *in vivo* nonclinical studies (Type 1 SMA-like SMNΔ7 mouse model) and *ex vivo* systems. The increase in SMN protein levels translated into efficacy in rescuing disease phenotype (reduction in weight loss) in mouse model. Although the exact MoA has not been fully elucidated experimentally, further data supports the mechanistic assumption of the splicing modifier specificity for *SMN2* splicing of risdiplam: studies with small molecules closely related

to risdiplam suggest that direct binding to two distinct sites of the *SMN2* pre-mRNA increases levels of SMN protein and SMN mRNA; approved medicines for SMA targeting the inclusion of exon 7 in *SMN2* pre-mRNA are considered a valid therapeutic approach for SMA. This MoA is considered plausible and targets a specific pathway for the treatment of the disease, with similar pathophysiology across all ages and all SMA types, that increases the expression of a functional and stable SMN protein, necessary for normal motor neuron functioning.

Animal safety studies and mechanistic investigations allowed to identify secondary splice targets, including FOXM1 and MADD, involved in cell cycle regulation and apoptosis, respectively.

Primary Pharmacology

Primary PD was explored in *in vitro and in vivo* nonclinical pharmacology studies showing that an increase in SMN protein production translates into disease-modifying efficacy, rescuing the disease phenotype. Dosing of risdiplam resulted in around 2-fold increased SMN protein levels in muscle and brain tissues of the two SMA model mice used. Risdiplam major human metabolite (M1) was less potent for inducing the generation of FL SMN2 transcript in Type 1 SMA patient fibroblasts and did not affect SMN2 exon 7 splicing, in whole blood from healthy volunteers, supporting the claim of a negligible primary pharmacological effect.

Blood levels of SMN protein and *SMN2* mRNA (PD biomarkers) have been measured in all SMA patients in the clinical studies: BP39056 (Type 1 SMA patients, 1-7 months); BP39055 (Type 2 or Type 3 SMA patients, 2-25 years) and BP39054 (Type 2 or Type 3 SMA patients previously treated with other SMA therapeutic products).

The PD biomarker SMN protein has increased within 4 weeks after treatment start (median >2 fold-increase at the last observation, from baseline absolute SMN protein values), and was maintained over the entire treatment duration, with follow-up available to date for 104 weeks (Type 2 or Type 3 SMA patients) and 52 weeks (Type 1 SMA patients). Baseline absolute SMN protein values were generally lower in Type 1 SMA patients (See table 22), compared to Type 2 or 3 SMA , which explained the larger variability in SMN protein increase between these two populations . SMN protein is considered the biomarker of choice for SMA, as all the approved therapies are aimed to restore its expression. Since SMN protein is an obvious pharmacodynamic biomarker, a 2-fold increase in SMN protein *versus* baseline is predicted to lead to significant clinical benefit, based on the animal pharmacology data in SMA mouse models and in clinical data from the dose-finding part of the pivotal studies.

The PD biomarker, *SMN2* full-length mRNA change from baseline (%), after risdiplam oral administration to human was well predicted based on combined *in vitro, in vivo* preclinical data and PK/PD integrated analysis. The mode of action of risdiplam as a *SMN2* splicing modifier was confirmed by the observed shift in *SMN2* splicing (increase in full-length *SMN2* mRNA and a decrease in SMN2⊗7 mRNA). No difference in the relationship between risdiplam exposure and the shift in SMN mRNA splicing was seen among the SMA populations (i.e., SMA Type 1, 2 or 3 in Study BP39054, BP39055 and BP39056), and there was no difference in response in patients previously treated with other SMA targeted therapies *versus* treatment-naïve patients.

Secondary Pharmacology

Data from *in vitro* transcriptomics assays confirmed that risdiplam has significant specificity for SMN2 exon 7 splicing, however, a number of secondary splice targets, which all share the same 5' splice site, were identified as being alternatively spliced by risdiplam: human genes FOXM1, STRN3 and SLC25A17. In patients, therapeutic effect in terms of shifting the splicing to inclusion of exon 7 is achieved at a mean exposure not exceeding the NOAEL for *off-target* effects observed in nonclinical

toxicity studies. Risdiplam moved into clinical development with a mean exposure cap corresponding to the NOAEL for retinal toxicity in monkeys, with extensive safety monitoring.

Regarding QTc analysis, PK-PD evaluation aimed to assess the effect of risdiplam on QTc was carried-out throughout a 'Change from baseline Concentration-QT response analysis' and a 'Time-matched concentration-QT response analysis'. The first analysis apparently pooled both acute and chronic ECG data and treatment time was not analysed as a covariate. The second analysis also included ECGs following repeated administration. No analysis was performed in order to assess the effect of time. According to the applicant, no evidence for a prolongation in QTcF was identified, since the upper limit of the two-sided 90%-CI of ΔQTcF did not exceed 10ms.

Also, although no analysis of the QTc effect was performed of high (but still in the range of therapeutic levels) risdiplam concentrations there is no trend observable within the measured range, and there is no signal from the clinical safety data that would indicate a QTc prolongation in human at higher concentrations.

The applicant will conduct in 2021-2022 a dedicated single-dose tQT-study in healthy adult subjects that is considered to be sufficient to further support current conclusions on absence of Q-T prolongation by risdiplam.

Regarding plasma protein binding, based on protein binding measured in human plasma from cord blood, neonates and children (non-SMA and type 1, 2 and 3 SMA patients), there is no age dependency of risdiplam plasma protein binding. These results are in contrast to the observations in rodents where a higher free fraction of risdiplam was observed in young animals.

Pharmacodynamic interactions with other medicinal products or substances

Considering the specific target and unique MoA of risdiplam, no pharmacodynamic drug-drug interaction studies were performed, which may be considered acceptable. Although some data has been presented for PK interactions no PD interactions were mentioned and no pharmacodynamic DDIs are expected via other pathways, except for substrates of the MATE 1/2K transporters (PK interactions).

Genetic differences in PD response

Genotype was confirmed at baseline. All patients enrolled in the pivotal studies have been genetically diagnosed with SMA (SMN1 gene), carrying two SMN2 gene copies (Type 1 SMA) or higher SMN2 gene copies (Type 2 or Type 3 SMA). All patients responded to risdiplam, regardless of genotype and no obvious difference in exposure *versus* PD biomarkers (SMN protein and SMN mRNA) relationship was noted among the SMA patient populations (Type 1 vs. Type 2 or Type 3 SMA). In general, infants with Type 1 SMA (study BP39056) presented lower baseline absolute SMN protein values, compared with patients with SMA Type 2 or Type 3. In an ethnicity study in healthy Japanese subjects, PD biomarkers behaviour (SMN protein and SMN mRNA) in Japanese subjects matched the results observed in Caucasian subjects.

Relationship between plasma concentration and effect

The proposed dosing regimen was based on the results from 4 clinical studies (BP29840, BP39054, BP39055, and BP39056) and simulated results from modelling PK/PD data (popPK).

Dose selection and Dosing Regimen

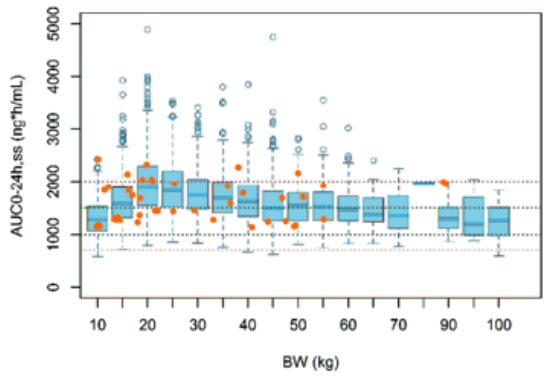
The rational for dose selection is based in: a) dose response data for survival in the mouse SMA model; b) the NOAEL in monkey (mean AUC 2000 ng.h/mL); c) exposure close to but not above the exposure

cap (mean AUCss 2000 ng.h/mL), with at least 2-fold SMN protein increase (PD marker) at the dose levels at which efficacy was observed; and d) comparison of baseline SMN protein across SMA types.

Dose levels were investigated in a staggered and dose-escalating manner in different age groups, assessing the exposures with body weight. In BP39055 study (SMA Type 2/3), a median SMN protein increase of 2.5-fold was observed with 5 mg in patients aged 12–25 years old, and a 2-fold increase with 0.25 mg/kg in the 2–11 years age group. Based on PPK model simulations, a dosing regimen of 5 mg once daily (body weight ≥20 kg) and 0.25 mg/kg once daily (body weight < 20 kg) obtained an exposure very close to the targeted mean $AUC_{0\text{-}24h,ss}$ 2000 ng.h/mL: 2250 ng.h/mL (BW < 20 kg, dose of 0.25 mg/kg OD) and 2010 ng.h/mL (BW ε20 kg, dose 5 mg OD).Based on this data and specially on PK simulations (PPK model), assessing the exposures with body weight (Figure 29), the dosing regimen of 5 mg once daily for patients with a body weight ≥20 kg and 0.25 mg/kg once daily for patients with a body weight < 20 kg was selected as the pivotal dose for Part 2, where a total of 180 non-ambulant male and female patients aged 2 to 25 years with Type 2 or Type 3 SMA (stratified by age) were enrolled.

Figure 18

Figure 29 Study BP39055: Predicted Exposure for Dosing Regimen of 5 mg (BW ≥20 kg) / 0.25 mg/kg (BW <20 kg)



Blue bars: simulations using SMA Foundation data set; orange circles: predictions using estimated CL/F of BP39055 patients Part 1.

$AUC_{0-24,ss}$ = area under the concentration-time curve from time zero to 24 h at steady state; BW=body weight.

The observed exposure in Part 2 confirms the dose selection approach; the selected dosing regimen indeed obtained an exposure very close to the targeted mean $AUC_{0\text{-}24h,ss}$ 2000 ng.h/mL. The mean $AUC_{0\text{-}24h,ss}$ at the Month 12 visit in Part 2 was 2250 ng.h/mL (range 1560–3020, n=28) for patients with a body weight <20 kg receiving a dose of 0.25 mg/kg, and 2010 ng•h/mL (range 1060–3800, n=89) for patients with a body weight ≥20 kg receiving a dose of 5 mg, with an overall mean $AUC_{0\text{-}24h,ss}$ of 2070 ng.h/mL.

In BP39056 study (SMA Type 1), IMC was responsible for dose selection/escalation and emerging PK data lead the dose adjustments. A median 2-fold increase in SMN protein was observed with a mean exposure (AUC_{0-24h}) ≤ 1000 ng•h/mL, and a median 3.2-fold increase was obtained with an exposure (AUC_{0-24h}) > 1000 ng•h/mL.

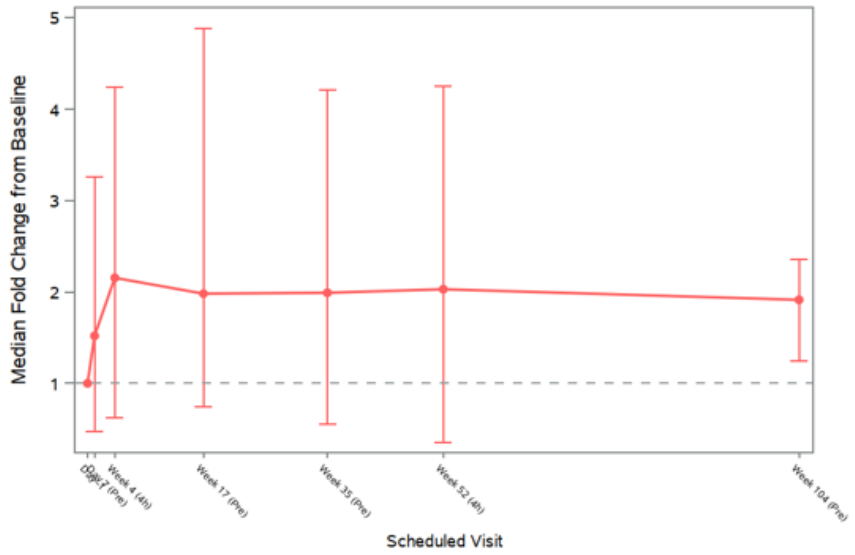
Based on this data, a dose of 0.2 mg/kg was selected for infants ≥ 5 months of age. Limited data existed from 4 infants age 3–5 months in Part 1 of this study at the start of Part 2, where the escalation approach was a starting dose of 0.08 mg/kg for infants 3–5 months old, and 0.04 mg/kg for infants 1–3 months. Upon review of the PK for every infant, the dose was increased to the target exposure of mean $AUC_{0-24h,ss}$≤ 2000 ng.h/mL per protocol, and the dose was adjusted to 0.2 mg/kg for

all infants. The mean $AUC_{0\text{-}24h,ss}$ for all infants enrolled at 12M was 1930 ng.h/mL at the dose of 0.2 mg/kg.

In Studies BP39056 (Type 1 SMA patients, 1-7 months) and BP39055 (Type 2 or Type 3 SMA patients, 2-25 years), an at least 2-fold median increase in SMN protein was obtained within 4 weeks after start of treatment with risdiplam at the pivotal dose in all three studies, and this increase was maintained over the entire treatment duration, with follow-up available to date for more than 2 years (Figure 16 and Figure 17).

Figure 19

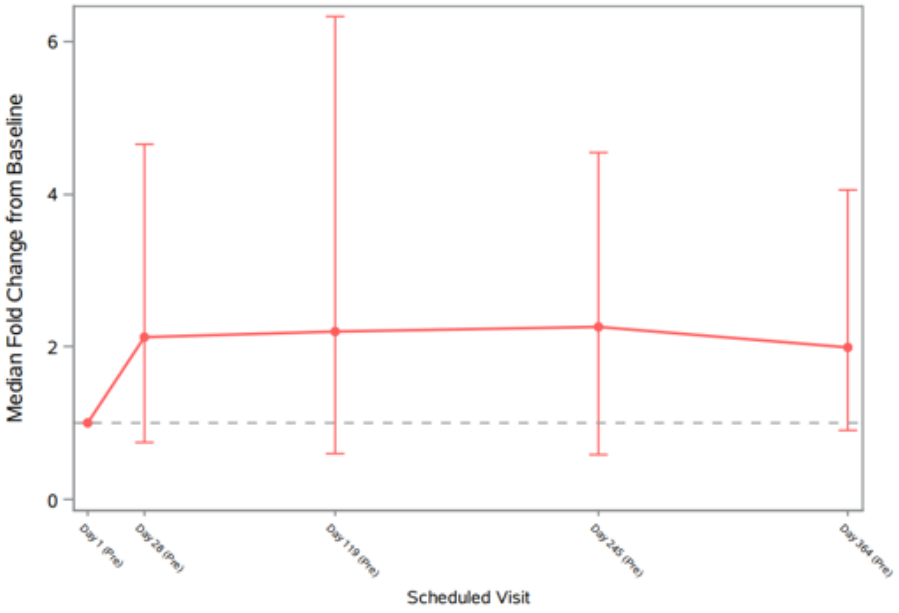
Figure 16 Study BP39055 Part 2: SMN Protein (Change from Baseline) in SMA Type 2 and 3 Patients after Risdiplam Treatment



Note: Error bars show minimum and maximum values.

Figure 20

Figure 17 Study BP39056 Part 2: SMN Protein (Change from Baseline) in SMA Type 1 Infants after Risdiplam Treatment



Note: Error bars show minimum and maximum values.

According to Table 22 containing the SMN protein values at last observation by study, baseline absolute SMN protein values were generally lower in Type 1 SMA patients (Study BP39056), but the fold-increase at the last observation was comparable to Type 2 or 3 SMA patients (study BP39055):

Figure 21

Table 22 SMN Protein at Last Observation by Study

Study	Last observation (Day)	Baseline SMN protein (ng/mL)	Absolute SMN protein (ng/mL)	Fold change from baseline
BP39054	90	3.44	7.41	2.16
(n=153)	[0–740]	[0.527–12.5]	[1.2–14.5]	[0.751–4.34]
BP39055				
Part 1	912	2.75	7.13	2.62
(n=51)	[244–1110]	[0.57–5.16]	[1.18–17.5]	[1.15–7.5]
Part 2 Active	365	3.58	7.04	1.98
(n=120)	[127–736]	[1.54–11.4]	[0.786–13.8]	[0.359–4.25]
Part 2 Placebo [a]	246	3.55	3.16	0.883
(n=59)	[0–365]	[1.26–6.75]	[1.29–7.14]	[0.471–1.67]
BP39056				
Part 1	610	2.48	4.73	1.83
(n=21)	[0–771]	[0.58–6.4]	[1.78–8.39]	[0.592–7.04]
Part 2	363	2.93	5.37	2.01
(n=41)	[27–602]	[0.423–5.8]	[0.761–9.39]	[0.9–4.06]

Note: Median [range] are presented.

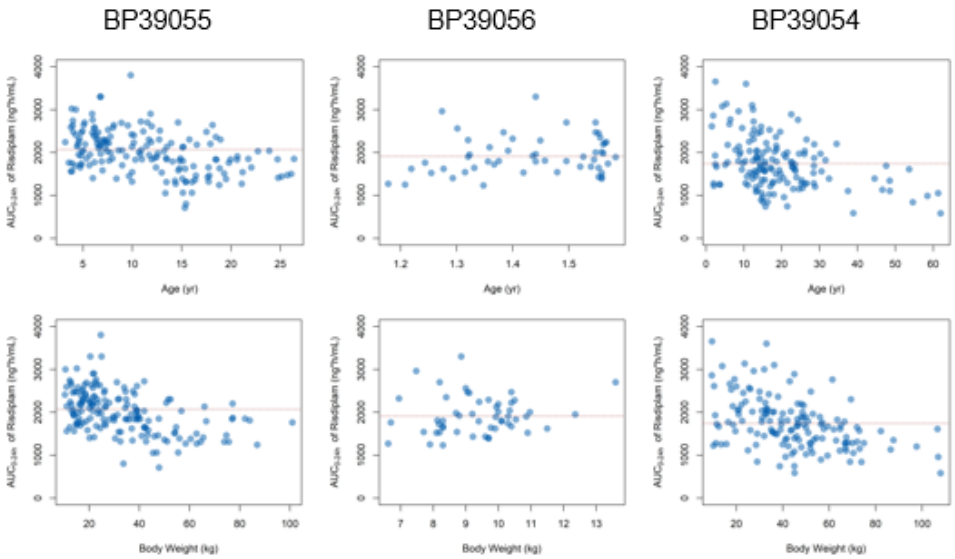
[a] Only the data collected during placebo treatment.

Larger variability was noted in Type 1 SMA patients from study BP39056, with some infants obtaining greater SMN protein increase compared to Type 2 or 3 SMA patients from study BP39055, due to the lower baseline values in Type 1 patients.

The PPK analysis confirms the first dose selection for BP39055 (SUNFISH) and the following dose selection for BP39056 (FIREFISH), to obtain an exposure of $\leq$ 2000 ng.h/mL $AUC_{0-24h,ss}$ (mean). The selected dosing regimen achieved similar exposure (Figure 15) across the wide age and body weight range.

Figure 22

Figure 15 Risdiplam $AUC_{0\text{-}24h}$ (Last Dose) vs. Age or Body Weight across SMA Studies

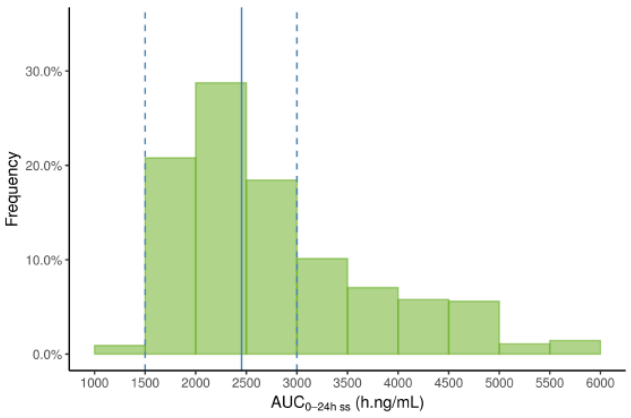


$AUC_{0\text{-}24h}$ = area under the concentration-time curve from time zero to 24 hours
Note: Dotted lines indicate the median $AUC_{0\text{-}24h}$ of each study.

Distribution of $AUC_{0\text{-}24,ss}$ exposures, following administration of 0.2 mg/kg Risdiplam in Type 1 SMA paediatric patients, truncated at 7 months and 24 months of age, are presented in Figure 21 and Figure 22, respectively.

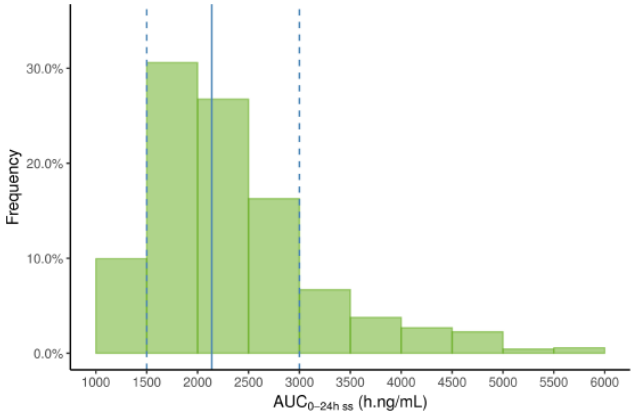
Figure 23

Figure 21: Histogram of $AUC_{0\text{-}24h,ss}$ following Dosing of 0.2 mg/kg Risdiplam in Type 1 SMA Pediatric Patients up to 7 Months of Age



Blue solid line displays median Risdiplam $AUC_{0\text{-}24,ss}$, while the dashed blue lines refer to $AUC_{0\text{-}24,ss}$ cut-off values of 1500 ng·h/mL and 3000 ng·h/mL.

Figure 22: Histogram of $AUC_{0\text{-}24h,ss}$ following Dosing of 0.2 mg/kg Risdiplam in Type 1 SMA Pediatric Patients up to 24 Months of Age

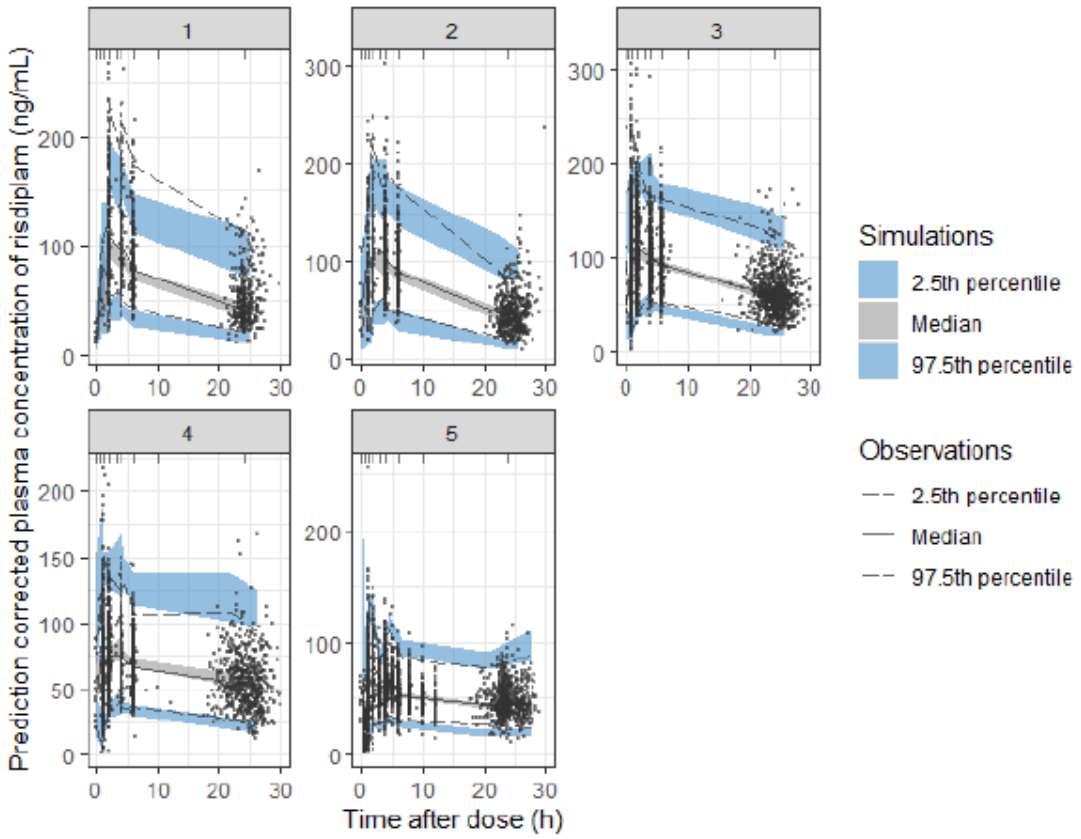


Blue solid line displays median Risdiplam $AUC_{0\text{-}24,ss}$, while the dashed blue lines refer to $AUC_{0\text{-}24,ss}$ cut-off values of 1500 ng·h/mL and 3000 ng·h/mL.

These exposures in SMA patients have also been stratified by age group (Figure 16). The prediction corrected visual predictive checks (pc-VPC) with time after the last dose stratified by age (Figure 16) showed consistent median between the predictions and observations in all age groups. Although minor deviations were seen in 2.5th or 97.5th percentiles in some of the time points, the observations were mostly within the respective confidence interval and prediction of central tendency and variability was considered acceptable. Based on the pc-VPCs, the predictive performance of the final PK model of risdiplam was considered satisfactory.

Figure 24

Figure 16 Prediction Corrected Visual Predictive Check (All Populations) of the Final PK Model of Risdiplam with Time After Dose (by Age Groups)

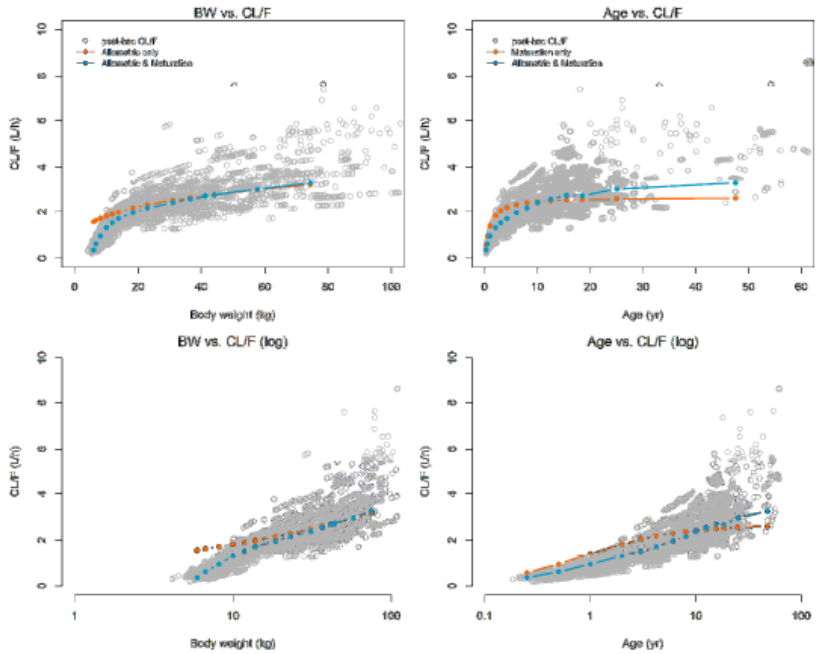


The age groups are 1 (infants): Age < 1 y, 2 (toddlers): 1 y ≤Age<4 y, 3 (children): 4 y ≤Age< 12 y, 4 (adolescents):12 y ≤Age≤18 y, 5 (adults): Age> 18 y

The role of allometric and maturation functions in description of risdiplam CL/F of the model is presented in Figure 12. Allometric function alone would lead to significant bias in CL/F in young children, particularly with body weight <10 kg. Both allometric and maturation functions were therefore required to capture risdiplam CL/F across the age and body weight range.

Figure 25

Figure 12 The Role of Time-Varying Age (Maturation Function) and -Body Weight (Allometric Function) as Covariate on Description of Risdiplam CL/F



Actual age and median body weight for each age group of the data base were used for calculating typical CL/F with 1) allometric function only (orange), 2) maturation function only (orange) and 3) combination of allometric and maturation functions (blue) to illustrate how these functions describe risdiplam CL/F across the patient population.

Based on all available PK, PD, safety, and efficacy data, the following regimen is recommended: Infants below 2 years of age receive a daily dose of 0.2 mg/kg. Infants above 2 years of age receive a daily dose of 0.25 mg/kg, if < 20 kg; or a dose of 5 mg/day, if ≥ 20 kg.

The applicant proposes a chronic administration of risdiplam, based on the sustained level of functional SMN protein with increase levels maintained over the entire treatment duration, with follow-up available to date for more than 2 years (Study BP39055) and 12 months (Study BP39056).

Treatment with risdiplam has been well tolerated so far at all dose levels and in all age groups. Treatment with a daily dose beyond 5 mg has not been studied. According to popPK, the selected dosing regimen for the first dose selection for BP39055 and BP39056 achieved similar exposure across the wide age and body weight range. In the model, both allometric and maturation functions were considered to capture risdiplam CL/F across the age and body weight range. The prediction corrected visual predictive checks (pc-VPC) with time after the last dose stratified by age showed consistent median between the predictions and observations in all age groups. The predictive performance of the final PK model of risdiplam can be considered satisfactory. According to the applicant no conclusive PK data is currently available in infants below 2 months of age (only 5 infants were enrolled to date), and therefore no dosing recommendation can be provided yet for these very young infants.

Observed Exposure-Response Relationship for PD biomarkers

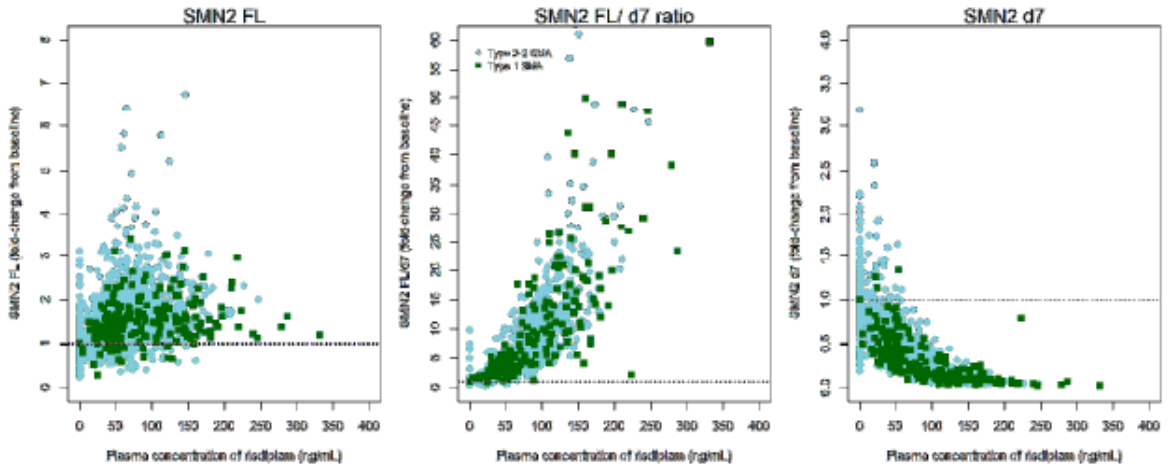
An exposure-dependent response in SMN2 mRNA and SMN protein was observed in all studies in SMA patients. Time-matched plasma concentration of risdiplam showed strong negative correlation with SMNΔ7 mRNA, with a maximum effect starting to be reached for concentrations above 100 ng/mL. A positive but less strong correlation was observed with full-length SMN2 mRNA. Patients with a

risdiplam $AUC_{0\text{-}24h}$ of 2000 ng.h/mL (average concentration of 83 ng/mL) achieve a reduction of SMNΔ7 mRNA by 75%.

Data from studies BP39056 (FIREFISH; Type 1 SMA patients, 1-7 months); BP39055 (SUNFISH; Type 2 or Type 3 SMA patients, 2-25 years) and BP39054 (JEWELFISH; Type 1, Type 2 or Type 3 SMA patients previously treated with other SMA therapeutic products), revealed that the increase in full-length *SMN2* mRNA (*SMN2FL* mRNA), and the corresponding decrease in *SMNΔ7* mRNA (depicted as fold change from baseline), correlates well with the time-matched plasma concentration of risdiplam (Figure 22 and Figure 23 below, from Population PK Analyses Report for Risdiplam).

Figure 26

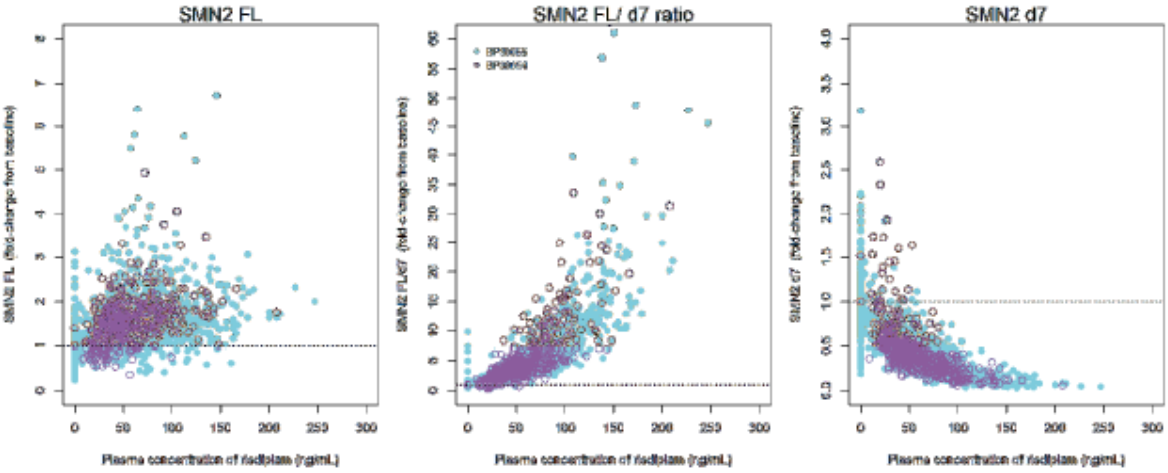
Figure 22 Fold Change from Baseline in SMN2 mRNA versus Time-Matched Risdiplam Plasma Concentration in Type 1 vs. Type 2 or 3 SMA patients



Dashed lines indicate 1, i.e., no change

Figure 27

Figure 23 Fold Change from Baseline in SMN2 mRNA versus Time-Matched Risdiplam Plasma Concentration in Treatment Naïve (BP39055) vs. Previously Treated (BP39054) Type 2 or 3 SMA patients



Dashed lines indicate 1, i.e., no change

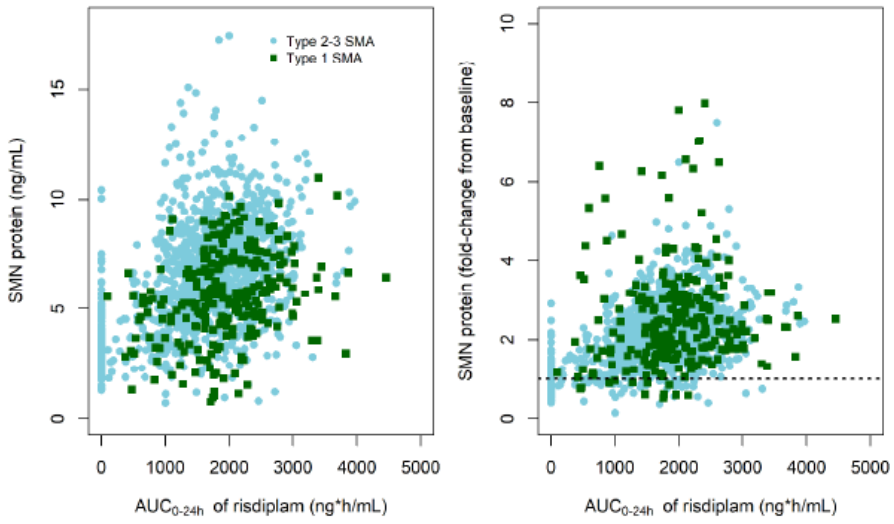
According to the applicant, the almost complete depletion of *Δ7* mRNA at the highest concentrations indicates that although the plateau of the PD response has not been reached completely, the effect at the selected dose levels are not far from the maximum possible effect (shift in mRNA splicing) for almost complete depletion of SMNΔ7 mRNA.

Exposure-dependent linear ($AUC_{0\text{-}24h}$) increase in absolute SMN protein was observed in all SMA types, with similar increase between treatment naïve and previously treated Type 2/3 SMA patients and a comparable median SMN protein at the last observation. Absolute and change from baseline of SMN protein were slightly higher with $AUC_{0\text{-}24}$ > 2000 ng·h/mL in all patients (Type 1-3). Absolute SMN protein values were generally lower in Type 1 SMA patients (greater variability was noted with several infants obtaining a 4-8-fold increase SMN protein), but the fold-increase at the last observation was comparable to Type 2/3 SMA patients.

Comparable PK-PD relationship was seen between treatment-naïve patients from studies BP39056 (Type 1 SMA) and BP39055 (Type 2 or Type 3 SMA), according to Population PK analysis (Figure 20):

Figure 28

Figure 20 Relationship between Risdiplam $AUC_{0\text{-}24h}$ and SMN Protein Compared between SMA Type 1 vs. Type 2 or 3 SMA Patients: 28 Days After First Dose and Onwards

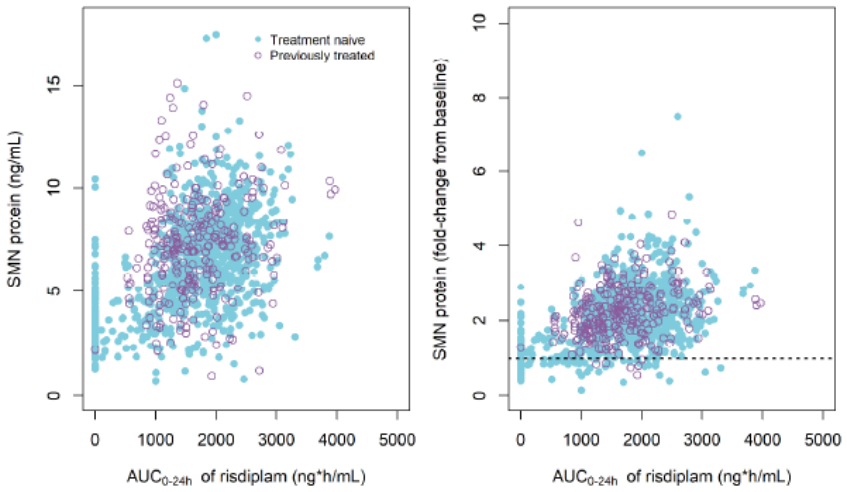


Dashed lines indicate 1, i.e., no change

Comparable PK-PD relationship was also seen between Type 2 or 3 SMA treatment-naïve patients, from study BP39055 and previously treated patients with currently approved SMA therapies, from study BP39054 (Figure 21 below, from Population PK Analyses Report for Risdiplam):

Figure 29

Figure 21 Relationship between Risdiplam $AUC_{0\text{-}24h}$ and SMN Protein Compared between Treatment Naïve vs. Previously Treated Type 2 or 3 SMA Patients: 28 Days After First Dose and Onwards



Dashed lines indicate 1, i.e., no change

Efficacy - Exposure Response Analysis

There was no clear correlation between risdiplam individual exposure (C_{av}, average concentration over the treatment period of 12 months) and efficacy outcomes in Part 2 of studies BP39056 and BP39055.

Safety - Exposure Response Analysis

There was no signal of a relationship between the occurrence of (serious) adverse events and individual exposure (C_{av}) of patients in Part 2 of studies BP39056 and BP39055. Average risdiplam concentration (C_{av}) was comparable in patients experiencing adverse events or serious adverse events *versus* patients not experiencing these events.

2.4.3. Discussion on clinical pharmacology

Pharmacokinetics

The PK profile of risdiplam was sufficiently characterised in healthy subjects through single- and multiple-dose, ADME, DDI, hepatic impairment completed studies and in SMA patients through three ongoing studies and a PPK model. No major issues have been identified. Several concerns were identified and further discussion was provided by the applicant. Clarification with respect to validation and bioanalytical reports, were provided. The expected bioavailability was also clarified. Only a limited available data for a food effect conclusion (derived from Study BP29840) is available. The clinical studies in SMA patients were conducted with the recommendation to take risdiplam with the morning meal. Therefore, the applicant proposes to update the SmPC to indicate that risdiplam shall be taken with a meal, as done during the clinical studies. Clarifications on the distribution and binding with red blood cells and metabolites' profile were satisfactory. Discussion of data on mean half-life and renal clearance, also in terms of risdiplam C_{trough} results to better elucidate the time the steady state is attained both in healthy subjects and SMA patients, along with DDI interactions with CYP3A4 and posology was provided and no further issues require clarification in this regard.

Pharmacodynamics

In general the pharmacodynamics of risdiplam have been sufficiently evaluated. No major issues have been identified and all the concerns previously raised have been adequately addressed.

2.4.4. Conclusions on clinical pharmacology

Pharmacokinetics

From a clinical pharmacokinetics point of view, all aspects raised during the assessment have been adequately addressed.

Pharmacodynamics

Clinical pharmacodynamics of risdiplam have been sufficiently evaluated and the data presented is adequate to support a positive opinion from a pharmacodynamics point of view.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- The applicant will conduct in 2021-2022 a dedicated single-dose tQT-study in healthy adult subjects to support the conclusions on absence of Q-T prolongation by risdiplam.

2.5. Clinical efficacy

Table 16: Ongoing Clinical Studies of Risdiplam in the Treatment of SMA

Study Number	Study Design	Population	Objectives	Dose, Route, Regimen	Number of Patients, CCOD
Pivotal Clinical Studies Contributing Efficacy Data					
BP39056 (FIREFISH): an ongoing pivotal Phase 2/3 study	Open-label, two-part operationally seamless[1] multicentre study	Infants with Type 1 SMA aged 1–7 months at enrolment		Once daily oral administration	
	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. • 0.0106, 0.04, 0.08, 0.2, 0.25 mg/kg once daily. The final selected dose for all patients was 0.2 mg/kg for patients <2 years, and patients ≥2 years received 0.25 mg/kg.	**Part 1:** 21 patients CCOD for 12-month analysis: 27 Feb 2019 (Interim CSR)
	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.	**Part 2:** 41 patients CCOD for 12-month primary analysis: 14 November 2019 (Primary CSR)

				The dose for all infants <2 years has been adjusted to 0.2 mg/kg. Infants ε2 years: 0.25 mg/kg. OLE phase in Parts 1 and 2 (after 24 months of treatment): pivotal dose of 0.2 mg/kg for infants <2 years and 0.25 mg/kg for infants ≥2 years.	
BP39055 (SUNFISH): an ongoing pivotal Phase 2/3 study	Two-part operationally seamless[1] randomised, multicentre, placebo-controlled, double-blind, study	Patients with Type 2 and 3 SMA aged 2–25 years at enrolment		Once daily oral administration	
	Part 1: double-blind, randomised (2:1), placebo-controlled, dose-finding phase, followed by open-label phase to complete 24 months. Afterwards patients can continue in the open-label treatment phase.[2]	**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: placebo, 3 mg or 5 mg ● Age 2–11 years: placebo, 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 ● 2–11 years, n=31 ● 12–25 years, n=20 CCOD for 12-month analysis: 09 Jan 2019 (Interim CSR) CCOD for 24-month analysis: 15 January 2020 (Update CSR)
	Part 2: double-blind, randomised (2:1), placebo-controlled, parallel group treatment period, followed by an OLE phase.[2]	**Part 2:** Type 2 and non-ambulant Type 3 SMA patients	**Part 2:** Efficacy, safety and tolerability, PK and PD	**Part 2:** Placebo or 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. Open-label treatment phase of Part 1 and OLE of Part 2: pivotal dose.	**Part 2:** 180 patients ● Risdiplam, n=120 ● Placebo, n=60 CCOD for 12-month primary analysis: 06 September 2019 (Primary CSR)
Study Number	**Study Design**	**Population**	**Objectives**	**Dose, Route, Regimen**	**Number of Patients, CCOD**
Other Clinical Studies in SMA					

BP39054 (JEWELFISH): an ongoing supportive Phase 2 study	Multicentre, 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 plus extension phase	Type 1, 2, or 3 SMA patients aged 6 months - 60 years	Safety, tolerability, PK and PD	Once daily oral administration 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: 31 January 2020 (Interim CSR)
BN40703 (RAINBOWFISH): an ongoing supportive Phase 2 study	Multicentre, 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 mean $AUC_{0\text{-}24h,ss}$≤2000 ng.h/mL.	Up to 25 patients planned **N=12 as of 25 February 2021**

Study BP39054 (JEWELFISH) due to the limited treatment duration for most patients in this ongoing study at the CCOD (median treatment duration at the CCOD of 31 January 2020 was 3.0 months), efficacy results from Study BP39054 (JEWELFISH) are not available yet. An Interim CSR reports the safety data from this CCOD which is included in the Summary of Clinical Safety.

Study BN40703 (RAINBOWFISH) is a study to assess the efficacy, safety and tolerability, and PK/PD of risdiplam in pre-symptomatic infants from birth to 6 weeks who were genetically diagnosed with SMA. Recruitment is ongoing; up to 15 January 2020, 4 patients had been enrolled. Due to the current small number of patients and limited data from this ongoing study, efficacy results from Study BN40703 (RAINBOWFISH) are not yet available.

Dose-response studies and main clinical studies

Both pivotal studies Study BP39056 (FIREFISH) and BP39055 (SUNFISH) shared a Part 1 which was designed to provide a dose-response and proof of concept insight. Study designs are shown in main studies.

2.5.1. Dose-response studies

Type 1 SMA

Part 1 of Study BP39056 (FIREFISH) was designed as the initial dose-finding part to assess safety, PK, and PD of risdiplam. Efficacy measures were included in Part 1 and were exploratory (CCOD: 27 February 2019).

Both Parts 1 and 2 of Study BP39056 (FIREFISH) share the same inclusion/exclusion criteria, enrolling symptomatic infants with well-established Type 1 SMA at baseline; however, the 21 patients enrolled in Part 1 were not rolled over to Part 2. Therefore, Parts 1 and 2 can be considered as two independent studies.

No hypothesis testing was performed for Part 1; however, the benchmarks (performance criteria) that were derived for the Part 2 analysis, as documented in the Part 2 SAP for Study BP39056 (FIREFISH), were used for exploratory comparisons of Part 1 data. A similar level of confidence would be achieved in Part 1 if at least 4 out of 21 infants (19.0% [90% CI: 6.8%-38.4%]) are sitting without support after 12 months of treatment. Based on this number, the lower limit of the 90% CI would be above 5%.

Study Population

A total of 21 patients with Type 1 SMA were enrolled into Part 1 of Study BP39056 (FIREFISH) across 7 different sites in 5 countries (Belgium, France, Italy, Switzerland, and the United States). At the time of the CCOD (27 February 2019), 18 of 21 patients (85.7%) in Part 1 were still on study; these 18 patients were older than 16 months of age. Three patients (14.3%) had died due to SMA-related respiratory complications; of these, two died before Month 12 (on Day 21 and Day 236) and one died after Month 12 (on Day 387).

All patients received treatment with risdiplam. Two cohorts (Cohort 1 and 2) were defined based on the target exposure specified in the protocol, respectively, for Dose Levels 1 and 2.

Per protocol, the first 4 infants enrolled into the study had to remain at Dose Level 1 at the low target exposure of mean AUC0-24h,ss 700 ng.h/mL. Per protocol, the dose of the 5th patient enrolled was foreseen to be increased to the higher dose level. However, the 5th patient died due to disease-related complications approximately 3 weeks after enrolment into the study, and therefore the dose of the 4th patient was increased instead. As no dose-escalation stopping rules were met after administration of risdiplam in all 5 enrolled patients (for a minimum of 1 week in the one infant receiving Dose Level 2, and longer treatment duration in all previously enrolled infants at Dose Level 1), 3 additional patients were enrolled and received risdiplam at this higher target exposure of mean AUC0-24h,ss ≤2000 ng·h/mL (Dose Level 2). The protocol specified that further patients (up to a maximum total of 24 patients) could be enrolled in Part 1 to enable the dose selection for Part 2. Therefore, after enrolment of the minimum 8 patients described above, a further 13 patients were enrolled at Dose Level 2 (target exposure of mean AUC0-24h,ss ≤2000 ng·h/mL), giving a total number of 21 patients in Part 1 of the study.

The dose administered in Cohort 2 was the same as the pivotal dose used in Part 2 of the study (target exposure of mean AUC0- 24h,ss ≤2000 ng·h/mL), after some initial dose adjustments.

The dose-selection in Part 1 targeted the following:

Starting dose: The first patient was to receive a single dose of 0.00106 mg/kg risdiplam. This dose was predicted to result in an exposure (AUCinf) at least 10-fold below the target exposure of AUC0-24h,ss 700 ng·h/mL (AUC of free fraction: 77 ng.h/mL) for Dose Level 1. This dose was selected based on the most conservative PBPK modelling scenario, plus an additionally applied safety factor of 10.

Dose Level 1: Target exposure of mean AUC0-24h,ss 700 ng·h/mL; an exposure predicted to result in a doubling of SMN protein levels (i.e., a 2-fold increase versus the patient's baseline). The actual dose to achieve this target exposure was calculated based on the PK data obtained.

Dose Level 2: Target exposure of mean AUC0-24,ss ≤2000 ng·h/mL, i.e., a higher exposure than Dose Level 1, leading to the maximum possible SMN protein increase, but not above the exposure cap of an AUC0-24,ss of 2000 ng·h/mL (mean), which corresponds to the no observed adverse effect level (NOAEL) from the animal toxicology studies.

PK monitoring was conducted per protocol in this dose-finding part of the study, and the dose was adjusted throughout Part 1 of the study based on the emerging data. Many patients therefore changed dose during the study. Of the 21 patients enrolled in Part 1 of the study at 7 sites in 5 countries, 15

(71.4%) were female and 6 (28.6%) were male. At enrolment, the median age of all patients was 6.7 months, thus on the older end of the permitted age (range: 3.3-6.9 months); 15 of 21 patients (71.4%) were older than 5 months. The median age at diagnosis was 3.0 months (range: 0.9-5.4 months) and the median age at onset of symptoms was 2 months (range 0.9 - 3.0 months).

In accordance with the inclusion criteria, all patients had a genetic confirmation of Type 1 SMA (SMN1) and had two SMN2 gene copies.

At baseline, the median BSID-III Gross Motor Scale score was 2.0 (range: 0.0-4.0), the median CHOP-INTEND score was 24.0 points (range 10.0-34.0), the median HINE-2 score was 1.0 point (range 0.0-3.0), and the median baseline CMAP amplitude was 0.2 mV (range: 0.0-0.6), confirming all enrolled patients had well-established Type 1 SMA disease at the time of study enrolment. The median time between the onset of symptoms and first treatment was 4.0 months (range: 2.0 - 5.8 months).

At the CCOD of 27 February 2019, patients enrolled in Part 1 had been treated for a median of 14.8 months (range: 0.6-26.0 months), and 19 of 21 patients had at least 12 months of treatment on risdiplam.

Table 17- Summary of Efficacy Endpoints in Part 1 at Month 12 (ITT Population, Part 1 Patients)

Endpoint	Cohort 1 (n=4)	Cohort 2 (n=17)	All Patients (n=21)
Motor Function and Development Milestones			
Proportion of patients sitting without support for 5 seconds (BSID-III) at Month 12 (90% CI)	0 (0.0, 52.7)	7 (41.2%) (21.2, 63.6)	7 (33.3%) (16.8, 53.6)
Proportion of patients who achieve a score of 40 or higher in the CHOP-INTEND at Month 12 (90% CI)	1 (25.0%) (1.3, 75.1)	10 (58.8%) (36.4, 78.8)	11 (52.4%) (32.8, 71.4)
Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12 (90% CI)	3 (75.0%) (24.9, 98.7)	15 (88.2%) (67.4, 97.9)	18 (85.7%) (67.1, 96.0)
Proportion of patients who achieve head control (defined as a score of ≥3 for Item 12 of the CHOP-INTEND) at Month 12 (90% CI)	2 (50.0%) (9.8, 90.2)	9 (52.9%) (31.1, 74.0)	11 (52.4%) (32.8, 71.4)
Proportion of patients who achieve head control assessed by HINE-2 at Month 12 (90% CI):			
Wobbles	2 (50.0%) (9.8, 90.2)	4 (23.5%) (8.5, 46.1)	6 (28.6%) (13.2, 48.7)
All the time maintained upright	0 (0.0, 52.7)	9 (52.9%) (31.1, 74.0)	9 (42.9%) (24.5, 62.8)
Proportion of motor milestone responders [a] as assessed by the HINE-2 at Month 12 (90% CI)	1 (25.0%) (1.3, 75.1)	13 (76.5%) (54.0, 91.5)	14 (66.7%) (46.4, 83.2)
Survival and Ventilation-Free Survival			
Proportion of patients alive without permanent ventilation at Month 12 (90% CI)	3 (75.0%) (22.3, 94.6)	16 (94.1%) (73.0, 98.8)	19 (90.5%) (72.6, 96.9)
Proportion of patients alive at Month 12 (90% CI)	3 (75.0%) (22.3, 94.6)	16 (94.1%) (73.0, 98.8)	19 (90.5%) (72.6, 96.9)
Respiratory			
Proportion of patients who do not require invasive or non-invasive respiratory support at Month 12 (90% CI)	1 (25.0%) (1.3, 75.1)	3 (17.6%) (5.0, 39.6)	4 (19.0%) (6.8, 38.4)
Proportion of patients who achieve a reduction of at least 30 degrees in their phase angle from baseline, as measured by RP at Month 12 (90% CI)	0 (0.0, 52.7)	5 (29.4%) (12.4, 52.2)	5 (23.8%) (9.9, 43.7)
Nutrition			
Proportion of patients with the ability to feed orally [b] at Month 12 (90% CI)	3 (75.0%) (24.9, 98.7)	15 (88.2%) (67.4, 97.9)	18 (85.7%) (67.1, 96.0)

Endpoint	Cohort 1 (n=4)	Cohort 2 (n=17)	All Patients (n=21)
Muscle Electrophysiology			
Proportion of patients with an increase of ≥0.3mV from baseline in CMAP negative peak amplitude at Month 12 (90% CI)	0 (0.0, 52.7)	13 (76.5%) (53.9, 91.5)	13 (61.9%) (41.7, 79.4)
Healthcare Utilization			
Number of hospitalizations [c] per patient-year at Month 12 (90% CI)	1.91 (0.83, 3.76)	1.03 (0.65, 1.54)	1.17 (0.80, 1.65)
Proportion of patients with no hospitalizations at Month 12 (90% CI)	0 (0.0, 52.7)	8 (47.1%) (26.0, 68.9)	8 (38.1%) (20.6, 58.3)
Patient/Caregiver Reported Outcomes			
ITQOL-SF47 patient overall health item score: median (range) change from baseline to Month 12 [d]	N=3 0.0 (0.0 - 60.0)	N=16 0.0 (-70.0 - 60.0)	N=19 0.0 (-70.0 - 60.0)

Abbreviations: BSID-III=Bayley Scales of Infant and Toddler Development – Third Edition; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP=compound muscle action potential; HINE-2=Module 2 of the Hammersmith Infant Neurological Examination; ITQOL-SF47=Infant/Toddler Quality of Life Questionnaire – Short Form 47-Item Version; RP=respiratory plethysmography.

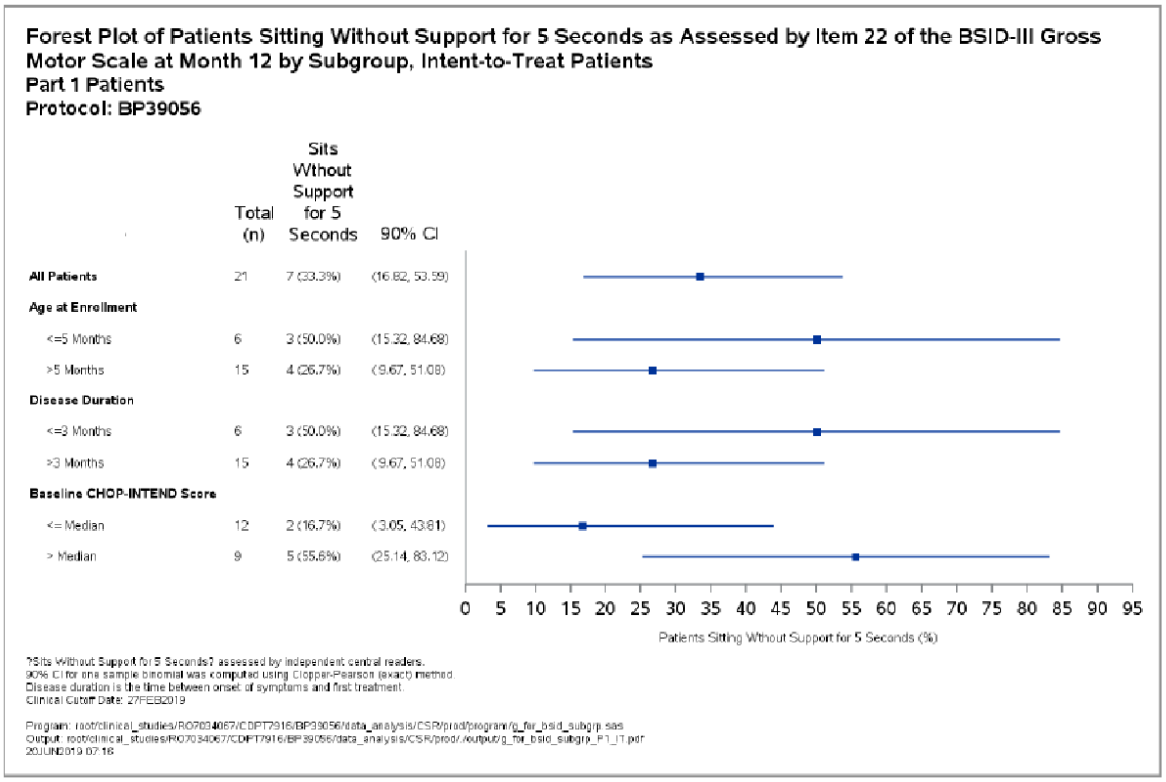
[a] An improvement in a motor milestone was defined as at least a 2-point increase in the ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing, or walking. Voluntary grasp was excluded from the definition. An infant was classified as a responder if more motor milestones show improvement than show worsening.

[b] Includes patients who were fed exclusively orally (15 patients overall) and those who were fed orally in combination with a feeding tube (3 patients overall) at Month 12.

[c] Hospitalizations include all hospital admissions which spanned at least two days.

[d] No imputation was performed for ITQOL-SF47; therefore, Ns are based on patients with available data at Month 12.

Figure 30 - Forest Plot of Patients Sitting without Support for 5 seconds at Month 12 by Subgroup (ITT Patients; Part 1 Patients)



In Part 1 of the interim summary for FIREFISH Study only 4 infants aged 3.3-5 months were enrolled, with higher exposure observed in 3 of these infants, and no data were available in infants < 3 months.

Later onset SMA: Type 2 and 3

SUNFISH study consists of two parts: an exploratory dose-finding part (Part 1) and a confirmatory part (Part 2), starting once the dose was selected in Part 1. The two parts of the study are independent, have their own objectives and eligibility criteria, and have been analysed separately. Patients in Part 1 did not roll over into Part 2 of the study.

SUNFISH Exploratory Part 1

Key inclusion criteria: Type 2 or ambulatory and non-ambulatory Type 3 SMA, with confirmed genetic diagnosis of 5q autosomal recessive SMA.

Key exclusion criteria were previous participation in an SMN2-targeting study or gene therapy study and planned (within 18 months) or previous (<1 year prior) surgery for scoliosis or hip fixation.

First Patient Enrolled in Part 1: 19 Oct 2016; Last Patient Enrolled in Part 1: 06 Jul 2017

Clinical cut-off date (CCOD): 09 Jan 2019 (when all patients in Part 1 had been treated with risdiplam for at least 12 months).

The objectives of Part 1 are:

- To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics 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.

- To investigate the PK/PD relationship of risdiplam by PK/PD modeling

- To explore the effect of risdiplam on motor function, respiratory function, and pre-specified adverse events and patient-reported QOL measures.

NUMBER OF SUBJECTS: Part 1 (2:1 active placebo): minimum of 36 (planned); 51 (actual) (35 initially to risdiplam; 16 to placebo)

DOSE: Part 1 initial doses: 0.02, 0.05, 0.25 mg/kg (2-11 year old patients), and 3 and 5 mg (12-25 year old patients). Patients in Part 1 switched to the pivotal dose after the dose selection decision: 5 mg (BW ≥20 kg) and 0.25 mg/kg (BW <20 kg). Oral, once daily administration.

Rationale for Dosage Selection:

Two target exposure levels ('Dose Levels') were planned to be tested in Part 1 of the study and evaluated to select the most appropriate dose for Part 2 of the study (pivotal dose).

- **Dose Level 1**: Based on physiologically based pharmacokinetic (PBPK) modelling using available data in healthy subjects and taking into account the tissue distribution and different body weight and body composition in SMA patients compared with healthy subjects, an oral dose of 3 mg once daily was selected for Dose Level 1 and was administered to Group A (patients aged 12-25 years at age of randomisation) who were initially enrolled into this study. The dose of 3 mg was predicted to result in an AUC0-24h,ss of 700 ng · h/mL in SMA patients aged 12-25 years, which is approximately 3-fold (2.8) below the specified exposure cap and was anticipated to result in the targeted 2-fold SMN protein increase. This dose and exposure were anticipated to be safe and well-tolerated based on the single ascending dose data obtained in healthy subjects (single-dose administration of up to 18 mg) and the animal toxicology studies.

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

- **Dose Level 2**: a higher exposure, leading to the maximum possible SMN protein increase (provided all clinical and non-clinical safety data support this), which was predicted to provide greater benefit based on nonclinical data as well as published clinical data with the antisense oligonucleotide nusinersen. The highest possible SMN protein increase was assumed to be 3-fold, based on *in vivo* studies and *in vitro* cell culture data with SMA patient fibroblasts and motor neurons. Modelling predicted that this SMN protein increase may be reached at an exposure not exceeding the mean exposure cap of 2000 ng · h/mL AUC0-24h,ss. Under no circumstances was a dose to be selected that would lead to an exposure above a mean AUC0-24h,ss of 2000 ng · h/mL or a mean Cmax of 400 ng/mL.

In line with this dose selection approach based on SMN protein increase and PK data , and based on nonclinical data not showing new toxicities (beside retinal findings) beyond a few weeks of treatment, 4 weeks of treatment appeared sufficient to reach PK steady state and to assess acute safety and tolerability of the respective dose levels and make dose decisions (dose escalation in Part 1 and selection of the pivotal dose level).

Considering the study design and pace of enrolment, at these decision points patients enrolled first had longer treatment durations.

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

Table 18 - Part 1: Summary of Age Groups and Dose Cohorts (Initially Assigned Dose)

	Dose Level 1 [a]		Dose Level 2 [b]	
	Placebo n	Active n	Placebo n	Active n
Group A (12–25 years)				
Cohort A1 (3 mg)	3	7	-	-
Cohort A2 (5 mg)	-	-	3	7
Group B (2–11 years)				
Cohort B1 (0.02 mg/kg)*	3	7	-	-
Cohort B2 (0.05 mg/kg)*	4	7	-	-
Cohort B3 (0.25 mg/kg)	-	-	3	7

[a] Dose Level 1: target $AUC_{0\text{-}24h,ss}$ 700 ng•h/mL (mean)
[b] Dose Level 2: target maximum possible SMN protein increase not exceeding the exposure cap of 2000 ng•h/mL $AUC_{0\text{-}24h,ss}$ (mean)
*The initial dose selected for Cohort B1 (0.02 mg/kg) resulted in lower exposure than predicted, and therefore an additional cohort (Cohort B2, dose of 0.05 mg/kg) was started to target the exposure level foreseen for 'Dose Level 1', i.e. a mean $AUC_{0\text{-}24h,ss}$ 700 ng•h/mL; the dose in Cohort B1 was also increased to 0.05 mg/kg . Upon further PK evaluation, the dose for both cohorts was increased to 0.15 mg/kg.

BLINDING: For the exploratory Part 1 of this study, the Sponsor was unblinded (in a restricted manner) to patient treatment assignment to enable the IMC to review the data in order to make dose-escalation decisions and determine the dose for Part 2 of the study.

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

EFFICACY OUTCOMES: The main exploratory efficacy outcomes measures for Part 1 were:

- **Motor Function**: Motor Function Measure-32 item version (MFM32); Hammersmith Functional Motor Scale-Expanded (HFMSE); Revised Upper Limb Module (RULM)

The **MFM32** is a 32-item ordinal assessment classified into three domains [Domain 1: Standing, transfers and ambulation); Domain 2: Axial and proximal motor function in supine and sitting position (3/12 items evaluate arm function with the patient seated on a chair); Domain 3: Distal motor function] on a 4-point Likert scale based on the patient's maximal abilities without assistance (0-96, higher scores indicate motor function). The MFM32 has been validated for measuring motor function in

patients with neuromuscular diseases, including SMA (Bérard et al. 2005; Vuillerot et al. 2013; Trundell et al. 2019).

The 32 scores are summed and then transformed onto a 0-100 scale (i.e., sum of 32 items scores divided by 96 and multiplied by 100) to yield the MFM32 total score expressed as a percentage of the maximum score possible for the scale. The lower the total score, the more severe the functional impairment.

Although a shorter version of the MFM (the 20-item MFM [**MFM20**]) has been previously used in children younger than 7 years, the 12 excluded items assess functions important for daily life.

Please refer to Part 2 Outcome section for the description of Hammersmith Functional Motor Scale-Expanded (**HFMSE**); Revised Upper Limb Module (**RULM**)

- **Respiratory:** Forced vital capacity (FVC)

STATISTICAL METHODS: Exploratory efficacy analyses (except disease related AEs) are mainly based on the all exposure to risdiplam treatment period using an adjusted baseline (defined as the last measurement prior to the first dose of risdiplam treatment at any dose). Efficacy data are summarised descriptively by time point and patient age group (2-11 and 12-25 years).

Sensitivity analyses were conducted on MFM analyses:

-summarised by age group of 2- 11 and 12- 25 years, and total for all patients, on the full 32 items scale (MFM32 scores) by excluding patients who performed the MFM20 scale at any time point as confirmed by a protocol deviation;

- MFM analyses on the 20-item scale (MFM20 scores) for those patients who performed the MFM20 scale as confirmed by a protocol deviation, at any time point.

Subgroup Analyses

The consistency of the efficacy endpoints for MFM32, HFMSE and RULM were explored for the following subgroups for the all exposure to risdiplam treatment period:

- Age group (2-5, 6-11, 12-17, and 18-25 years at randomisation).

- SMA type and ambulatory status (SMA Type 2, SMA Type 3 ambulant, SMA Type 3 non-ambulant)

- SMN2 Copy number

In addition, the change from adjusted baseline in the MFM32 total score at Month 12 was explored by investigational site for the all exposure to risdiplam treatment period. Sites with less than 5 patients enrolled were pooled for analysis.

Changes to Planned Analyses after Database Lock - MFM20 Performed Instead of MFM32

Per protocol, all patients should have completed the MFM32 at all visits. However, as described in Section 5.4 (Protocol Deviations), for 7 patients aged 4-5 years, the MFM20 was administered in error at baseline and some subsequent visits up to Week 35:

- 7 patients: MFM20 was performed at baseline

- 3 patients: MFM20 was performed at baseline and Week 17

- 1 patient: MFM20 was performed at baseline, Week 17 and Week 35

In accordance with the MFM scoring manual, the missing 12 items at these visits were imputed as 0 leading to bias in the primary analysis method (i.e., at Month 12, the actual MFM32 scores are

assessed and therefore the missing 12 items for these patients at baseline could only show an improvement post-baseline). To remove any such bias, a sensitivity analysis on the MFM32 was already planned excluding patients who performed the MFM20 scale at any time point as confirmed by a protocol deviation. The results excluding patients who performed the MFM20 at any time point are considered to show the true treatment effect of risdiplam and therefore additional analyses based on this population were conducted as described below.

- Waterfall plots of individual change from adjusted baseline in the MFM32 total score at Month 12 (excluding patients who performed MFM20 at any time point) plotted with x-axis by ascending values of 1) age, 2) total MFM32 score at adjusted baseline and 3) duration of disease prior to first risdiplam treatment in months.

- Subgroup analysis based on MFM32 excluding patients who performed MFM20 at any time point.

- MFM32 domain score analysis excluding patients who performed MFM20 at any time point.

The focus of the efficacy results and conclusions are based on the sensitivity analysis method (i.e., MFM32 scores excluding patients who performed MFM20 at any time point).

Addendum CSR SUNFISH: Changes in Conduct of Study or Planned Analyses

- For safety reporting in Study BP39055 (SUNFISH), when a patient had multiple records within the same visit window, the "last" record was used for clinical laboratory tests, vital signs, ECGs, and ophthalmology data and was reported as such in the interim CSR. This approach is correct, but deviates from the Study BP39055 Part 1 Statistical Analysis Plan (SAP) which states, due to a typographical error, that the "worst" record will be selected for the summary of the data.
- In the responder analyses of MFM, HFMSE and RULM the number of patients with an assessment at the respective timepoint was used to calculate the percentage of responders. This deviated from the SAP, which stated that patients who withdrew or had missing values would be treated as non-responders.

METHODS: In Part 1, 51 patients were enrolled in five cohorts in a staggered dose escalating design.

Patients were randomised to either placebo or risdiplam at initially assigned doses of 0.02, 0.05 and 0.25 mg/kg for the age group of 2-11 years, and 3 and 5 mg for the age group of 12-25 years. After patients in Part 1 completed the minimum 12-week double-blind treatment period, patients on placebo were switched to risdiplam at the dose tested in their cohort until the Independent Monitoring Committee selected the dose for Part 2 (triggered by data availability from the last cohort enrolled). Patients initially on placebo had to complete the scheduled visit at Week 17 prior to switching and then followed the Schedule of Assessments starting again at Day 1.

After selection of the pivotal dose, all patients in Part 1 were switched to the pivotal dose to complete 24 months of treatment (pivotal dose ≥2 years: 5 mg once daily for patients with body weight ≥20 kg and 0.25 mg/kg once daily for patients with body weight <20 kg.

After completion of the 24-month treatment period, the patient will be given the opportunity to enter the open-label extension (OLE) phase of the study, which will include regular monitoring of safety, tolerability and efficacy. Unless the development of the drug is stopped, the patient's treatment in the OLE may continue for an additional 3 years (i.e., patients will be treated for a total duration of at least 5 years). Thereafter, treatment will continue until the drug is available commercially in the patient's country. The treatment with study medication in the extension phase will continue as per the main study with regards to dosing.

As a consequence of the study design, out of the 51 in Part 1:

- 14 patients have been treated at the selected pivotal dose from study start

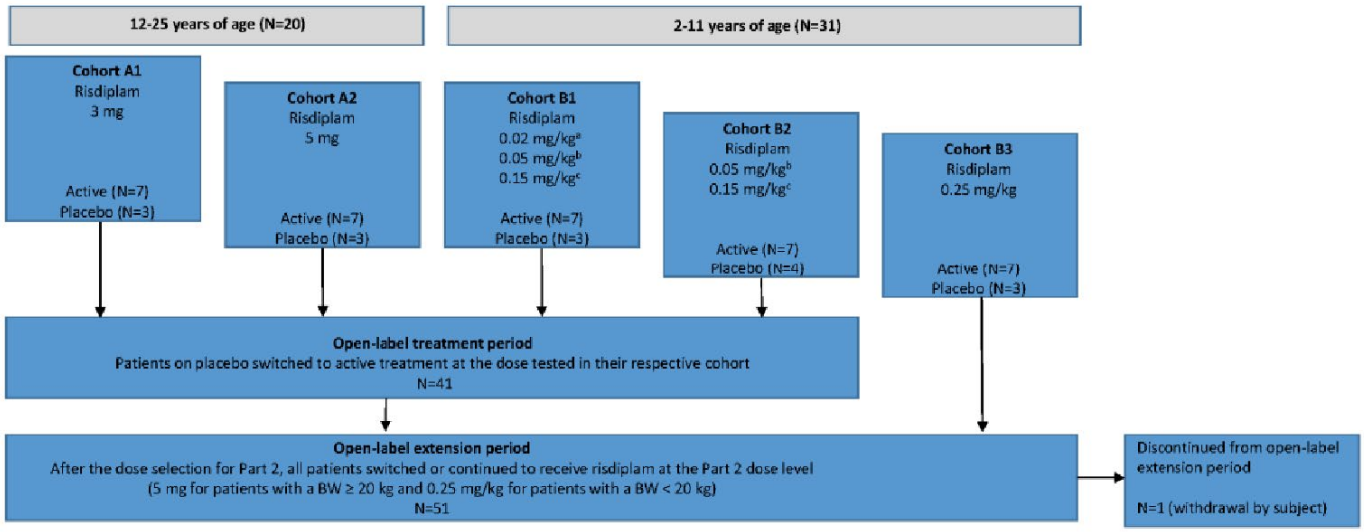
- 21 patients have been on active treatment from study start, initially receiving a lower dose of risdiplam

- 16 patients received placebo for at least 17 weeks prior to switching to active treatment, either on a lower dose of risdiplam initially (10 patients) or straight to the pivotal dose (6 patients).

STUDY POPULATION: Part 1 involved 5 investigational sites across 4 countries (Italy [2], Germany [1], France [1], Belgium [1]).

51 patients (37 [73%] with Type 2, and 14 [27%] with Type 3 SMA) were enrolled. Overall, 27 patients (52.9%) were female. At screening, the median age of all patients was 7.0 years (range: 2-24 years); 20 patients (39.2%) were 12 years or older. The proportion of Type 2 SMA patients was similar across the two age groups (2-11 and 12-25 years), and the majority of patients were non-ambulatory (86.3%). Twenty-nine patients (60%) had scoliosis at screening, including 6 patients with severe scoliosis.

Figure 31 - Disposition Flowchart by Age Group and Treatment Cohort



Notes: Cohorts A1, B1 and B2 targeted exposure (Dose Level) 1; Cohorts A2 and B3 targeted exposure (Dose Level) 2.
Dose escalation and cohort opening decisions were taken by the IMC following review of safety, PK and PD data as described in the protocol.
Cohorts were enrolled in a staggered manner therefore the length of time in each study period per cohort is variable. The placebo-controlled period was a minimum of 12 weeks and varied between the cohorts depending on when the IMC decision was taken to switch patients from placebo to active. Patients initially on placebo had to complete the scheduled visit at Week 17 prior to switching and then followed the Schedule of Assessments starting again at Day 1.
The IMC selected the pivotal dose, as described in the protocol, prior to all patients in the last enrolling cohort (B3) completing 12 weeks of treatment. Placebo patients in Cohort B3 remained on placebo for at least 12 weeks and were then switched to the Part 2 risdiplam dose at their next scheduled visit (Week 17 at the earliest), hence patients in Cohort B3 did not have an open-label treatment period.

[a] Cohort starting dose.
[b] The IMC recommended increasing the dose to 0.05 mg/kg for patients in Cohorts B1 and enrolling an additional Cohort (B2) starting at 0.05 mg/kg targeting patients aged 2-6 years.
[c] The IMC recommended increasing the dose for patients in Cohorts B1 and B2 to 0.15 mg/kg.

Source tables: t_ds_CHT_DB_IT_P1; t_ds_DB_IT_P1; t_ds_OLT_IT_P1; Table 5.

Table 19 - SMA Baseline Disease Characteristics (Part 1; ITT Population)

Summary of SMA Disease Baseline Characteristics, Intent-to-Treat Patients, Part 1 Patients
Protocol: BP39055

	Patients (Age 2-11 yrs) (N=31)	Patients (Age 12-25 yrs) (N=20)	All Patients (Age 2-25 yrs) (N=51)
Ambulatory/Non-ambulatory			
AMBULATORY	6 (19.4%)	1 (5.0%)	7 (13.7%)
NON-AMBULATORY	25 (80.6%)	19 (95.0%)	44 (86.3%)
SMN2 copy number (central laboratory)			
2	0	1 (5.0%)	1 (2.0%)
3	28 (90.3%)	18 (90.0%)	46 (90.2%)
4	3 (9.7%)	1 (5.0%)	4 (7.8%)
SMA type			
TYPE II	23 (74.2%)	14 (70.0%)	37 (72.5%)
TYPE III	8 (25.8%)	6 (30.0%)	14 (27.5%)
Initial SMA symptoms (best response)			
DEVELOPMENTAL MOTOR DELAY	8 (25.8%)	7 (35.0%)	15 (29.4%)
GAIT ABNORMALITY	3 (9.7%)	0	3 (5.9%)
HEAD DROPS	1 (3.2%)	0	1 (2.0%)
HYPOTONIA	10 (32.3%)	1 (5.0%)	11 (21.6%)
LIMB WEAKNESS	7 (22.6%)	11 (55.0%)	18 (35.3%)
LIMBS PAIN	1 (3.2%)	0	1 (2.0%)
MISSING AUTONOMOUS DEBULATION	1 (3.2%)	0	1 (2.0%)
THE PATIENT DID NOT REACH THE ERECTED STATION	0	1 (5.0%)	1 (2.0%)
Age of onset of initial symptoms (in Months)			
n	31	20	51
Mean (SD)	15.4 (12.0)	15.8 (8.2)	15.6 (10.6)
Median	13.0	16.0	14.0
Min - Max	4 - 70	2 - 34	2 - 70
Age at diagnosis (in Months)			
n	31	20	51
Mean (SD)	17.3 (5.9)	21.7 (14.0)	19.0 (10.0)
Median	16.0	17.0	16.0
Min - Max	8 - 30	11 - 67	8 - 67
Tracheotomy (yes/no)			
No	31 (100%)	20 (100%)	51 (100%)

Patient are grouped by initial treatment received and/or by age.
Clinical Cutoff Date: 09JAN2019

Summary of SMA Disease Baseline Characteristics, Intent-to-Treat Patients, Part 1 Patients
Protocol: BP39055

	Patients (Age 2-11 yrs) (N=31)	Patients (Age 12-25 yrs) (N=20)	All Patients (Age 2-25 yrs) (N=51)
Time between onset for initial SMA symptoms to first treatment (in Months)			
n	31	20	51
Mean (SD)	54.2 (28.2)	181.7 (41.8)	104.2 (71.4)
Median	49.9	167.4	78.1
Min - Max	21 - 127	133 - 275	21 - 275
Patient level of motor function(baseline/screening)			
MAINTAINS HEAD CONTROL	0	1 (5.0%)	1 (2.0%)
ROLLS	6 (19.4%)	4 (20.0%)	10 (19.6%)
CREEP/CRAWLS	2 (6.5%)	2 (10.0%)	4 (7.8%)
SITS WITH ASSISTANCE (BRACE OR WHEELCHAIR SUPPORT)	1 (3.2%)	5 (25.0%)	6 (11.8%)
SITS WITHOUT ASSISTANCE	9 (29.0%)	4 (20.0%)	13 (25.5%)
STANDS WITH ASSISTANCE KAFOS/AFOS	4 (12.9%)	0	4 (7.8%)
WALKS WITH KAFOs/AFOs	3 (9.7%)	2 (10.0%)	5 (9.8%)
INDEPENDENT WALKING	6 (19.4%)	2 (10.0%)	8 (15.7%)
No Pulmonary Care (Non-Invasive or Invasive)			
Yes	9 (29.0%)	13 (65.0%)	22 (43.1%)
Cough Assist - Used Daily For Therapy, Not Illness Related			
Yes	9 (29.0%)	1 (5.0%)	10 (19.6%)
Cough Assist - Used With An Illness			
Yes	7 (22.6%)	4 (20.0%)	11 (21.6%)
BiPAP Support For Less Than 16 Hours Per Day			
Yes	8 (25.8%)	4 (20.0%)	12 (23.5%)
Airway Clearance Through Cough Assistance			
Yes	2 (6.5%)	4 (20.0%)	6 (11.8%)

– Patient are grouped by initial treatment received and/or by age.
Clinical Cutoff Date: 09JAN2019

Summary of SMA Disease Baseline Characteristics, Intent-to-Treat Patients, Part 1 Patients
Protocol: BP39055

	Patients (Age 2-11 yrs) (N=31)	Patients (Age 12-25 yrs) (N=20)	All Patients (Age 2-25 yrs) (N=51)
Scoliosis (yes/no)			
Yes	13 (41.9%)	16 (80.0%)	29 (56.9%)
No	18 (58.1%)	4 (20.0%)	22 (43.1%)
Degree of curvature due to scoliosis (<10, 10-40, >40)			
0-10	1 (3.2%)	4 (20.0%)	5 (9.8%)
10-40	11 (35.5%)	7 (35.0%)	18 (35.3%)
>40	1 (3.2%)	5 (25.0%)	6 (11.8%)
Scoliosis surgery before screening (yes/no)			
Yes	1 (3.2%)	8 (40.0%)	9 (17.6%)
No	20 (64.5%)	11 (55.0%)	31 (60.8%)
Highest motor function achieved			
ROLLS	4 (12.9%)	3 (15.0%)	7 (13.7%)
BOTTOM SHUFFLES	2 (6.5%)	0	2 (3.9%)
CREEP/CRAWLS	3 (9.7%)	0	3 (5.9%)
SITS WITHOUT ASSISTANCE	5 (16.1%)	2 (10.0%)	7 (13.7%)
STANDS WITH ASSISTANCE KAFOS/AFOS	3 (9.7%)	1 (5.0%)	4 (7.8%)
STANDS INDEPENDENTLY	0	1 (5.0%)	1 (2.0%)
WALKS WITH CRUTCHES/FRAME/ROLLATOR	0	1 (5.0%)	1 (2.0%)
WALKS WITH KAFOs/AFOs	7 (22.6%)	6 (30.0%)	13 (25.5%)
INDEPENDENT WALKING	7 (22.6%)	6 (30.0%)	13 (25.5%)
Number of fractures (None, 1-2, 3-5 or >= 6)			
1-2	4 (12.9%)	6 (30.0%)	10 (19.6%)
3-5	0	3 (15.0%)	3 (5.9%)
NONE	27 (87.1%)	11 (55.0%)	38 (74.5%)
Hip subluxation or dislocation (yes/no)			
Yes	0	1 (5.0%)	1 (2.0%)
No	31 (100%)	19 (95.0%)	50 (98.0%)
Hip surgery (yes/no)			
Yes	0	1 (5.0%)	1 (2.0%)
No	31 (100%)	19 (95.0%)	50 (98.0%)

Patient are grouped by initial treatment received and/or by age.
Clinical Cutoff Date: 09JAN2019

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Adapted from t_dm_sma_IT_P1 and t_dm_smncopy_IT_P1 (for *SMN2* copy number from central laboratory)

RESULTS: PART 1 DOSE SELECTION

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

- Was judged to be safe and well-tolerated, based on all available safety data from Part 1 and as confirmed by the iDMC.

- Resulted in an exposure at steady-state below the exposure cap (mean value) of AUC0-24h,ss 2000 ng · h/mL (adjusted for free-fraction, if required).

- Resulted in an SMN protein increase that is expected to be clinically relevant.

Overall, the approach was to target the highest SMN protein increase that could be achieved with risdiplam; however, the shape of the PK/PD curve was taken into account to determine the most appropriate target exposure (and therefore, dose), considering safety and tolerability data across exposure levels in Part 1 and a pre-defined exposure cap threshold.

Based on review of all available PK, PD, safety, and tolerability data when the last patient of the last cohort in Part 1 reached 4 weeks of treatment, the IMC selected the dose to be administered in Part 2 of the study as 5 mg once daily for patients with BW ≥20 kg and 0.25 mg/kg once daily for patients with BW <20 kg. This dose was expected to lead to a mean exposure (AUC0-24h,ss) of 1690 ng·h/mL [95% CI 1600-1780 ng·h/mL] across all patients 2-25 years of age, and was not expected to significantly exceed the exposure cap for any age or BW category.

The iDMC reviewed all available Part 1 data and confirmed the dose selected by the IMC. The final decision based on the iDMC recommendation was made by the Sponsor.

EXPLORATORY EFFICACY RESULTS Part 1:

Table 20 -Part 1: MFM Results at 12 Months of Risdiplam Treatment (Part 1; ITT Population)

Endpoint	Patients Ages 2–11 Years (n=31)	Patients Ages 12–25 Years (n=20)	All Patients All Ages (2–25 years) (n=51)
MFM32 Total Score (primary analysis)[a]			
Baseline, Mean (SD) **Month 12** Change from baseline, Mean (SD) Proportion of patients (95% CI) who achieve improvement (i.e., change from baseline of ≥3)	43.3 (11.9) **n=31** 7.5 (8.9) 77.4% (58.9%, 90.4%)	40.9 (18.2) **n=19** 1.6 (3.4) 42.1% (20.3%, 66.5%)	42.3 (14.5) **n=50** 5.3 (7.8) 64.0% (49.2%, 77.1%)
MFM32 Total Score (excluding patients who completed the MFM20)[b]			
Baseline, Mean (SD) **Month 12** Change from baseline, Mean (SD) Proportion of patients (95% CI) who achieve improvement (i.e., change from baseline of ≥3)	44.4 (11.9) **n=24** 3.5 (3.8) 70.8% (48.9%, 87.4%)	40.9 (18.2) **n=19** 1.6 (3.4) 42.1% (20.3%, 66.5%)	42.9 (15.0) **n=43** 2.7 (3.7) 58.1% (42.1%, 73.0%)
MFM20 Total Score (patients who completed the MFM20)[c]			
Baseline, Mean (SD) **Month 12** Change from baseline, Mean (SD)	62.6 (18.9) **n=7** 2.6 (2.1)	- **n=0** -	62.6 (18.9) **n=7** 2.6 (2.1)

Notes: Baseline is the last measurement prior to patients first dose of risdiplam.

CCOD: 9 January 2019.

[a] Based on the pre-specified primary analysis method which includes patients who completed the MFM32 and those who completed the MFM20 at baseline (with imputed 0s for the missing 12 items at baseline for the MFM20).

[b] MFM32 results are based on patients who completed the MFM32 at baseline and subsequent time points (i.e., patients who performed MFM20 at any time point are excluded).

[c] MFM20 results are based on patients who completed only the MFM20 at baseline (i.e., patients had 12 items removed from MFM32 at subsequent time points to be able to compare to baseline MFM20)

Sources: t_ef_mfm32r_IT_P1, t_ef_mfm32r_prop_IT_P1; t_ef_mfm32r_exc_IT_P1; t_ef_mfm32r_prop_exc_IT_P1; t_ef_mfm20r_exc_IT_P1.

Table 21 - Part 1: HFMSE, RULM and FVC Results at 12 Months of Risdiplam Treatment (Part 1; ITT Population)

Endpoint	Patients Ages 2–11 Years (n=31)	Patients Ages 12–25 Years (n=20)	All Patients All Ages (2–25 years) (n=51)
HFMSE Total Score			
Baseline, Mean (SD)	20.4 (16.9)	13.0 (16.1)	17.5 (16.8)
Month 12	**n=31**	**n=19**	**n=50**
Change from baseline, Mean (SD)	0.8 (4.0)	0.1 (3.5)	0.5 (3.8)
Proportion of patients who achieve improvement (i.e., a change from baseline ≥2)	48.4% (30.2%, 66.9%)	31.6% (12.6%, 56.6%)	42.0% (28.2%, 56.8%)
RULM			
Baseline, Mean (SD)	18.2 (7.8)	19.0 (9.1)	18.5 (8.2)
Month 12	**n=31**	**n=19**	**n=50**
Change from baseline, Mean (SD)	2.1 (3.4)	1.1 (1.8)	1.7 (2.9)
Proportion of patients who achieve improvement (i.e., a change from baseline of ≥2)	54.8% (36.0%, 72.7%)	42.1% (20.3%, 66.5%)	50.0% (35.5%, 64.5%)
FVC (best percentage predicted value)			
Baseline, Mean (SD)	73.7% (33.1%)	48.0% (28.0%)	58.1% (32.2%)
Month 12	**n=13**	**n=19**	**n=32**
Change from baseline, Mean (SD)	2.3% (16.7%)	0.4% (8.5%)	1.2% (12.3%)

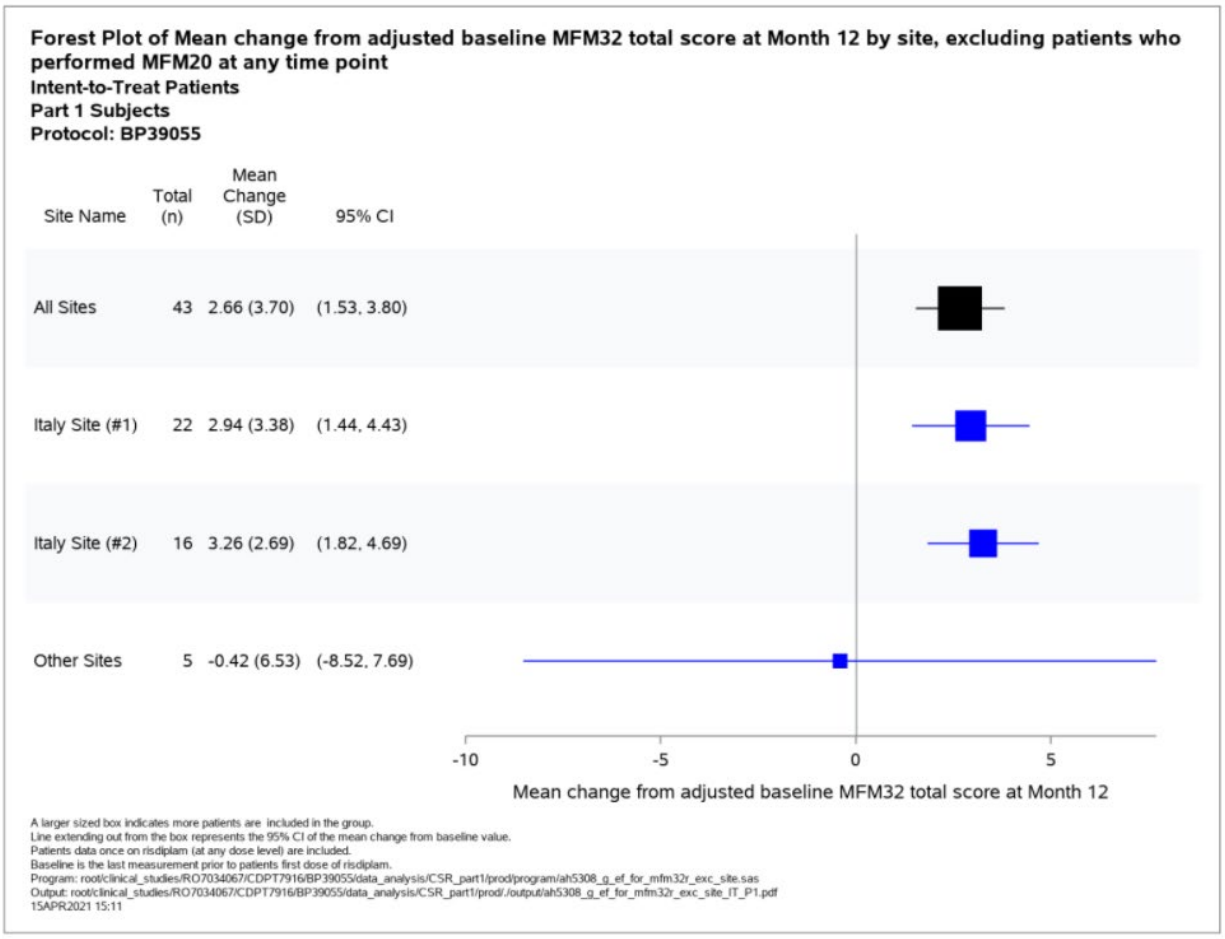
FVC=forced vital capacity; HFMSE=Hammersmith Functional Motor Scale Expanded; MFM=Motor Function Measure; RULM=Revised Upper Limb Module.

Notes: Baseline is the last measurement prior to patients first dose of risdiplam.

CCOD: 9 January 2019.

Sources: (HFMSE) t_ef_hfmser_IT_P1, t_ef_hfmser_prop_IT_P1; (RULM) t_ef_rulmr_IT_P1, t_ef_rulmr_prop_IT_P1; (FVC) t_ef_resp_FVC_IT_P1.

Figure 32 - Forest Plot of Mean Change from Adjusted Baseline MFM32 Total Score (Excluding Patients Who Performed MFM20 at any Time Point) at Month 12 by Site (Part 1; ITT Population)



Updated efficacy data of risdiplam in SUNFISH Part 1, based on a clinical cut-off date (CCOD) of 15 Jan 2020, when all patients in Part 1 had been treated with risdiplam at the pivotal dose for at least 24 months are described in the "Supportive Studies" Section.

2.5.2. Main study(ies)

Two pivotal studies support the application: one in infantile-onset SMA - Study BP39056 (FIREFISH) Part 2- and the other in late onset SMA - Study BP39055 (SUNFISH) Part 2.

Part 1 of FIREFISH trial and Part 1 of SUNFISH trial provide supportive evidence of efficacy.

Study BP39056 (FIREFISH)

Study BP39056 (FIREFISH) is an ongoing open-label single-arm study in infants with genetically confirmed Type 1 SMA. The study inclusion criteria allowed the characterisation of the effects of risdiplam treatment in infantile-onset SMA. The enrolment criteria selected infants with two *SMN2* copies and early onset of SMA symptoms, ensuring only patients with symptoms and diagnosis of Type 1 SMA disease at baseline were recruited, warranting the most representative patient population for the assessment of risdiplam benefits in infants living with SMA.

A comparator placebo group was not included in Study BP39056 (FIREFISH), given the rapid decline of the disease. At the time of study start there were no approved disease modifying therapies, which precluded an active comparator arm. Instead, the MAA has used a natural history source, with similar population, to define thresholds of achievement.

The primary endpoint for Part 2 (sitting unassisted) can be objectively measured. Sitting without support is never achieved in untreated patients with Type 1 SMA, thus developing this motor milestone would clearly diverge from the natural disease course of infantile-onset SMA.

Other relevant outcomes have been assessed, namely overall survival, for young infants diagnosed with infantile-onset SMA. In addition, the effect of risdiplam therapy was assessed in a combined endpoint: the survival rates of affected infants and the ability to breathe without chronic ventilatory support (proportion of infants who are alive without permanent ventilation), two severe complications of Type 1 SMA. Risdiplam efficacy was supported by assessments of further clinical outcomes, such as the maintenance of the swallowing function and the ability to feed orally, and further gains in motor milestones and motor function.

The scales used in this trial to assess further motor milestone development (Hammersmith Infant Neurological Examination Module 2 [HINE-2]) and motor function development (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP-INTEND]) are the most widely used and well-known scales for the assessment of changes in Type 1 SMA in both clinical practice and clinical research, including clinical trials.

In terms of GCP conduct, it was noted that study BP39056 report did not clarify how corrective and preventive measures were implemented to mitigate the critical finding in GCP conduct, and whether these have been adequately transmitted across the study investigator community. (FIREFISH GCP aspects). The applicant has forwarded detailed measures implemented for correction and to prevent repetition of the findings.

Study BP39055 (SUNFISH)

Study BP39055 (SUNFISH) was designed to include a broad sample of patients with Type 2 and non-ambulant type 3 SMA, representative both in age and disability status of patients seen in clinical practice. Consequently, recruited patients had a wide range of disease duration at the time of enrolment, and experienced different degrees of SMA-related complications such as severe scoliosis, muscle weakness and joint contractures. A more narrow study population focusing, for example, on young patients only would have allowed a more homogeneous and easier assessment of efficacy (as size and type of treatment effects may vary by age) and could lead to a higher chance for the study to be successful. On the other hand, however, the heterogeneity of patients enrolled in Study BP39055 (SUNFISH) allowed characterisation of the effects of treatment with risdiplam on the most prevalent SMA patient population: children, teenagers and adults living with Type 2 and non-ambulant type 3 SMA, representative of the broad clinical spectrum of the disease.

Study BP39055 (SUNFISH) enrolled adults up to 25 years of age. Patients with disease onset at adulthood (such as Type 4) were not included in this study. Type 4 SMA is a very rare type of the disease and enrolment of a sufficient number of patients would have been challenging to achieve in a timely manner. In addition, the majority of Type 4 patients are stronger and their disease progresses much more slowly as compared to other SMA types.

Study BP39055 (SUNFISH) Part 2 was designed based on two sets of data: a longitudinal, retrospective, natural history study of Type 2 and 3 SMA patients where the MFM was used to monitor disease progression (Vuillerot et al. 2013) and the data from the placebo control arm of Study WN29836 (a Phase II SMA study for a discontinued development compound, olesoxime), including Type 2 and non-ambulant Type 3 patients. Both sources of data helped to determine the treatment effect of Study BP39055 (SUNFISH) as they assessed a population of similar SMA type and age range. After consideration of all options, including the rare nature of the disease and limited patient pool available, Roche decided to power the trial for a 3-point difference leading to a trial size still feasible in the SMA population.

Independence and the ability to perform basic personal tasks have been described as a priority by Type 2 and 3 SMA patients. Existing outcome measures (e.g., Generic Paediatric Quality of Life Inventory and Neuromuscular modules) lack specificity to SMA. The MAA developed a new tool – the SMA Independence Scale (SMAIS) - which has been validated along the development plan.

Type 1 SMA

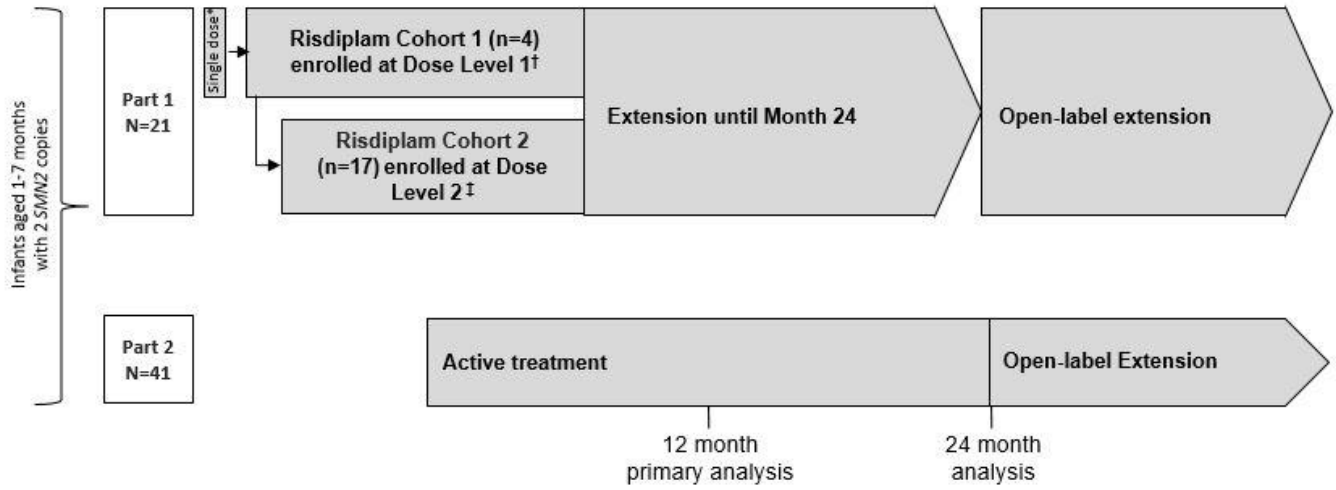
Infantile-Onset SMA: Study BP39056 (FIREFISH)

Title: A Two-Part Seamless, Open-Label, Multi-Center Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam in Infants with Type 1 Spinal Muscular Atrophy.

Methods

Study BP39056 (FIREFISH) is being conducted in two parts, both with a treatment period of 24 months followed by an open-label extension (OLE) phase (see Figure 1).

Figure 33 - Study Design of Parts 1 and 2 of Study BP39056 (FIREFISH)



*The first infant enrolled received a single dose of risdiplam. Approximately 6 weeks later, as per the Schedule of Assessments, the patient started administration of once daily risdiplam at a dose that was selected based on the PK data obtained from the first single dose, targeting the exposure specified for Dose Level 1 ($AUC_{0\text{-}24h,ss}$ 700 ng□h/mL).

† Cohort 1 includes the first three infants enrolled in the study (including the first infant who received an initial single dose of risdiplam) who all received Dose Level 1 for at least 12 months and the infant enrolled at Dose Level 1 who discontinued from the study on Study Day 19.

‡ Cohort 2 includes the infant enrolled at Dose Level 1 whose dose was escalated to Dose Level 2 on Study Day 83 and all other infants enrolled at Dose Level 2.

The primary analysis of Part 2 was performed at Month 12 of the active treatment phase. The Part 2 active treatment phase is ongoing in order to continue to assess the efficacy of risdiplam at the pivotal dose through Month 24, after which patients can enter the OLE phase.

Study Participants

Table 22 - Key Inclusion and Exclusion Criteria for Study BP39056 (FIREFISH)

Key Inclusion Criteria	
Age	Male and female infants born at a gestational age of 37 to 42 weeks, aged between 28 days (1 month) of life and 210 days (7 months) (inclusive) at enrollment.
SMA diagnosis	Confirmed diagnosis of 5q-autosomal recessive SMA, including: a. Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the *SMN1* gene. b. Clinical history, signs or symptoms attributable to Type 1 SMA with onset after the age of 28 days, but prior to the age of 3 months (inclusive), and inability to sit independently (without support) at the time of screening.
SMN2 copy number	Infant has two *SMN2* gene copies, as confirmed by central testing.
Respiratory status	If not already in place at the time of screening, parent or caregiver of infant is willing to consider the use of non-invasive ventilation during the study, as recommended by the Investigator.
Key Exclusion Criteria	
Respiratory status, recent hospitalisation, conditions	Patients who required invasive ventilation or tracheostomy, have a hypoxemia without ventilation support, had required hospitalisation for a pulmonary event within the last 2 months, and/or have a presence of non-SMA related comorbidities.
Concomitant medication	Concomitant or previous administration of a *SMN2*-targeting antisense oligonucleotide, *SMN2* splicing modifier, or gene therapy, either in a clinical study or as part of medical care.

SMA=spinal muscular atrophy; *SMN1*=survival of motor neuron 1 gene; *SMN2*=survival of motor neuron 2 gene.

Other exclusion criteria:

Recently initiated treatment (within < 6 weeks prior to enrollment) with oral salbutamol or another beta2-adrenergic agonist taken orally was not allowed. Infants who had been on oral salbutamol (or another beta2-adrenergic agonist) for ≥ 6 weeks before screening and had shown good tolerance were allowed. The dose of beta2-adrenergic agonist was to remain stable as much as possible for the duration of the study. Use of inhaled beta2-adrenergic agonists (e.g., for the treatment of asthma) was allowed.

Prior use (at any time in the patients' lives) and/or anticipated need for quinolines (chloroquine and hydroxychloroquine), thioridazine, vigabatrin, retigabine, or any other drug known to cause retinal toxicity during the study did not allow participation in the trial. Infants exposed to chloroquine, hydroxycholoroquine, thioridazine, vigabatrin, retigabine or drugs with known retinal toxicity given to mothers during pregnancy (and lactation) were not to be enrolled.

Recent history (less than 6 months) of ophthalmic diseases (e.g., glaucoma not controlled by treatment, central serous retinopathy, inflammatory/infectious retinitis unless clearly inactive, retinal detachment, intraocular trauma, retinal dystrophy or degeneration, optic neuropathy, or optic neuritis) that would have interfered with the conduct of the study as assessed by an ophthalmologist. Any other abnormalities detected with optical coherence tomography (OCT) at screening (e.g., retinal layer

abnormalities, oedema, cystic or atrophic changes) were to be discussed with the Investigator, Ophthalmologist, and with the Sponsor, who jointly made the decision on whether the infant could be enrolled in the study. Infants in whom OCT measurement of sufficient quality could not be obtained at screening were not enrolled.

Investigation sites:

Part 1: 7 sites across 5 countries (Belgium [1], France [1], Italy [2], Switzerland [1], and the United States [2]). Part 2: 14 sites across 10 countries (Croatia [1], France [1], Italy [4], Poland [1], Russia [1], Brazil [1], China [2], Japan [1], Turkey [1], and the United States [1]).

Prohibited Therapy

The following medications were explicitly prohibited for patients and the mother if breastfeeding the patient:

- Any inhibitor of CYP3A4, including but not limited to: ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, cimetidine.

- Any inducer of CYP3A4, including but not limited to: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John's wort.

- Any OCT-2 and MATE substrates were to be avoided, including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine.

- Any known FMO1 or FMO3 inhibitors or substrates.

Medications with known phototoxicity and retinal toxicity liabilities

- Oral or topical retinoids, including over-the-counter formulations, amiodarone, phenothiazines, and chronic use of minocycline.

The following drugs were prohibited during the study, and prior use of these drugs was an exclusion criterion for the study.

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

Use of the following therapies was prohibited for patients and for the mother if breastfeeding the infant during the study and in the preceding 90 days of enrolment:

- Deferoxamine, topiramate, latanoprost, niacin, rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon, or any other drugs known to cause retinal toxicity.

Prohibited Foods

Subjects were to avoid grapefruit juice and Seville orange (juice) starting at least 2 weeks prior to study drug administration.

Safety stopping rules

The following specific safety stopping rules for an individual subject were defined a priori:

- Skin or subcutaneous reaction, pharyngeal/laryngeal or mucosal reaction (Grade >=2 CTCAE v4.03) considered to be clearly related to study drug as confirmed by a Dermatologist/Ear, Nose and Throat (ENT) specialist, making the benefit-risk ratio non-favorable.
- Functional or structural eye abnormalities.
- Significant and clinically relevant changes in laboratory parameters, ECG, or vital signs

- Any elevated ALT of >3 x ULN, alkaline phosphatase (ALP) < 2 x ULN, and associated with an increase in bilirubin (>= 2 x upper limit of normal)
- Other findings such as a SAE or any other severe AE that, at the joint discretion of Roche TML, Roche Safety Science Leader, and the Investigator, indicate that dosing should be halted.

Treatments

Study medication (risdiplam) was taken orally once daily. Patients who were breastfed were to be fed prior to dosing, winded (i.e., maneuvered to release air from stomach), and then study medication was to be administered. For patients able to swallow, study drug was administered with a syringe inserted between baby's gum and cheek. Thereafter, water (approximately 10-20 mL) was to be administered with a baby's bottle to prevent prolonged contact of study drug with buccal mucosa. Similarly, the peribuccal area of the infant was to be washed with water, in case of drug drooling or spitting.

Breastfeeding was to be avoided within 1 hour after risdiplam administration, and women were advised to rinse their breasts with water if breastfeeding occurred shortly (<1 hour) after risdiplam administration. This is being added to SmPC: *"Method of administration (...): Evrysdi is taken orally once a day after a meal at approximately the same time each day, using the re-usable oral syringe provided. In infants who are breastfed, EVRYSDI should be administered after breastfeeding. Evrysdi should not be mixed with milk or formula milk."*

Patients who were unable to swallow the study medication and who had a nasogastric or gastrostomy tube in situ received the study medication by bolus via the tube.

Based on safety, tolerability, PK, and PD data from Part 1 of the study (up to the CCOD of 5 January 2018, plus data that became available prior to the database snapshot on 6 February 2018), the following starting dose levels were selected for Part 2 (dose levels were to be modified and adapted upon review of individual patient's PK data):

- Infants >1 month old and <3 months old at enrolment: 0.04 mg/kg

- Infants ≥3 months old and <5 months old at enrollment: 0.08 mg/kg

- Infants ≥5 months old at enrollment: 0.2 mg/kg

Limited data from only 4 infants aged 3.3-5 months were available at the time of dose selection for Part 2 (with higher exposure observed in 3 of these infants), and no data were available in infants < 3 months of age. Therefore, as for Part 1, a dose-escalation approach was chosen for Part 2, with a lower starting dose for the younger age groups and dose adjustment upon review of the individual PK data. PK samples were obtained from each infant and, based on the actual observed PK in each infant, the dose was increased to 0.2 mg/kg for all Part 2 patients (which occurred in general for most infants within 2 months of treatment start).

Objectives

The Part 1 and Part 2 were single arm with active treatment only. The results are compared to natural history data on SMA type I / infantile onset both published and owned by the MAA.

The primary objective and many of the secondary and exploratory objectives for Part 2 were also applied to Part 1 of the study, to support the analysis of the Part 1 data provided in this Clinical Study Report (CSR).

Statistical hypothesis: The purpose of Part 2 of the study was to estimate the proportion of infants who were sitting without support at 12 months of treatment and to test whether this proportion was higher than the pre-defined performance criterion of 5%. This 5% threshold was chosen based on the well-

defined natural history of Type 1 SMA, in which infants never achieve sitting without support (Cobben et al. 2008; Finkel et al. 2014a, 2017; De Sanctis et al. 2016).

Outcomes/endpoints

Primary endpoint: Sitting without support for at least 5 seconds, as measured by item 22 of the Bayley Scales of Infant and Toddler Development - Third Edition (BSID-III) Gross Motor Scale.

The **Bayley Scales of Infant and Toddler Development - Third Edition (BSID-III)** is a measure of infant and toddler development that has been standardised on an American paediatric population. A supplemental study has also demonstrated strong measurement properties for the BSID-III in 221 infants in the United Kingdom and Ireland. The BSID consists of a core battery of five scales. Three scales (cognitive, motor, language) are administered with child interaction and two scales (social-emotional, adaptive behaviour) are conducted with parent questionnaires. The BSID-III also includes a Behavior Observation Inventory, a separate scale for validating examiner and parent perceptions of the child's responses. For the FIREFISH study only the Gross Motor scale of the BSID-III was used as an outcome measure to assess attainment of motor milestones. The other BSID-III scales were not used.

As per the scoring manual, **Item 22** of the **BSID-III** was not considered to have been achieved if the infant sat alone for less than 5 seconds before losing balance and falling over, or if the infant used his or her arms to prop him- or herself up. To ensure minimal bias in the assessment of sitting without support, the evaluation of sitting was recorded via video in a standardised manner and centrally reviewed and scored by two independent readers in addition to the trained site clinical evaluator. The assessment of the central independent readers was used for the primary analysis; only if both readers classified the infant as having sat for 5 seconds or more was the patient classified as a responder for this endpoint. Infants were classified as non-responders (i.e., non-sitters) for the primary analysis if they did not achieve sitting, did not maintain sitting achieved earlier, were withdrawn, died, or had a missing assessment at Month 12.

The pre-defined performance criterion for the primary endpoint was 5%.

Table 23 - Efficacy Endpoints at Month 12 in Study BP39056 (FIREFISH)

Motor Function and Development Milestones
Proportion of patients sitting without support for at least 5 seconds, as assessed by Item 22 of the BSID-III gross motor scale [a]
Proportion of patients who achieve a CHOP-INTEND score of 40 or higher
Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline
Proportion of motor milestone responders as assessed by the HINE-2 [b]
Proportion of patients able to support weight or stand with support as assessed by the HINE-2
Proportion of patients able to bounce while assessing the walking item of the HINE-2
Survival and Ventilation-Free Survival
Proportion of patients alive without permanent ventilation
Proportion of patients alive
Nutrition
Proportion of patients with the ability to feed orally
Proportion of patients with the ability to swallow
Healthcare Utilisation
Number of hospitalisations per patient-year
Proportion of patients with no hospitalisations

BSID-III=Bayley Scales of Infant and Toddler Development III; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2=Hammersmith Infant Neurological Examination Module 2.

[a] The BSID-III gross motor scale was administered in a modified order, starting with the assessment of sitting positions (including the primary endpoint in Part 2).

[b] An infant was classified as a motor milestone responder if more HINE-2 motor milestones showed improvement than showed worsening, as defined in the SAP. Improvement was defined as at least a 2-point increase in the ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as at least a 2-point decrease in the ability to kick (or lowest score) or a 1-point decrease in the other milestones. Voluntary grasp was excluded from the definition.

Secondary efficacy endpoints

Motor Function

CHOP-INTEND: The CHOP-INTEND (The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disorders) score is a sensitive score for motor function ability designed and validated specifically for severely affected SMA patients. The patients are scored on 16 items (including joint flexion and extension, spontaneous movement and head control), ranging from 0-4 per item. This gives a total maximum score of 64. The CHOP-INTEND score represents measures of disease severity.

Development Motor Milestones

The **Hammersmith Infant Neurological Examination (HINE-2)** evaluates the neuromuscular development of infants in 8 motor milestone categories (head control, sitting, grasping, ability to kick in supine position, rolling, crawling, standing and walking) with 3 to 5 progressively more difficult items for each milestone category (with 0 meaning inability to perform a task and 3 or 4 -depending on the task- meaning full milestone development).

The applicant defines a responder as at least a 2-point increase in ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening is similarly defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing, or walking. Voluntary grasp is excluded from the definition. An

infant was classified as a responder if more motor milestones showed improvement than showed worsening; infants who died or withdrew were classified as non-responders. Infants with a totally missing HINE-2 assessment at Month 12 or Month 24 were also classified as non-responders.

Infants were classified as non-responders if they did not meet the endpoint or if the assessment was missing for any reason. For the calculation of the CHOP-INTEND score, BSID-III total raw score and HINE-2 total score, if any individual item score contributing to the total score was missing or if 'Cannot test (CNT)' was recorded, then the item score was set to 0 (if there was at least one non-missing item at the assessment). If all items were missing, then the total score was set to missing.

Other development motor milestones secondary endpoints (in addition to the ones listed in Table 3):

- Proportion of infants who are alive and sitting without support for 5 seconds at Month 24 (defined as per the primary endpoint).

- Proportion of infants who are alive and sitting without support for 30 seconds at Month 24 (defined as 'Sits without support for 30 seconds' as assessed in Item 26 of the BSID-III gross motor scale).

- Proportion of infants who are alive and standing at Month 24 (defined as 'Stands alone' as assessed in Item 40 of the BSID-III gross motor scale).

- Proportion of infants who are alive and walking at Month 24 (defined as 'Walks alone' as assessed in Item 42 of the BSID-III gross motor scale).

Other Survival and Ventilation-Free Survival secondary endpoints (in addition to the ones listed in Table 3)

- Time to death or permanent ventilation (from enrolment). Permanent ventilation is defined as ≥ 16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy.

- Proportion of infants alive without permanent ventilation at Month 24

- Time to death (from enrolment).

- Proportion of infants alive at Month 24.

Respiratory secondary endpoints

- Time to permanent ventilation (from enrolment).

- Proportion of infants who are without permanent ventilation at Month 12 and Month 24.

Permanent Ventilation Adjudication Committee

Time to permanent ventilation was determined by a central, independent Permanent Ventilation Adjudication Committee. This committee reviews all pertinent data for patients who may have met the definition of permanent ventilation (≥16 hours of non-invasive ventilation such as BiPAP per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy) and confirms if the endpoint has been met.

Additional Secondary and Other Exploratory Efficacy Endpoints

Motor Function and Development Milestones

- Proportion of infants who achieve head control at Month 8, Month 12, and Month 24 (defined as a score of 3 or higher for item 12 of the CHOP-INTEND).

- Change from baseline in the Total Raw Score of the BSID-III gross motor scale at Month 12 and Month 24.

- Proportion of infants who achieve the attainment levels of the motor milestones as assessed in the HINE-2* at Month 8 (subset #), Month 12 and Month 24.

*Milestones of: head control#, sitting, voluntary grasp, ability to kick#, rolling#, crawling, standing and walking.

- Highest motor milestone ** achieved by Month 12 and Month 24

**Milestones of: head control (item 9 'Controls head while upright for 15 seconds'), rolling (item 14 'Rolls from side to back'), sitting without support (primary endpoint), crawling (item 30 'Crawls on stomach'), standing (item 40 'Stands alone') and walking (item 42 'Walks alone') as assessed in the BSID-III gross motor scale.

Nutrition

- Proportion of infants with the ability to feed orally at Month 12 and Month 24.

Muscle Electrophysiology

- Proportion of infants who achieve an increase of at least 0.3mV from baseline in their CMAP negative peak amplitude at Month 12 and Month 24.

Healthcare Utilisation

- Number of hospitalisations (for any reason) per patient-year and number of nights admitted to hospital per infant at Month 12 and Month 24.

Swallowing and Nutrition

- Proportion of infants with the ability to swallow at Month 8, Month 12, and Month 24.

Growth Measures

- Ratio between the chest and head circumference at Month 8, Month 12, and Month 24.

- Change from baseline in weight percentiles at Month 12 and Month 24.

- Change from baseline in length/height percentiles at Month 12 and Month 24.

Parent/Caregiver Reported Outcomes

- Change from baseline in the ITQOL-SF47 Questionnaire domains and single item scores* at Month 12 and Month 24.

*Parent-proxy domains of physical abilities, growth and development, bodily pain/discomfort, temperament and moods, behaviour, general health perception, parent emotional impact and parent time impact. Single item scores include overall health, change in health and family cohesion.

Clinician Reported Respiratory Function and Swallowing Ability Items

- Proportion of infants with no change or improvement in respiratory function as assessed by the clinician reported Clinical Global Impression of Change (CGI-C) at Month 12.

- Proportion of infants with no change or improvement in the ability to swallow as assessed by the clinician reported CGI-C at Month 12.

Sample size

The target sample size for Part 2 was 40 infants. This sample size provided at least 90% power to test the null hypothesis Ho: $p \leq 5\%$ versus the alternative hypothesis Ha: $p > 5\%$, if the true proportion of infants who would sit on treatment was 20%, based on an exact binomial test with a one-sided 5% significance level. With a planned sample size of 40 infants, a minimum of 5 infants sitting without support would provide a statistically significant difference from the pre-defined performance criterion (i.e., the lower limit of the two-sided 90% Clopper-Pearson [exact] confidence interval would be above 5%). In the sample size calculations, no allowance was made for infants who withdraw early, as these infants would be classified as non-responders/non-sitters and included within the primary analysis.

Randomisation

Not applicable. This was an open-label study, and all patients received risdiplam.

Blinding (masking)

Not applicable. This was an open-label study, and all patients received risdiplam.

•Statistical methods

For Part 1 and Part 2 of Study BP39056 (FIREFISH), the Intent-to-Treat (ITT) population (defined as all patients enrolled, regardless of whether they received treatment or not) of each part is the primary analysis population for all efficacy analyses (with the exception of weight-for-age and length/height-for-age percentiles, which were analysed based on the safety population).

Efficacy results from Part 2 are compared to, and put into context with, data describing the natural history of untreated infants with Type 1 SMA. These natural history data were used to define thresholds of achievement, i.e. objective performance criteria or performance goals, against which to assess the efficacy of treatment.

Part 2 of Study BP39056 (FIREFISH) is designed to test whether the proportion of patients sitting without support after 12 months of treatment (as assessed by Item 22 of the BSID-III gross motor scale) is higher than a performance criterion set at 5% (i.e., a threshold of achievement for risdiplam-treated patients to be assessed against within this study). This 5% threshold was chosen to allow sufficient confidence that any effect seen in treated patients is greater than what could be expected from the natural history of the disease; as per definition, Type 1 SMA patients never sit unsupported (Cobben et al. 2008; Finkel et al. 2014). A statistically significant result would be achieved when a minimum of 6 out of 41 infants are sitting without support for 5 seconds after 12 months of treatment with risdiplam, based on an exact binomial test with a one-sided 5% significance level. If, in Part 2 of the study, 6 out of 41 patients (14.6% [90% CI: 6.6%–26.9%]) are sitting without support at Month 12, the lower limit of the two-sided 90% Clopper-Pearson (exact) confidence interval (CI) would be above 5%.

The performance criteria for the milestones of sitting without support, standing alone and walking alone have been pre-defined in the study protocol (set at 5%) and will not be based on benchmarks derived from the historical data sources.

For the analysis of the primary endpoint 'proportion of patients who are sitting without support at 12 months of treatment', patients who did not achieve the milestone of sitting, who did not maintain a sitting status achieved earlier, who were withdrawn, or who died were classified as non-responders (i.e., non-sitters) at the time of assessment. The assessment of the independent central readers was used for the primary analysis.

Performance criteria were also derived for some of the secondary efficacy endpoints in Part 2. These criteria were derived using data from similar cohorts of untreated infants with Type 1 SMA constructed from real world data sources/natural history studies. If multiple sources of data were available for a secondary endpoint, the cohort with the baseline characteristics most similar to those targeted by the study inclusion and exclusion criteria was used. The benchmark was based on the associated upper limit of the 90% CI from the historical data. When a pre-defined benchmark could be determined for the secondary endpoint, hypothesis testing was performed (see Table 8).

To control for multiplicity across the different endpoints, a hierarchical testing approach was implemented. The first secondary efficacy endpoint, the proportion of infants who achieve a score of 40 or higher in the CHOP-INTEND at Month 12, was tested if and only if the primary endpoint had reached

the 5% significance level (i.e., p-value ≤0.05). Other secondary endpoints were tested at a 5% significance level according to the following hierarchy, as long as the p-value was ≤0.05 for endpoints higher in the hierarchy:

- Proportion of patients achieving a score of 40 or higher in their CHOP-INTEND scores at Month 12
- Proportion of patients achieving an increase of at least 4 points in their CHOP-INTEND scores from baseline at Month 12
- Proportion of motor milestone responders as assessed by HINE-2 at Month 12
- Proportion of patients who were alive without permanent ventilation at Month 12
- Proportion of patients sitting without support for 30 seconds at Month 24 (as assessed in item 26 of the BSID-III gross motor scale)
- Proportion of patients standing at Month 24 (as assessed in item 40 of the BSID-III gross motor scale)
- Proportion of patients walking at Month 24 (as assessed in item 42 of the BSID-III gross motor scale)

The Month 24 endpoints will be analysed when all infants have reached 24 months of treatment. Any other endpoints for which hypothesis testing was performed were simultaneously tested at the 5% significance level without adjustment for multiplicity, as they were considered to provide supportive information.

Proportions and 90% CIs are presented for the key efficacy outcomes at Month 12:

- Patients sitting without support for 5 seconds
- Patients achieving a score of 40 or higher in their CHOP-INTEND scores
- Patients achieving an increase of at least 4 points in their CHOP-INTEND scores from baseline
- Motor milestone responders as assessed by HINE-2
- Patients who were alive without permanent ventilation
- Patients who were alive
- Patients with the ability to feed orally
- Patients with the ability to swallow
- Patients with no hospitalisations

Through Scientific Advice, CHMP previously agreed that matching on an individual basis may be difficult in this limited and heterogeneous patient population. Therefore, CHMP at the time of SA agreed that the approach for generating performance criteria with a 90% upper and lower limit of the confidence interval may the next best option, but the applicant was encouraged to continue developing the best possible understanding and description of the disease course relevant to the population that are included in the trial.

Sources of natural history

The applicant identified the following sources of data describing natural history:

Clinical Study of Spinal Muscular Atrophy (PNCR Network)

The PNCR Network are conducting a multi-centre, observational cohort study designed to allow for a comprehensive baseline characterisation of the SMA patient population and collect longitudinal follow-up data on this population (Protocol version 6, March 2007). The study includes Type 1, 2 and 3 patients with a clinical diagnosis of SMA, a genetic diagnosis of SMN1 gene deletion, and a diagnosis of SMA before 19 years of age. The PNCR Network was established to evaluate SMA patients at three sites in the United States. Patients from a fourth site in the United States have subsequently been included in the database.

A prospective cohort study to characterize the clinical features of Type 1 SMA has been published by the PNCR Network (**Finkel et al., 2014b**), and data from the PNCR Network was included in a retrospective study to assess developmental milestones in infants with Type 1 SMA (**De Sanctis et al., 2016**).

The applicant has access to patient-level data from the PNCR Network through the SMA Foundation.

NeuroNEXT SMA infant biomarker study

The population in the NeuroNEXT SMA infant biomarker study (**Kolb et al., 2016; Kolb et al., 2017**) was judged to be most similar to the expected population in Study BP39056. Whenever possible, the performance criterion derived from this study was selected as the benchmark to be used for hypothesis testing. When data for an endpoint was not available from the NeuroNEXT SMA infant biomarker study, the benchmark was derived from the study conducted by **De Sanctis et al. (2016)**. The upper limit of the 90% CI was used to define the performance criterion for each endpoint following Committee for Medicinal Products for Human Use (CHMP) scientific advice. The 90% CI is expected to be conservative when the sample size of the selected study is smaller. **The NeuroNEXT SMA infant biomarker study includes 16 infants with 2 copies of the SMN2 gene, and the study conducted by De Sanctis et al. (2016) includes 24 infants classified as Type 1B.**

Table 25 shows the performance criteria that will be used for hypothesis testing in Study BP39056.

Table 24 - Performance Criteria to Use for Hypothesis Testing in Study BP39056

Endpoint	Source	N	Performance Criterion (upper limit of 90% CI)
Proportion of infants who achieve a score of 40 or higher in the CHOP-INTEND at Month 12	*NeuroNEXT SMA Infant Biomarker Study*	*16*	0.17
Proportion of infants who achieve an increase of ≥ 4 points in their CHOP-INTEND score from baseline at Month 12	*NeuroNEXT SMA Infant Biomarker Study*	*16*	0.17
Proportion of motor milestone responders as assessed by HINE-2 at Month 12	*De Sanctis et al. (2016)*	*24*	0.12
Proportion of infants who are alive without permanent ventilation at Month 12	*NeuroNEXT SMA Infant Biomarker Study*	*16*	0.42
Proportion of infants who are alive at Month 12	*NeuroNEXT SMA Infant Biomarker Study*	*16*	0.60
Proportion of infants who are without permanent ventilation at Month 12	*NeuroNEXT SMA Infant Biomarker Study*	*16*	0.89
Proportion of infants who achieve an increase of ≥ 0.3mV from baseline in their CMAP negative peak amplitude at Month 12	NeuroNEXT SMA Infant Biomarker Study	15	0.18

Due to the lack of patient-level data available for the majority of observational studies, benchmarks derived from these studies were set at approximately 18 months of age for the Month 12 endpoints, and approximately 30 months of age for the Month 24 endpoints. These ages were chosen to reflect the expected average age of the infants that will be enrolled in Part 2 of Study BP39056 after 12 (and 24) months of treatment. When individual patient-level data was available (e.g., data from the PNCR Network), patients who had their first visit before 7 (+1) months of age were included in the analyses (not including time-to-event analyses) in order to reflect the expected age of enrollment in Study BP39056. In these cases, benchmarks were set at approximately 12 and 24 months of follow-up.

Kaplan-Meier curves for time-to-death or permanent ventilation, time-to-death and time to permanent ventilation were estimated from published material, or from individual patient-level data, where available. Patients with no event reported prior to the analysis cutoff date were censored at the latest date before the cutoff in which they were known to be event-free (i.e., the latest date before the cutoff in which they were known to be: (1) alive and without permanent ventilation for time-to-death or permanent ventilation, (2) alive for time-to-death, and (3) without permanent ventilation for time to permanent ventilation). For time to permanent ventilation, patients who died but did not require permanent ventilation were censored at the death date.

Survival probabilities (proportion of patients who were event-free at a given time-point) were estimated using Kaplan-Meier methodology, and 60%, 80% and 90% CIs were estimated using the complimentary log-log transformation for the estimated survivor function S(t). Standard errors were computed via Greenwood's formula. Two-sided 60%, 80% and 90% Clopper-Pearson (exact) CIs were calculated for proportions of responders. For responder/non-responder definitions, patients who did not

maintain an earlier response or had a missing assessment at the time-point of interest (for any reason) were classified as non-responders.

LIMITATIONS

Despite attempts to derive the performance criteria from cohorts of patients who are similar to the population in Study BP39056, there are a number of limitations to this approach:

- There are a limited number of studies available to describe some of the endpoints in Study BP39056, and the number of patients available for some of the endpoints is small.

- The use of the upper limit of the CI instead of the point estimate to define the performance criteria may be overly conservative, especially at the 90% level, given that the width of the CI is governed by the sample size.

- The majority of the sources used to derive a performance criterion for one of the endpoints in Study BP39056 were based on data from a limited number of countries and sites, with studies primarily conducted in the United States. Some of the endpoints included in Study BP39056 are determined by treatment decisions and standard of care in treating centres, as well as cultural norms, and so may vary across countries and sites. Examples include the extent of supportive medical care, the decision to permanently ventilate an infant, and the decision to intervene for nutritional support. Study BP39056 is a global, multi-centre study potentially including sites in Europe, North America, South America, Asia-Pacific, and the Middle East, and differences in the standard of care across countries and sites may lead to substantial variability in patient outcomes. This will make comparisons between study results and observational studies more challenging.

- Benchmarks derived from observational data sources at 18 (and 30) months of age may not reflect the average age of the infants enrolled in Study BP39056 after 12 (and 24) months of treatment.

- The endpoint definitions or assessments used to measure a certain concept in the different studies may not match the definitions or assessments used in Study BP39056. Specifically,

- The definition of permanent ventilation varies across the different sources and does not match the definition used in Study BP39056 (defined as ≥ 16 hours of non-invasive ventilation per day or intubation for > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event; or tracheostomy). This includes differences in the number of hours of ventilation per day, the number of consecutive days with this level of respiratory support, and the type of respiratory support provided.

- The HINE-2 was used to assess motor milestones in the study conducted by De Sanctis et al. (2016), while Study BP39056 will use the modified BSID-III gross motor scale, and item 12 of the CHOP-INTEND for head control.

Since some endpoints may be affected by differences in standard of care between centres, Roche plans to conduct a global, multi-centre, retrospective, chart review study of infants with Type 1 SMA who have similar clinical characteristics to the infants included in Study BP39056, and who received care at the same sites (Roche no. BP39859). This will generate additional data on the natural history of Type 1 SMA in a similar cohort to Study BP39056. As the data extraction will occur at the time of site set-up and patient inclusion in Study BP39056, the results of this study will not inform the pre-defined thresholds used to assess the efficacy of treatment, but once available, data from this study will provide additional context for the results of Study BP39056. The results of this study will contribute to sensitivity analyses of Study BP39056.

Sensitivity Analyses

As a sensitivity analysis, the analysis described for the primary efficacy endpoint (the proportion of infants sitting without support for 5 seconds at Month 12) was performed using the assessment of the site clinical evaluator instead of the assessment of the two independent central readers. Sensitivity analyses were also performed using an alternative definition of sitting without support, with sitting defined by the HINE-2 categories of 'Stable sit' or 'Pivots (rotates).'

Results

Participant flow

PART 2

A total of 52 patients were screened for enrolment in Part 2 of the study, of whom 11 patients were screen failures. Reasons for screen failure are provided; the most common reasons were death (4 patients) and failure to meet inclusion criteria (3 patients).

A total of 41 patients with Type 1 SMA were enrolled into Part 2 of pivotal Study BP39056 (FIREFISH) across 14 different sites in 10 countries (Brazil, China, Croatia, France, Italy, Japan, Poland, Russia, Turkey, and the United States). At the time of the CCOD, 38 of 41 patients (92.7%) in Part 2 were still ongoing in the study; these 38 patients were older than 14 months of age. Three patients (7.3%) died due to SMA-related respiratory complications within the first three months following enrolment. All patients received treatment with risdiplam.

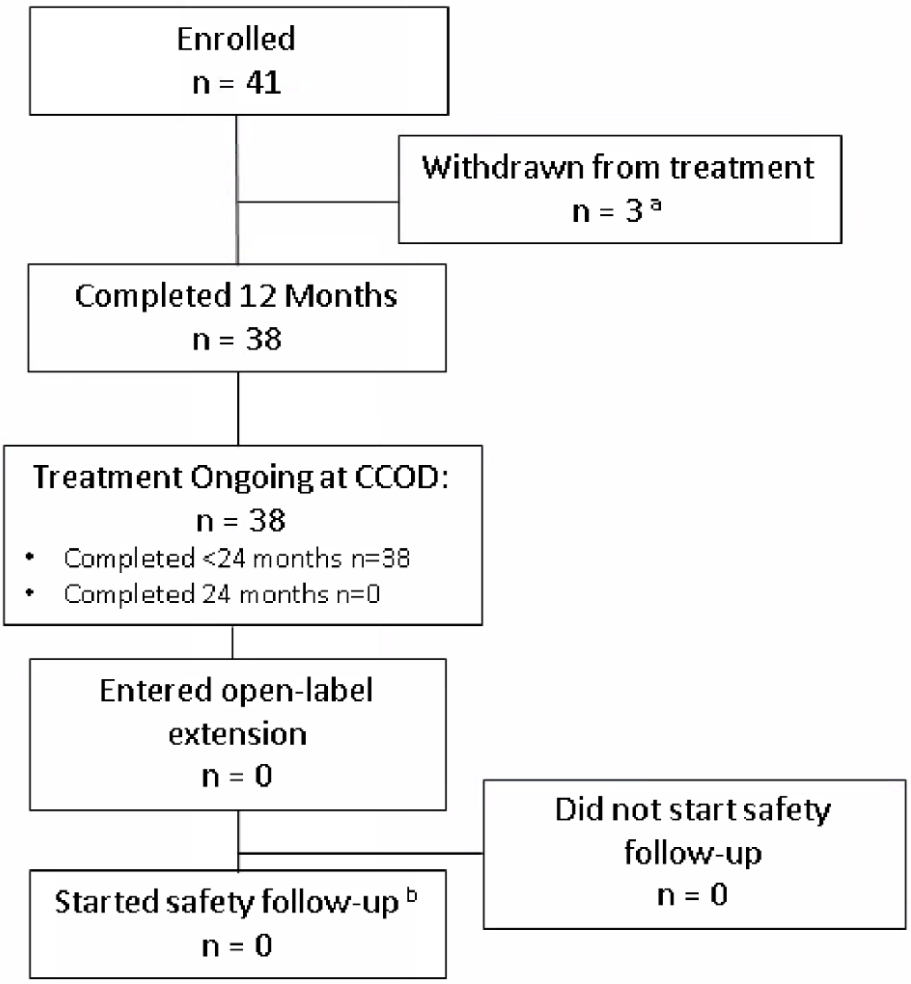
Of the 41 patients enrolled in Part 2, 22 (53.7%) were female and 19 (46.3%) were male. At enrolment, the median age of all patients was 5.3 months (range: 2.2□6.9 months); 22 of 41 patients (53.7%) were older than 5 months. The median age at diagnosis was 2.8 months (range: 0.9□6.1 months) and the age at onset of symptoms ranged from 1.0 to 3.0 months. Patients' weight-for-age values were at or below the 50th percentile at baseline, based on World Health Organization (WHO) Child Growth Standards, for the majority of patients (29/41, 70.7%) with a median weight-for-age percentile of 24.0 (range: 0.2–99.0th percentile). Patients' length/height-for-age values were above the 50th percentile at baseline for the majority of patients (26/41, 63.4%), with a median length/height-for-age percentile of 66.2 (range: 0.3–100th percentile).

In accordance with the inclusion criteria, all patients had a genetic diagnosis of SMA (*SMN1*) and had two *SMN2* gene copies.

At baseline, the median BSID-III Gross Motor Scale score was 2.0 (range: 0.0–8.0), the median CHOP-INTEND score was 22.0 points (range: 8.0–37.0), the median HINE-2 score was 1.0 point (range 0.0–5.0), and the median baseline CMAP amplitude was 0.2 mV (range: 0.0–0.8), confirming all enrolled patients had well-established symptomatic SMA disease at baseline.

At the CCOD of 14 November 2019, patients enrolled in Part 2 had been treated for a median of 15.2 months (range: 1.6-20.1 months).

Figure 34: Patient Disposition (ITT Population, Part 2 Patients)

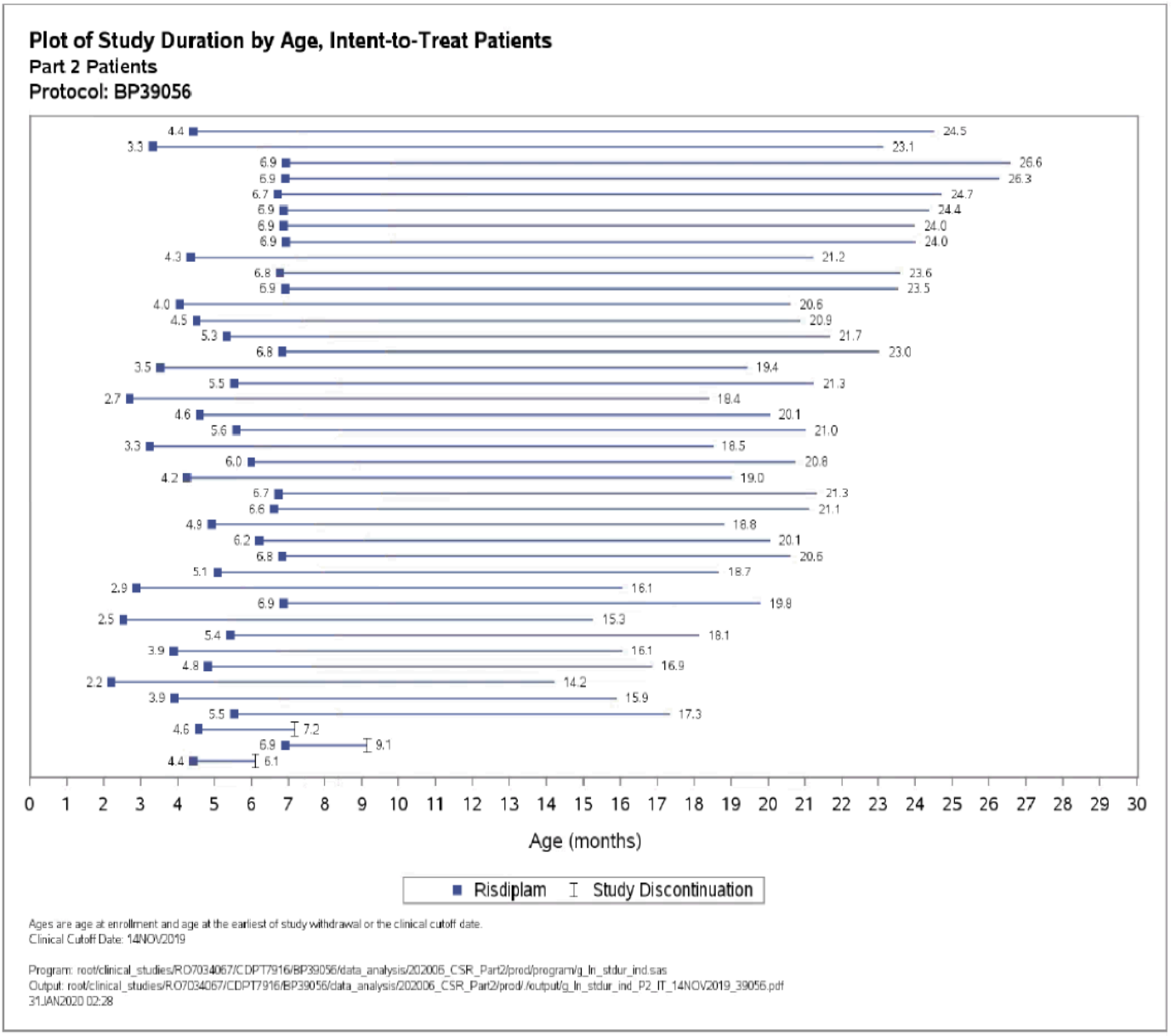


Abbreviations: CCOD=clinical cut-off date (14 November 2019)

a Three patients died from SMA-related respiratory complications

b Patients who complete the study or discontinue from the study early are to complete the safety follow-up period.

Figure 35



First Patient Enrolled in Part 1: 23 Dec 2016; Last Patient Enrolled in Part 1: 21 Feb 2018. First Patient Enrolled in Part 2: 13 Mar 2018; Last Patient Enrolled in Part 2: 19 Nov 2018. Clinical cutoff date (CCOD): 14 Nov 2019.

Baseline data

PART 2

Of the 41 patients enrolled in Part 2, 22 were female (53.7%). The majority of patients were White (22/41, 53.7%) or Asian (14/41, 34.1%); race was reported as unknown for 5 patients (12.2%). Five patients (12.2%) were of Hispanic or Latino ethnicity.

Patients in Part 2 had a median age of 5.3 months (range: 2.2-6.9 months) at enrolment. The majority of patients were enrolled at sites in Europe (24/41, 58.5%); 1 patient (2.4%) was enrolled in the United States, and 16 patients (39.0%) were enrolled at sites in the rest of the world. The countries with the highest enrolment were China (11/41, 26.8%) and Italy (10/41, 24.4%). Of the 41 patients in

Part 2, 16 were international patients who were relocated with their families from their country of residence to one that had a study site.

Patients' weight-for-age values were at or below the 50th percentile at baseline, based on WHO Child Growth Standards, for the majority of patients (29/41, 70.7%). For 15 patients (36.6%), the baseline weight-for-age values were at or below the 10th percentile. The median weight-for-age percentile was the 24.0th (range: 0.2-99.0th percentile).

Table 25: Summary of Demographic and Baseline Characteristics (ITT Population, Part 2 Patients)

Demographics and Baseline Characteristics, Intent-to-Treat Patients
Protocol: BP39056
Part 2 Patients

	Risdiplam (N=41)
Age at Enrollment (Months)	
n	41
Mean (SD)	5.20 (1.47)
Median	5.32
IQR	4.2 - 6.8
Min - Max	2.2 - 6.9
Age Group at Enrollment (Months)	
n	41
<=5	19 (46.3%)
>5	22 (53.7%)
Sex	
n	41
Male	19 (46.3%)
Female	22 (53.7%)
Race	
n	41
Asian	14 (34.1%)
White	22 (53.7%)
Unknown	5 (12.2%)
Ethnicity	
n	41
Hispanic or Latino	5 (12.2%)
Not Hispanic or Latino	36 (87.8%)
Country	
n	41
Brazil	3 (7.3%)
China	11 (26.8%)
France	4 (9.8%)
Croatia	1 (2.4%)
Italy	10 (24.4%)
Japan	1 (2.4%)
Poland	4 (9.8%)
Russian Federation	5 (12.2%)
Turkey	1 (2.4%)
United States	1 (2.4%)
Region	
n	41
Europe	24 (58.5%)
Rest of the World	16 (39.0%)
US	1 (2.4%)

Clinical Cut-Off Date: 14NOV2019

According to the WHO Child Growth Standards, 6 patients were below the 3rd percentile at baseline. However, all of these patients met the inclusion criteria (body weight >=3rd percentile for age, using appropriate country-specific guidelines) at the screening visit based on local growth charts and investigator assessment.

Patients' length/height-for-age values were above the 50th percentile at baseline for the majority of patients (26/41, 63.4%), with a median length/height-for-age percentile of 66.2nd (range: 0.3-100th percentile).

At baseline, 51.2% of patients (21/41) were at or below the 50th percentile for head circumference for age values, and 48.8% (20/41) of patients were above the 50th percentile. The median head circumference-for-age percentile was the 47.3rd (range: 0.6-99.8th percentile).

At baseline, the median head circumference was 41.5 cm (range: 38.3-46.0 cm), the median chest circumference was 38.5 cm (range: 32.0-46.6 cm), and the median ratio of chest to head circumference was 0.93 (range: 0.7-1.1).

The baseline characteristics of patients in Part 2 were typical of a symptomatic Type 1 SMA population, with a median age of 1.5 months (range: 1.0-3.0 months) at symptom onset. The disease duration (time between onset of symptoms and first treatment) was >3 months in 27 patients (65.9%) and ≤3 months in 14 patients (34.1%), for a median disease duration of 3.4 months (range: 1.0-6.0 months).

All patients had an SMN2 copy number of 2, as required by the study inclusion criteria. Median baseline scores for CHOP-INTEND (22.0), BSID-III (2.0), HINE-2 (1.0), and CMAP amplitude (0.2 mV) were low, as expected for this symptomatic patient population. Patients' current levels of motor function at screening were also typical of this patient population, confirming that all patients had well-established disease by the time of study enrolment. The majority of patients (29/41, 70.7%) were receiving no pulmonary care at baseline; 10 patients (24.4%) were receiving non-invasive ventilation (BiPAP) support for <16 hours/day, and 4 patients were receiving cough assistance (3 patients [7.3%] received it daily as a prophylactic therapy [not acute-illness related] and 1 patient [2.4%] received it because of an ongoing illness. All but 1 patient were able to swallow at baseline. The majority of patients (33/41, 80.5%) were fed exclusively by mouth, 2 patients (4.9%) were fed via a combination of oral and tube feeding, and 4 patients (9.8%) were fed via a feeding tube at baseline; information about feeding route at baseline was missing for 2 patients (4.9%).

Concurrent medical conditions (i.e., those ongoing at screening) were reported in 11 patients (26.8%), the most frequent condition, by PT, being haemangioma (2/41, 4.9%).

Six patients (14.6%) in Part 2 underwent SMA-related surgeries or procedures prior to treatment with risdiplam; all 6 patients had a gastrointestinal tube inserted.

Nineteen patients (46.3%) underwent SMA-related surgeries or procedures after the date of first risdiplam dose; those performed in more than 1 patient, by MedDRA PT, were gastrostomy (6 patients [14.6%]); gastrointestinal tube insertion and gastrointestinal tube removal (each performed in 5 patients [12.2%]); endotracheal intubation, extubation, and mechanical ventilation (each performed in 4 patients [9.8%]); and bronchoalveolar lavage and tracheostomy (each performed in 2 patients [4.9%]).

Twenty-eight patients (68.3%) in Part 2 had at least one prior medication that was taken and completed prior to starting risdiplam treatment.

Twenty-seven patients (65.9%) received prior and ongoing medications (i.e., that were started prior to onset of risdiplam treatment and that were ongoing at the date of first dose). The most common medications, by medication class, were antispasmodics and anticholinergics (17 patients, 41.5%), vitamins and minerals (11 patients, 26.8%), and adrenergics/sympathomimetics (10 patients, 24.4%).

Twenty-two patients (53.7%) received concomitant medications for prophylaxis (defined as those within the medication classes of Vitamins and Minerals or Vaccines, Toxoids, and Serologic Agents).

Twenty-one patients (51.2%) received other concomitant medications (i.e., medications not taken for AEs or prophylaxis) on or after the date of the first dose of risdiplam. The most common of these other medications, by medication class, were antispasmodics and anticholinergics (15 patients, 36.6%).

Numbers analysed

PART 2

All enrolled patients were included in the analysis.

Outcomes and estimation

PART 2

The primary efficacy endpoint for this study was met. After 12 months of treatment with risdiplam, 29.3% of patients in Part 2 were sitting without support, as assessed by Item 22 of the BSID-III gross motor scale. This proportion is significantly higher than the pre-defined performance criterion of 5% based on natural history data ($p<0.0001$).

The results of the secondary and exploratory efficacy endpoints supported the primary endpoint, showing that risdiplam treatment was associated with clinically meaningful improvements in patients with Type 1 SMA at Month 12:

- 56.1% of patients achieved a CHOP-INTEND total score of 40 or higher, and 90.2% of patients achieved an increase of at least 4 points in their CHOP-INTEND score from baseline. These results are significantly higher than the pre-defined performance criteria of 17% based on natural history data ($p<0.0001$ for each of these endpoints).
- Motor milestone development was further confirmed by the HINE-2, as a second independent assessment; 78.0% of patients were classified as motor milestone responders (defined as having more milestones that showed improvement from baseline than showed worsening) as assessed by the HINE-2. This proportion was significantly higher than the pre-defined performance criterion of 12% based on natural history data ($p<0.0001$).
- 85.4% of patients were alive without permanent ventilation. This proportion is significantly higher than the pre-defined performance criterion of 42% based on natural history data ($p<0.0001$).
- 92.7% of patients were alive. This proportion is significantly higher than the pre-defined performance criterion of 60% based on natural history data ($p=0.0005$).
- 82.9% of patients had the ability to feed orally.
- 9 patients (22.0%) could either stand with support (2 patients) or support weight (7 patients) when assessing the standing item, and 1 patient (2.4%) could bounce when assessing the walking item according to the HINE-2.

Table 26: Summary of Key Efficacy Results in Part 2 at Month 12 (ITT Population, Part 2 Patients)

Endpoint	Risdiplam (N=41)	Performance Criterion	p-value [a]
Primary Efficacy Endpoint			
Proportion of patients sitting without support for at least 5 seconds (BSID-III) (90% CI)	29.3% (17.8%, 43.1%)	5%	<0.0001
Secondary Efficacy Endpoints			
Motor Function and Development Milestones			
Proportion of patients who achieve a CHOP-INTEND score of 40 or higher (90% CI)	56.1% (42.1%, 69.4%)	17%	<0.0001
Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline (90% CI)	90.2% (79.1%, 96.6%)	17%	<0.0001
Proportion of motor milestone responders [b] as assessed by the HINE-2 (90% CI)	78.0% (64.8%, 88.0%)	12%	<0.0001
Proportion of patients able to support weight or stand with support [c] as assessed by the HINE-2 (90% CI)	22.0% (12.0%, 35.2%)	NA	–
Proportion of patients able to bounce while assessing the walking item of the HINE-2 (90% CI)	2.4% (0.1%, 11.1%)	NA	–
Survival and Ventilation Free Survival			
Proportion of patients alive without permanent ventilation [d] (90% CI)	85.4% (73.4%, 92.2%)	42%	<0.0001
Proportion of patients alive (90% CI)	92.7% (82.2%, 97.1%)	60%	0.0005
Nutrition			
Proportion of patients with the ability to feed orally [e] (90% CI)	82.9% (70.3%, 91.7%)	NA	–
Endpoint	**Risdiplam (N=41)**	**Performance Criterion**	**p-value [a]**
Exploratory Endpoints			
Number of hospitalisations [f] per patient-year (90% CI)	1.30 (1.02, 1.65)	NA	
Proportion of patients with no hospitalisations [f] (90% CI)	48.8% (35.1%, 62.6%)	NA	
Proportion of patients with the ability to swallow (90% CI)	87.8% (76.1%, 95.1%)	NA	–

BSID-III=Bayley Scales of Infant and Toddler Development – Third Edition; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders;HINE-2=Module 2 of the Hammersmith Infant Neurological Examination; NA=not available.

[a] p-values for survival and ventilation-free survival are based on a Z-test; p-values for all other endpoints (BSID-III, CHOP-INTEND, HINE-2) are based on an exact binomial test.

[b] An improvement in a motor milestone was defined as a ε2-point increase in the ability to kick (or maximal score) or a ε1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as a ε2-point decrease in ability to kick (or lowest score) or a ε1-point decrease in head control, rolling, sitting, crawling, standing, or walking. Voluntary grasp was excluded from the definition. An infant was classified as a responder if more motor milestones showed improvement than showed worsening.

[c] Includes 7 patients (17.1%) who could support weight and 2 patients (4.9%) who could stand with support.

[d] Permanent ventilation defined as tracheostomy or ε16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event.

[e] Includes patients who were fed exclusively orally (28 patients overall) and those who were fed orally in combination with a feeding tube (6 patients overall) at Month 12.

[f] Hospitalisations include all hospital admissions that spanned at least two days.

Alternative Definitions of Sitting without Support

Endpoint	Risdiplam (N=41)	Natural History Data
Alternative Definitions of Sitting without Support)		
Sitting defined by the HINE-2 categories of "Stable sit" or "Pivots (rotates)"	10/ 41 (24.4%) (90% CI: 13.9%, 37.9%)	0/24 (De Sanctis et al, 2016) performance criteria: 5%
Sitting without support for 30 seconds (item 26 of the BSID-III gross motor scale) at 12 months	7/ 41 (17.1%) (8.30%, 29.69%)	

Ancillary analyses

Sensitivity Analyses of Primary Endpoint: The results of the primary analysis are supported by the results of sensitivity analyses performed using a different scale with an **alternative definition of sitting without support**. At 12 months of treatment, 10 of 41 patients (24.4%; 90% CI: 13.9%, 37.9%) in Part 2 were sitting without support, as assessed by the HINE-2 categories of 'Stable sit' and 'Pivots (rotates).'

Survival and Ventilation-Free Survival

Three patients died within the first three months following study enrolment and 3 patients met the endpoint of permanent ventilation. The median time to death or permanent ventilation was not estimable as too few patients had an event. Meeting the permanent ventilation endpoint did not represent an end-stage disease as all 3 patients showed improved CHOP-INTEND scores at Month 12 of treatment. The reasons for meeting the permanent ventilation endpoint were: prolonged intubation for the treatment of a serious adverse event (SAE; this patient was later extubated and was breathing without support of intubation or prolonged use of BiPAP at Month 12), tracheostomy due to difficulties in performing oral intubation to treat an SAE, and tracheostomy due to vocal cord palsy in the context of recurrent respiratory SAEs and repeated intubation/extubation.

Figure 36: Kaplan-Meier Plot of Time to Death in Study BP39056 (FIREFISH) (ITT Population, Part 2 Patients)

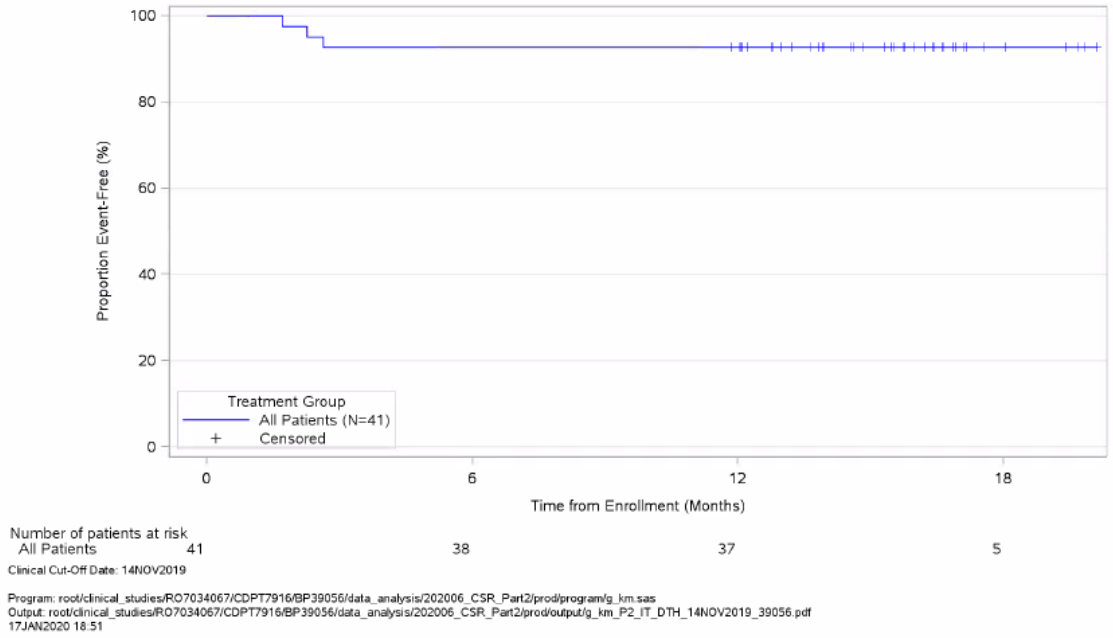
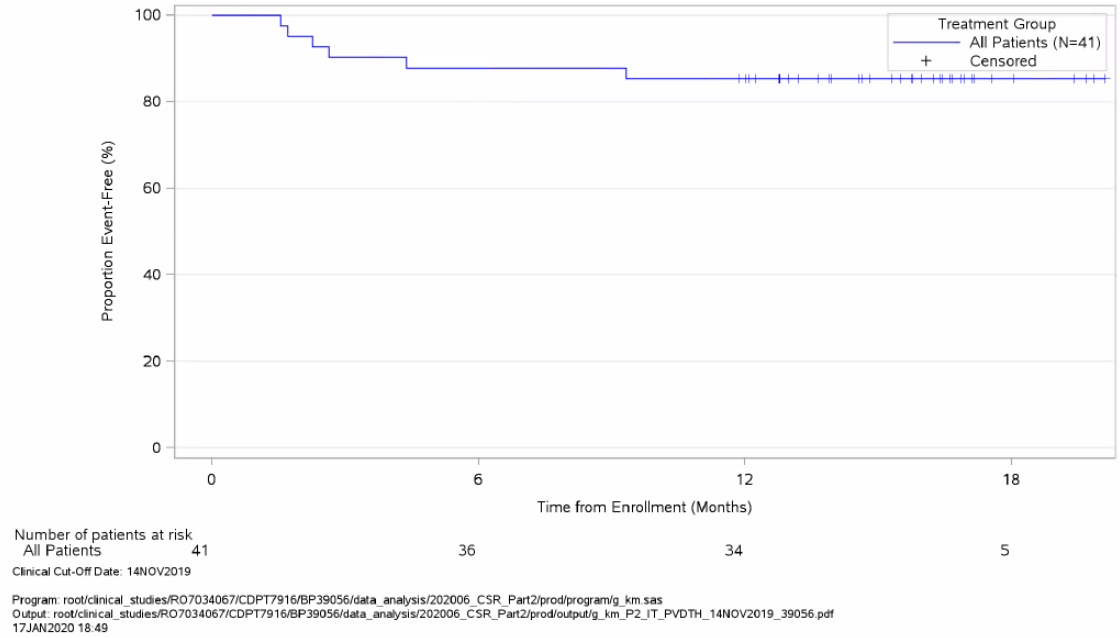


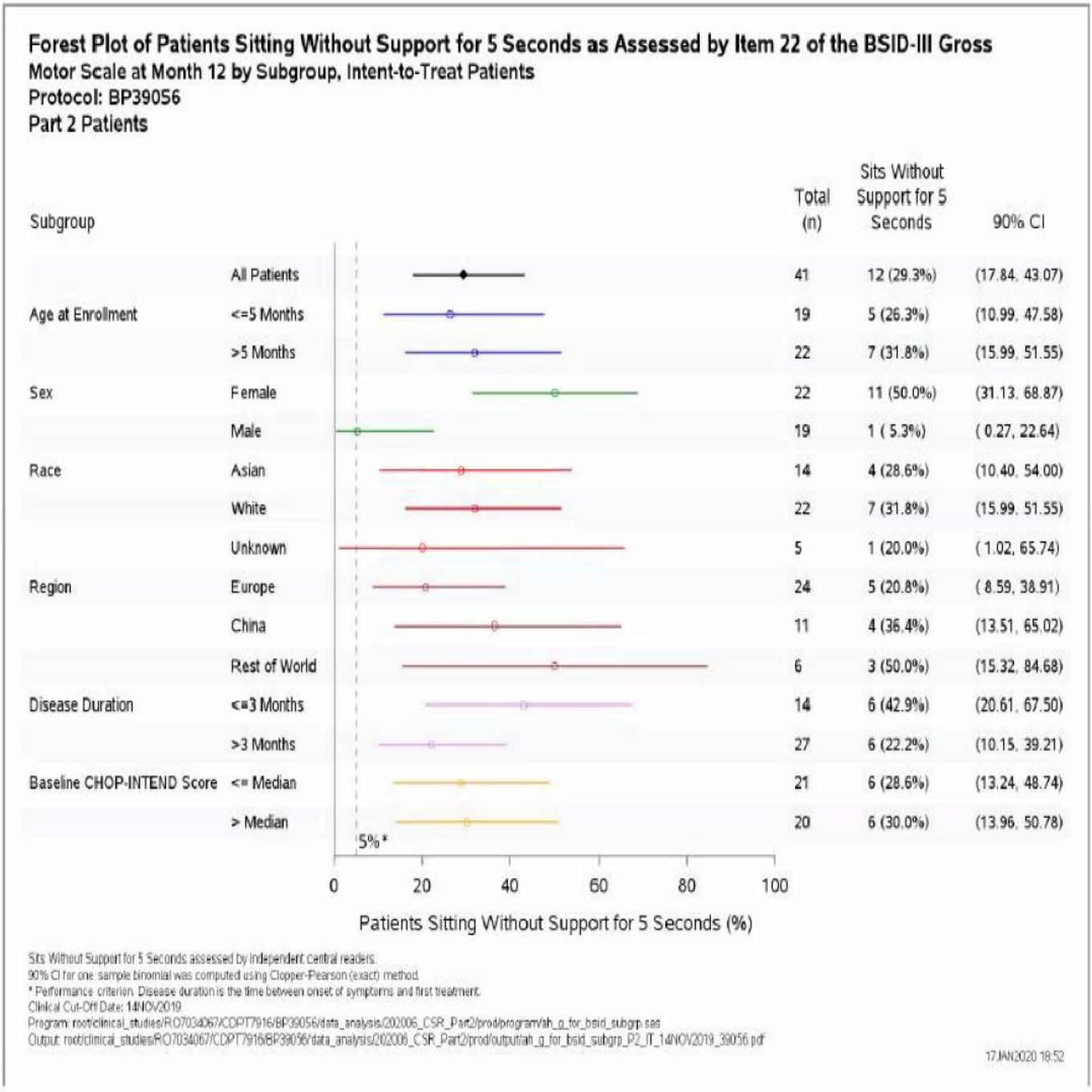
Figure 37: Kaplan-Meier Plot of Time to Death or Permanent Ventilation in Study BP39056 (FIREFISH) (ITT Population, Part 2 Patients)



SUBGROUP ANALYSES

Sitting without Support for 5 Seconds (BSID-III Gross Motor Scale)

Figure 38: Forest Plot of Patients Sitting without Support for 5 seconds at Month 12 by Subgroup (ITT Population; Part 2 Patients)



Later-Onset SMA

Type 2 and non-ambulant Type 3: Study BP39055 SUNFISH

The clinical programme includes one pivotal study in this population.

Methods

Study BP39055 (SUNFISH) is being conducted in two parts, Part 1 and Part 2. Patients in Part 1 did not enrol into Part 2 of the study, therefore, Parts 1 and 2 are considered as two independent studies.

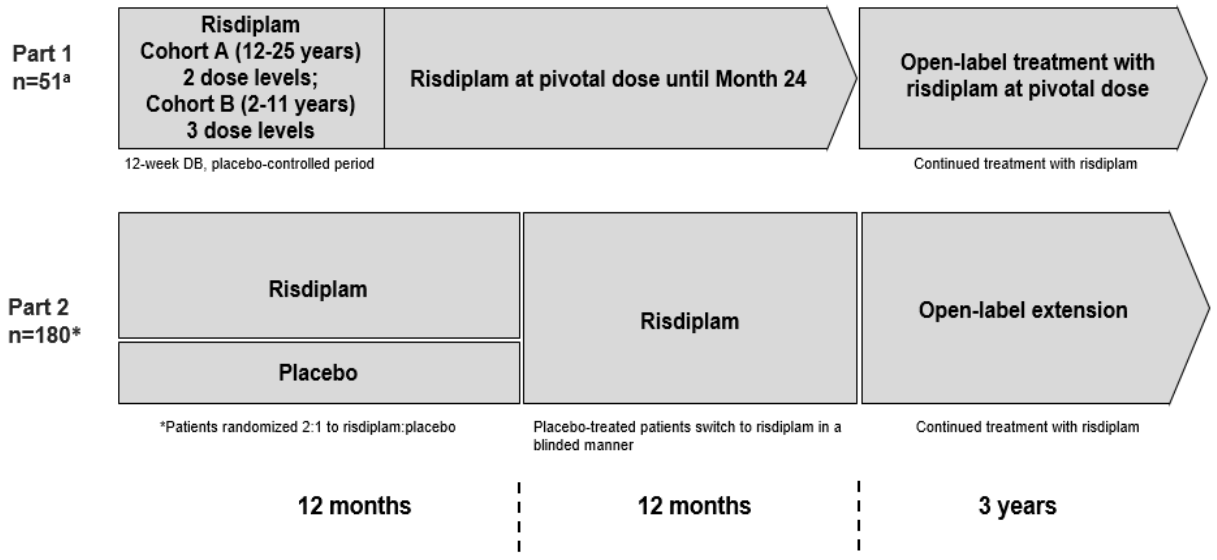
Part 1 was a double-blind, placebo-controlled, randomised (2:1, risdiplam: placebo), dose-finding study in patients with Type 2 and Type 3 (ambulant or non-ambulant) SMA (Figure 5). The primary objective of Part 1 was to evaluate the safety, tolerability, PK, and PD of risdiplam and to select the dose for Part 2, the confirmatory part of the study. The efficacy endpoints for Part 1 are identical to the main key efficacy endpoints used in Part 2, and were assessed in the same manner for both Part 1 and 2. All assessments and data collection was conducted by trained physicians and/or physical therapists.

Patients in Part 1 were enrolled in a dose escalating design. Upon completion of the minimum 12-week placebo-controlled treatment period, patients who were assigned to placebo were switched to active treatment at the dose tested in their respective cohort.

The pivotal dose decision for Part 2 was based on safety and PK/PD data from Part 1 of the study and was endorsed by the iDMC in August 2017. After selection of the pivotal dose for Part 2, all patients from Part 1 received the pivotal dose as part of the open-label treatment phase (Figure 5). The open-label treatment phase of Part 1 remains ongoing, and data from this period continues to be assessed to demonstrate the long-term efficacy of risdiplam.

Part 2, the confirmatory part, is a double-blind, placebo-controlled, randomised (2:1, risdiplam:placebo) study, investigating the efficacy and safety of risdiplam at the selected pivotal dose from Part 1 over a 24 month treatment period, in patients with Type 2 and non-ambulant Type 3 SMA aged 2 to 25 years (Figure 5). The primary analysis of Part 2 was conducted at the end of the 12-month placebo-controlled period, after which patients initially randomised to placebo were switched to active treatment in a blinded manner. Part 2 remains ongoing, with all patients receiving risdiplam. In Part 2, the primary objective is to evaluate the efficacy of risdiplam.

Figure 39: Study Design of Parts 1 and 2 of Study BP39055 (SUNFISH)



[a] Once the last patient in each cohort had reached the end of the 12-week double-blind, placebo-controlled period, all available data were reviewed for each cohort. Patients on placebo were switched to risdiplam at the dose tested in their respective cohort in the open-label treatment period. Patients on placebo had to complete the scheduled visit at Week 17 prior to switching to risdiplam and then followed the Schedule of Assessments starting again at Day 1. Cohort B3 did not have an open-label treatment period and progressed immediately into the OLE phase after completion of the 12-week double-blind, placebo-controlled period.

The two parts of the study are independent, have their own objectives and eligibility criteria, and are being analysed separately. Patients in Part 1 did not roll over into Part 2 of the study.

In certain countries (based on pre-established Health Authority and Ethics Committee approval), the study progressed in an operationally seamless manner from Part 1 into Part 2 after the dose-selection decision was taken by the independent Data Monitoring Committee (iDMC).

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

Part 2

Part 2 of Study BP39055 was designed to investigate the efficacy and safety of risdiplam over a 24-month treatment period, in patients aged 2-25 years with Type 2 and non-ambulant Type 3 SMA.

A total of 168 patients were planned to be randomised (2:1) to receive either risdiplam (at the pivotal dose of 5 mg once daily for patients with a body weight [BW] >=20 kg or 0.25 mg/kg for patients with a BW < 20 kg) or placebo. Randomisation was stratified by age group (2-5 years, 6-11 years, 12-17 years, and 18-25 years at randomisation). No more than 30 patients were to be randomised into the 18-25 years age group. A minimum of 45 patients were to be randomised into each of the other three age groups. Patients from Part 1 were not included in Part 2.

The duration of the study for each patient enrolled in Part 2 is up to 25 months.

Study participants

Part 2 of Study BP39055 (SUNFISH) was conducted in a heterogeneous population, with a broad and varied range of baseline characteristics

Inclusion / Exclusion criteria:

Key Inclusion Criteria	
Age	Males and females aged 2 to 25 years at screening.
SMA diagnosis	Confirmed diagnosis of 5q-autosomal recessive SMA, including: a. Genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the *SMN1* gene. b. Clinical symptoms attributable to Type 2 or Type 3 SMA.
Ambulatory status	For Part 1: Type 2 or 3 SMA patients (ambulant or non-ambulant). For Part 2: Type 2 and non-ambulant Type 3 SMA patients
Key Exclusion Criteria	
Previous SMA treatment	Concomitant or previous administration of a *SMN2*-targeting ASO, *SMN2* splicing modifier or gene therapy
Respiratory status	Invasive ventilation or tracheostomy
Surgery	Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 months

- For non-ambulant patients in Part 2 (at screening): a) Revised upper limb module (RULM) entry item A (Brooke score) ≥2 (i.e., "Can raise 1 or 2 hands to the mouth, but cannot raise a 200 g weight in it to the mouth"). b) Ability to sit independently (i.e., scores ≥1 on item 9 of the MFM 32 "with support of one or both upper limbs maintains the seated position for 5 seconds").

Further relevant exclusion criteria:

- Significant risk for suicidal behaviour, in the opinion of the Investigator as assessed by the SSRS (>6 years of age)
- Any OCT-2 and MATE substrates within 2 weeks before dosing (including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine).
- Use of the prohibited medication
- 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.

Treatments

Oral, once daily administration. Throughout the study, the study medication (risdiplam or placebo) was taken once daily in the morning with the patient's regular morning meal, except when site visits were planned and study medication was administered at the clinical site. The first dose of study medication was administered at the clinical site on Day 1 after all pre-dose assessments were conducted.

CONCOMITANT MEDICATIONS

Permitted Therapy

Concomitant therapy included any medication, e.g., prescription drugs, over-the-counter drugs, approved dietary and herbal supplements, nutritional supplements, and nonmedication interventions

(e.g., individual psychotherapy, cognitive behavioural therapy, smoking cessation therapy, physical therapy, and rehabilitative therapy) used by a patient within 30 days of study screening until the follow-up visit.

Physiotherapy, occupational therapy, and other forms of exercise therapy were encouraged but the frequency was to remain the same during the clinical study.

All medication administered to manage AEs was recorded on the AE eCRF.

In general, for any chronic treatment, patients were to be on a stable regimen for 6 weeks prior to screening and were to remain on a stable regimen throughout the study.

Examples of allowed medications for this study were provided in the Protocol.

Prohibited Therapy

Administration of nusinersen (SPINRAZA) either in a clinical study or for medical care at any time prior to or during the study was strictly prohibited.

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

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

During the study and for at least 90 days prior to randomisation, other medications intended for the treatment of SMA or with known phototoxicity liabilities or with potential retinal toxicity as detailed in the Protocol were also prohibited.

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

- Deferoxamine, topiramate, latanoprost, niacin, rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon or any other drugs known to cause retinal toxicity, including chronic use of minocycline.

Objectives

The primary objectives of Part 2 was: To evaluate the efficacy of risdiplam compared with placebo in terms of motor function in patients with Type 2 SMA and non-ambulant Type 3 SMA, as assessed by the change from baseline in the total score of the Motor Function Measure (MFM) at 12 months.

The controlled part of the study was a superiority over placebo study for the primary endpoint.

The hypothesis tested was that the difference in the mean change from baseline in the total MFM32 score at Month 12 between risdiplam and placebo was 0. If the two-sided p-value was <=5%, then the null hypothesis, of no difference in the mean change from baseline in the total MFM32 score at Month 12 between risdiplam and placebo, was rejected.

Outcomes/endpoints

Part 2

Primary Efficacy endpoint

The primary efficacy endpoint was the change from (original) baseline in the total motor function measure 32 (MFM32) score at Month 12. The MFM32 total score was calculated according to the user manual. The 32 scores were summed and then transformed onto a 0-100 scale (i.e., sum of 32 items scores divided by 96 and multiplied by 100) to yield the MFM32 total score expressed as a percentage of the maximum score possible for the scale (the one obtained with no physical impairment).

Secondary Efficacy Endpoints

The secondary efficacy endpoints were:

Motor Function

- Change from baseline in total score of the Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 12.
- Change from baseline in the total score of the revised upper limb module (RULM) at Month 12.
- Proportion of patients who achieve stabilisation or improvement (i.e., a change from baseline >=0) on the total MFM score at Month 12.
- Proportion of patients with a change from baseline MFM32 total score of 3 or more at Month 12.
- Proportion of patients who achieve an improvement of at least one standard error of measurement (SEM; calculated at baseline) on the total MFM score at Month 12
- Change from baseline in the each of the MFM domain scores of D1, D2, D3, and the total combined score of (D1 + D2) and D2 + D3 at Month 12.
- Proportion of patients who achieve stabilisation or improvement (i.e., a change from baseline >=0) on the total HFMSE score at Month 12.
- Proportion of patients who achieve stabilisation or improvement (i.e., a change from baseline >=0) on the total RULM score at Month 12.
- Proportion of patients with a change from baseline HFMSE total score of 2 or more (≥2) at Month 12.
- Proportion of patients with a change from baseline RULM total score of 2 or more at Month 12.

Respiratory

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

  For patients aged 6-25 years at screening only:

- Change from baseline in best percentage predicted value of the forced expiratory volume in 1 second (FEV1) at Month 12.
- Change from baseline in best percentage predicted value of the forced vital capacity (FVC) at Month 12.
- Change from baseline in the best percentage predicted value of the peak cough flow (PCF) at Month 12.
- Change from baseline in the best percentage predicted value of the maximal inspiratory pressure (MIP) at Month 12.
- Change from baseline in the best percentage predicted value of the maximal expiratory pressure (MEP) at Month 12.

Disease-Related Adverse Events

- Proportion of patients who experience at least one disease-related AE by Month 12.
- Number of disease-related AEs adjusted for patient-year (per 100 patient years) at Month 12.

Clinical Global Impression of Change

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

Patient- and Caregiver-Reported Outcomes

- Change from baseline in the total score of the caregiver-reported SMA independence scale (SMAIS) at Month 12. SMAIS scale is a new tool developed by the MAA, which has been validated along the development plan.

  In patients aged 12 to 25 years only:

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

Table 27: Motor Function Outcome Measure Overview for Study BP39055 (SUNFISH)

Outcome Measure	Clinical Meaningfulness
Motor Function Measure 32 (MFM32)	
MFM32 is a valid and reliable assessment of motor function ability in neuromuscular diseases, including SMA, validated in individuals aged 6 years and older (Bérard et al. 2005). A recent validation study has also demonstrated strong evidence of reliability (including excellent internal consistency and test-retest reliability results) and validity (including strong convergent validity and known-groups validity results) in individuals with neuromuscular diseases, including SMA, aged 2–5 years old (Trundell et al. 2019). Although a shorter version of the MFM (the 20-item MFM [MFM20]) has been used in children younger than 7 years (de Lattre et al. 2013), the 12 excluded items assess functions important for daily life. In clinical trials such as Study BP39055 (SUNFISH), the purpose of a functional scale is to assess changes following treatment intervention rather than to characterise cross-sectional scores. Thus, there is a practical and conceptual basis for inclusion of the 12 items in younger patients in clinical trials assessing treatment intervention, including 2–6-year olds. The MFM32 contains 32 items, all of which patients have confirmed are related to everyday activities of daily living (Duong et al. 2020a [draft]). The MFM32 is assessed in three domains of motor function: D1 (standing and transfers), D2 (axial and proximal motor function), and D3 (distal motor function). The 32 items scored on a 0–3 scale are summed and then transformed onto a 0–100 scale (i.e., sum	MFM32 is a clinically relevant scale as it evaluates different levels of motor function in individuals with SMA, from distal fine motor movements of the hands to more complex gross motor function activities such as standing and transfers. The MFM32, therefore, has the ability to assess a spectrum of motor function across a broad range of patients at different stages of SMA disease progression: from ambulant to non-ambulant patients with a progressed disease. This is particularly meaningful in the context of the heterogeneous Type 2 and 3 SMA patient population included in Study BP39055 (SUNFISH). Natural history data collected on patients aged 5.7 to 59 years, including Type 1, 2, and 3 SMA patients, demonstrated that the overall slope of decline over time using the MFM32 total score is in the range of –0.9 points/year for Type 2 patients and –0.6 points/year for Type 3 patients (Vuillerot et al. 2013). SMA patients describe stabilisation in their functional ability as a meaningful outcome (McGraw et al. 2017; Cure SMA 2015; Rouault et al. 2017). These results were confirmed by a recent survey conducted by SMA Europe covering 18 European countries and including over 1300 responses from patients and caregivers aged from 0 to 81 years across all SMA types. The survey confirmed that almost all participants (96.7%) considered stabilisation as progress

of 32 items scores divided by 96 and multiplied by 100) to yield the MFM32 total score expressed as a percentage of the maximum score possible for the scale (the one obtained with no physical impairment). The lower the total score, the more severe the functional impairment.	(Gusset 2020), even in the current clinical environment where some patients have access to a disease modifying treatment. In the context of the MFM32, a recent interview (n=40) and survey study (n=217) has demonstrated that for Type 2 and Type 3 patients and caregivers, maintaining current level of functional ability on the MFM32 over a 1 year period would be a meaningful outcome for 98% (interview data) and 90% (survey data) of the samples surveyed, respectively (Duong et al. 2020b [draft]). Moreover, 100% (interview data) and 98% (survey data) of subjects confirmed that gaining some level of improvement was meaningful. A threshold of improvement on the MFM32 scale, such as ≥3 points, should be considered as a marked improvement for patients because it may represent either the acquisition of a new function or the improvement in performance of several functions.
Revised Upper Limb Module (RULM)	
The RULM assesses upper limb motor performance in SMA patients. It is a validated scale in SMA, which has demonstrated good reliability and validity (Mazzone et al. 2017). The RULM has typically been used in conjunction with the HFMSE (which does not assess fine motor hand, wrist, or elbow function) to understand changes in upper limb ability and capture change in weaker SMA patients. The RULM is particularly important for non-ambulant patients who rely on preservation of upper limb ability to complete daily activities. The RULM consists of 19 items (scored on a 0–2 scale for 18 items and 0–1 for one item) assessing the performance of shoulder, elbow, wrist, and hand function. A total score from 0–37 is calculated with higher scores indicating greater upper limb functioning.	The preservation of upper limb function in SMA is particularly important as it ensures independence for essential everyday activities such as eating, washing, and dressing. In addition, the RULM includes items relating to upper limb strength (e.g., lifting a weighted object) which are not captured by the HFMSE and MFM32. Having the strength to lift objects is an important aspect of daily living as it may help patients to eat on their own, or to live independently in their own home. For non-ambulant patients with a progressed disease, fine motor skills are critical for social connections (e.g., use of phone or computer) and for operating a wheelchair. For this reason, assessing the impact of the disease in the upper extremities is of great importance for this patient population. Natural history data show that over 12 months, the mean change in RULM score is –0.4 points in Type 2 and Type 3 patients aged 2.7 to 49.7 years (Pera et al. 2019). Patients and caregivers have reported that small improvements and stabilisation on the RULM (in context of the ULM) have meaningful impacts on daily life (McGraw et al. 2017).

Hammersmith Functional Motor Scale Expanded (HFMSE)	
The HFMSE was developed to assess gross motor function in individuals aged two years or older, with Type 2 and 3 SMA (O'Hagen et al. 2007). The HFMSE has well-established psychometric properties in children with SMA (O'Hagen et al. 2007; Glanzman et al. 2011). The scale was modified and 13 items were added to the original version of the measure (HFMS) in order to also capture changes in stronger patients; those extra items were particularly aimed at ambulant individuals (Cano et al. 2014). The HFMSE contains 33 items designed to assess important functional abilities, including standing, transfers, ambulation, and proximal and axial function. Each item is scored on a 0–2 scale by a clinical evaluator. A total score from 0–66 is calculated with higher scores indicating greater functioning.	The scale has been widely used in SMA type 2 and 3 (Mercuri et al. 2019) and includes clinically relevant items assessing sitting, rolling, transitions relating to crawling and kneeling, and standing/stepping. There are no items that assess the fine motor function of the hand, wrist, or elbow, which are critical functions for weak, wheelchair bound non-ambulant patients. Natural history data from Type 2 and Type 3 patients aged 2–45 years collected using the HFMSE shows a change of 0.08 points over the course of 12 months, a decline of –0.24 points after 24 months, and a decline of –2.31 points after 36 months, on average (Kaufmann et al. 2012). Another study of Type 2 and Type 3 patients aged 2.5 to 55 years, including ambulant and non-ambulant individuals, demonstrated that the overall slope of decline in the HFSME total score over a 12-month period is -0.57 in non-ambulant patients (Mercuri et al. 2016). The change in HFMSE varied across age groups: +0.04 in children <5 years, –0.96 in children and adolescents aged ≥5 to <15 years, and –0.35 in adolescents ≥15 years (Mercuri et al. 2016). Patients and caregivers have also reported that stabilisation and small improvements on the HFMSE are meaningful in daily life (McGraw et al. 2017). A threshold of improvement on the HFMSE scale, such as ε3 points (Mercuri et al. 2018), should be considered as a marked improvement for patients, especially in the context of a progressive disease.Recent meaningful change analyses indicate that a 2-point change could be considered a meaningful difference (Williams et al. 2019).

Sample size

Part 2

The purpose of this part of the study is to estimate and test the treatment effect of RO7034067 at the selected dose from Part 1 relative to placebo. A target sample size of 168 patients will be randomised, 112 patients on RO7034067 and 56 patients on placebo (2:1 randomisation). For the primary endpoint of the mean change from baseline in the total MFM32 score at Month 12, this sample size (allowing for a 10% drop-out rate) provides at least 80% power at a two-sided 5% significance level for testing the null hypothesis that the true treatment difference is zero versus the alternative hypothesis, given that the true treatment difference is 3 and assuming that the common standard deviation will be 6 (twice the value seen in Vuillerot et al 2013). This corresponds to a hypothesised effect size of 0.5. The minimal detectable treatment difference is approximately 2.03.

In Protocol Version 3 released on 7 March 2017 (thus prior to first patient enrolment) changes were made to the Part 2 SUNFISH design, to mitigate expected recruitment and retention challenges considering launch of SPINRAZA (nusinersen) in the U.S. and ongoing Expanded Access Programme in Europe: the randomisation ratio was changed from 1:1 to 2 (active):1 (placebo), and the sample size was increased to maintain the same statistical power. The target sample size was 168 patients with 112 patients randomised to risdiplam and 56 patients randomised to placebo (2:1 randomisation).

Randomisation

Randomisation was performed using an Interactive (voice/web) Response System (IxRS). Separate randomisation lists were generated for the exploratory dose-finding Part 1 and the confirmatory Part 2 of the study. In both parts of the study, patients were randomised to risdiplam or placebo in a 2:1 ratio.

Blinding (masking)

In Part 2 of the study, patients and investigators are blinded to the initial treatment assignment until the last patient in Part 2 completes the 24-month assessments. All individuals in direct contact with the patient at the investigative site are blinded until this point, except for the unblinded pharmacist handling study drug. For this part of the study, the Sponsor remained blinded to treatment assignment information for patients randomised until the last patient randomised into Part 2 completed their 12-month assessment and the database was locked for the purpose of the primary and secondary efficacy analyses.

Statistical methods

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

The **primary efficacy estimand** is based on a hypothetical treatment strategy assuming no prohibited medications intended for treatment of SMA are available and patients continue on their randomised treatment until the primary analysis timepoint. The prohibited medications are defined in the protocol. A treatment policy strategy will also be applied if applicable. For any patients who discontinue study treatment but continue in the study, all data will be included regardless of initialisation on prohibited medications.

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

Primary analysis: Results from the primary endpoint were summarised descriptively for each timepoint by treatment group.

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

The model can be expressed as the following:

$Y_i = X_i \beta + Z_i v_i + \varepsilon_i$

where

- Yi is the ni x 1 vector of responses for patient i of the dependent variable.

- Xi is the known ni x p design matrix of fixed effects.

- β is a p x 1 vector of the unknown population parameters relate to the fixed effect.

- Zi is the known ni x r random effect design matrix.

- vi is the r x 1 vector of the unknown parameters for the subject/patient -effect which is distributed as N(0, $\sum$v)

- εi is the random error term for patient i which is a ni x 1 vector of random residuals distributed independently as N(0, $\sum$εi)

- vi and εi i are independent.

This is a mixed-effects model which contains components for fixed effects, random effect and the random error term. The dependent variable of this model was the absolute change from baseline total MFM32 score and the fixed effects of the model included variables of the baseline total MFM32 score, treatment group (placebo or risdiplam), time (i.e., relative to the first dose of randomised study medication in weeks-categorical), treatment-by-time interaction, baseline-by-time interaction and the randomisation stratification variable of age (categorical: 2 to 5, 6 to 11, 12 to 17, and 18 to 25 years at randomisation). The random effect will include the subject/patient effect. Time was treated as a repeated variable within a patient (random effects). Patient, treatment, and time were treated as factor variables and baseline total MFM32 score as covariate.

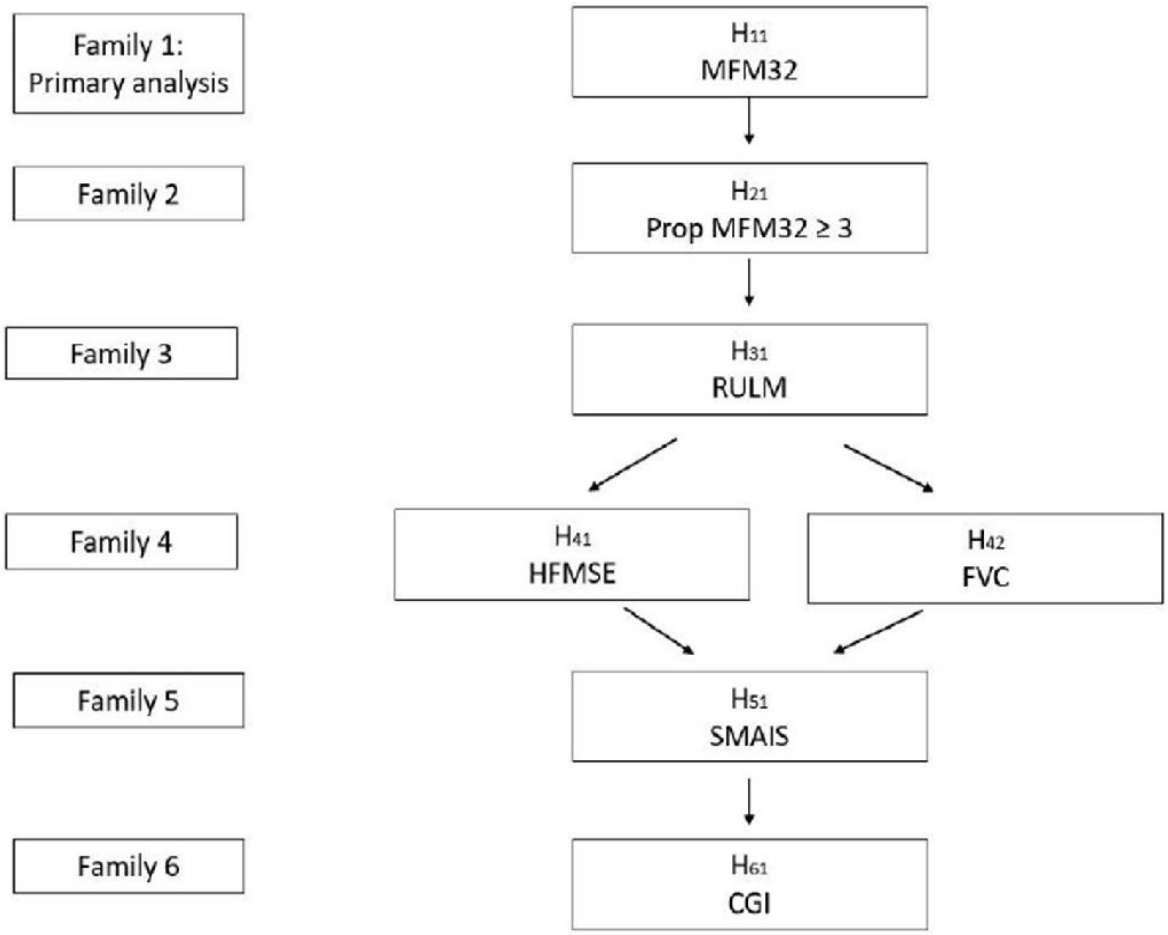
An unstructured variance-covariance matrix was applied to model the within-patient variability (Σεi) in the MMRM model. The components of variance and covariance matrix were estimated by the restricted maximum likelihood method. Denominator degrees of freedom were estimated using the Kenward - Roger approximation (Kenward & Roger 2009). If the model does not converge, a heterogeneous autoregressive variance-covariance matrix will then be applied to model the within-patient variability in the above model. The estimated treatment difference in the mean change from baseline in the total MFM score at Month 12 between risdiplam and placebo was presented with 95% CI.

Secondary endpoints: All analyses of the secondary efficacy endpoints were performed on data in Part 2 up to 12 months for each individual. MMRM analyses were performed for all continuous secondary endpoints similar to that specified for the primary analysis. Logistic regression models including baseline total score, treatment and age group as independent variables were used to analyse all secondary binary endpoints. All secondary endpoints were also summarised descriptively at each timepoint (at each scheduled assessment visit) by treatment group. For further details on the analysis of the secondary endpoints, please refer to Section 4.4.2 of the SAP.

Adjustment for Multiple Testing

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

Figure 40: Decision Tree for Part 2 Key Efficacy Endpoints for Hierarchical Testing



CGI= Clinical Global Impression; FVC=forced vital capacity; HFMSE=Hammersmith Functional Motor Scale Expanded; MFM=Motor Function Measure; RULM=Revised Upper Limb Module; SMAIS=Patient Reported and Parent/Caregiver reported SMA Independence Scale.

The unadjusted p-value is the p-value obtained when an endpoint is tested at 5% significant level. The adjusted p-values were derived based on all the (unadjusted) p values from endpoints in order of the hierarchy up to the current endpoint. Hence, the adjusted p-value of the primary endpoint is the same as its unadjusted p value. For endpoints that are not included in the hierarchy, the unadjusted p-values are presented (denoted by p-value in the results section).

Sensitivity Analysis

As a supportive analysis to assess the robustness of the primary analysis results based on the MMRM, sensitivity analyses, the tipping point analyses were performed on the primary efficacy endpoint, the change from baseline in MFM32 at Month 12 for the primary hypothetical efficacy estimand and for the treatment policy estimand.

Subgroup Analyses

The consistency of the primary efficacy endpoint and key efficacy endpoints (all secondary endpoints up to Family 4 in the hierarchical testing) were explored for the following subgroups:

- Age group (2-5, 6-11, 12-17, and 18-25 years at randomisation).
- Disease severity (Patient with MFM32 baseline total score below and equal to the first quartile <=Q1 (i.e., <=25th percentile), above the first quartile and below or equal to the third

quartile >Q1 to <=Q3 (i.e., >25th percentile and <=75th percentile) and above the third quartile >Q3 (i.e., >75th percentile).

- SMA type (Type 2, Type 3).
- Region (North America, Europe, China, Japan, rest of the world).
- SMN2 Copy number (<2, 2, 3, >=4 copies, unknown) from genotype analysis.

Changes to Planned Analyses after Database Lock

By the CCOD, there were 2 patients randomised to risdiplam with observed delayed puberty at baseline and no delayed puberty observed in any patients at post-baseline timepoints. As the results shown in the delayed puberty summary tables are the same for the placebo-controlled period and the all exposure to risdiplam treatment period, analysis on the all exposure to risdiplam treatment period was not performed. In addition, the analysis on the shift of the delayed puberty status from baseline to post-baseline timepoints for the placebo-controlled and all exposure to risdiplam treatment periods were not performed. Moreover, the number and percentage of patients with Tanner staging results within each stage (categorised by Stage I to Stage V) for post-baseline timepoints have not been summarised. Instead, a listing of all available Tanner staging and delayed puberty results for all applicable patients was created.

In addition, the normal range for patients age >12 years of the Diastolic Blood Pressure (vital signs) was based on 40-90 instead of 40-120 (previously stated in the SAP).

Since less than 5% of the ITT population were excluded from the primary analysis, the analysis on the imputation of the missing MFM items (as specified as a sensitivity analysis in the SAP) was not performed.

Additional analyses were performed, which included:

- MMRM analysis on the change from baseline in the total score of RULM at Month 12, by converting all item I scores of 2 into 1, and by age group.
- MMRM analysis on the change from baseline in absolute FVC (best value) in litres at Month 12.
- Responder analysis on the change from baseline in the total score of ≥0 at Month 12 by age group for MFM32, HFMSE and RULM
- Least square mean plots for HFMSE, RULM and SMAIS.
- Individual plots (scatter plots) of MFM32, HFMSE and RULM total scores by SMA Type with x-axis by ascending values of age
- Summary plot of gain and loss of function for each MFM32 item. Gain in function was defined as a score of '0' at baseline and a score of '1, 2 or 3' at Week 52. Loss of function was defined as a score of '1, 2 or 3' at baseline and a score of '0' at Week 52.
- Summary plot of gain and loss of function for each RULM item. Gain in function was defined as a score of '0' at baseline and a score of '1 or 2' at Week 52. Loss of function was defined as a score of '1 or 2' at baseline and a score of '0' at Week 52.
- AE rates per 100 patient-years (PY) by 3-monthly period for the placebo-controlled period.
- AE outcomes summary tables by patient counts for the placebo-controlled period.
- Serious disease-related AEs for the placebo-controlled period based on the narrow term basket

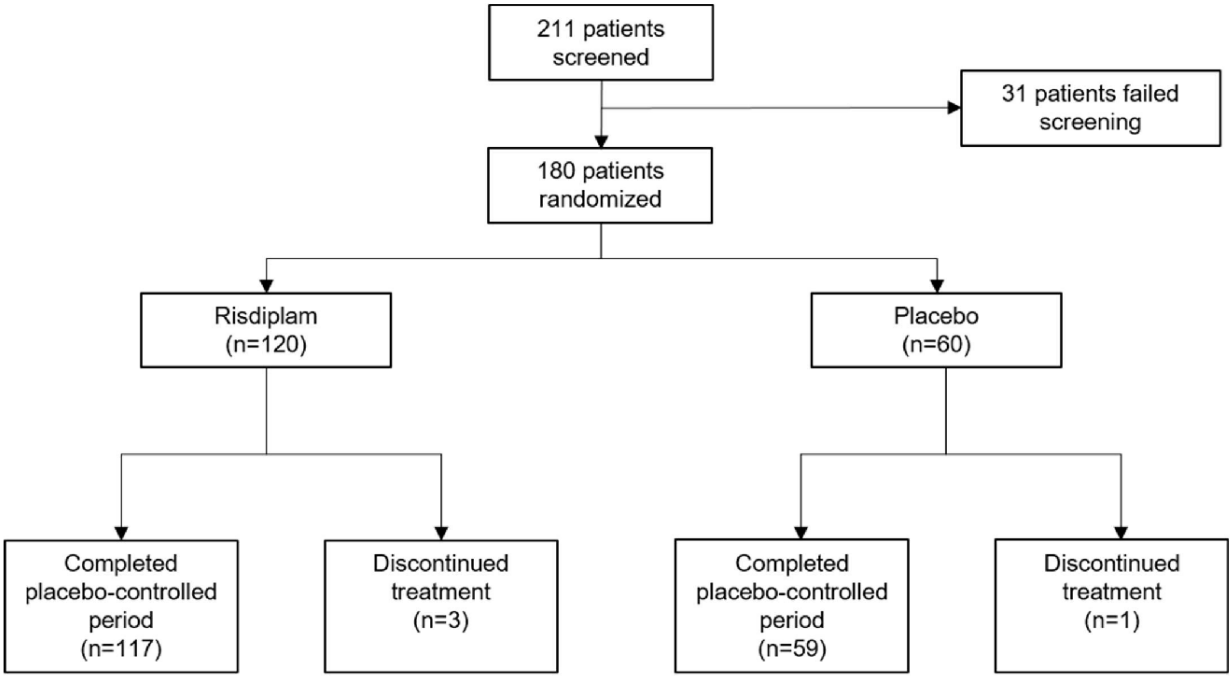
Results

Participant flow

Part 2

The first patient was randomised on 09 October 2017. The date of last patient last visit (LPLV) for the placebo-controlled, double-blind period was 06 September 2019. A total of 211 patients were screened for Part 2 of the study; of these, 31 patients were screen failures. Reasons for screen failure were mostly exclusion criteria or lack of cooperation for OCT examination.

Figure 41: Patient Disposition Flowchart



A total of 117 patients (97.5%) in the risdiplam arm and 59 patients (98.3%) in the placebo arm completed the placebo-controlled period.

At the time of the CCOD, 4 patients had discontinued the study during the placebo controlled period; 3 patients (2.5%) in the risdiplam arm, and 1 patient (1.7%) in the placebo arm. All 4 patients discontinued in order to switch to other treatment, specified as nusinersen in 3 patients, and not further specified in 1 patient.

Table 28: Patient Disposition (Placebo-Controlled Period), (ITT Population)

	Risdiplam (N=120)	Placebo (N=60)
Safety population	120 (100%)	60 (100%)
ITT population	120 (100%)	60 (100%)
No. completed placebo-controlled period	117 (97.5%)	59 (98.3%)
No. discontinued early from placebo-controlled period	3 (2.5%)	1 (1.7%)
Reason for early discontinuation#		
OTHER : ACCESS TO SPINRAZA	0	1 (1.7%)
OTHER : CHANGED TO OTHER TREATMENT	1 (0.8%)	0
OTHER : MOVE TO SPINRAZA TREATMENT	1 (0.8%)	0
OTHER : THE PATIENT'S FAMILY REQUESTED DISCONTINUATION OF THE STUDY TO INITIATE THE USE OF NUSINERSEN	1 (0.8%)	0

Percentages are based on all randomized subjects.
Safety population includes all subjects randomized in the study who received least one dose of study drug during the placebo-controlled period.
Reason for withdraw for 'other: free text field'.
Clinical Cutoff Date: 06SEP2019

Protocol deviations

Stringent criteria were applied for the evaluation of major protocol deviations given the vulnerability of the study population. As of the CCOD, 93 major protocol deviations (65 deviations in the risdiplam arm and 28 deviations in the placebo arm) were recorded in 62 patients (20 placebo- and 42 risdiplam-treated patients, respectively) during the whole treatment period. One ambulant patient was included by a site in error.

None of these protocol deviations are considered to impact the safety of patients in the trial or the interpretation of the efficacy results.

In conclusion, the number and type of major protocol deviations did not impact the wellbeing of the study participants, the integrity of the data, or the subsequent safety or exploratory efficacy analyses.

Baseline data

PART 2

A total of 211 patients were screened for Part 2 of Study BP39055 (SUNFISH); of these, only 31 patients (14.7%) failed screening. A total of 180 patients with Type 2 or non-ambulant Type 3 SMA were enrolled from 14 different countries across the US, Europe, Asia and the rest of the world. Of the 180 patients, 120 patients were randomised to treatment with risdiplam and 60 patients to placebo.

The median age of patients at screening was 9.0 years (range 2–25 years) in the risdiplam arm and 9.0 (range: 2–24 years) in the placebo arm. Overall, 68 patients (37.8%) were 12 years or older at screening. In each arm, approximately 50% of patients were male. The majority of the population were White (RIS: 66.7%; PLB: 68.3%) and of non-Hispanic or Latino ethnicity (95.0% in each arm).

Of the 180 patients in the ITT population, 128 patients (71.1%) had Type 2 SMA and 52 patients (28.9%) had Type 3 SMA. The proportion of Type 2 SMA patients was similar in the risdiplam (70.0%) and placebo (73.3%) arms. The majority of patients (87.2%) had 3 copies of the SMN2 gene (RIS:

89.2%; PLB: 83.3%). The median age of onset of initial SMA symptoms, as reported by the parents or patients, was 12.3 months (range: 0–57 months) in the risdiplam treatment arm and 12.8 months (range: 6–135 months) in the placebo arm. The median time between onset of initial SMA symptoms to first treatment (disease duration at baseline) was 106.3 months (min–max: 17–275 months) in the risdiplam arm and 96.6 months (min–max: 1–271 months) in the placebo arm.

Table 29: Motor Function Scale Scores by Treatment Arm at Baseline

	Risdiplam (N=120)	**Placebo (N=60)**
MFM32 total score		
n	115	59
Median (min–max)	46.88 (16.7–71.9)	47.92 (17.7–71.9)
RULM total score [a]		
n	119	58
Median (min–max)	19.00 (3.0–36.0)	20.00 (9.0–38.0)
HFMSE total score		
N	120	60
Median (min–max)	14.00 (0.0–48.0)	13.00 (2.0–43.0)

HFMSE=Hammersmith Functional Motor Scale Expanded; MFM32=Motor Function Measure 32; RULM=Revised Upper Limb Module.
n is the number of patients with valid observations after missing data rules applied.
Baseline is the last measurement prior to patient's first dose of risdiplam.
[a] The RULM total score ranges from 0 to 37. In 49 data points out of 720, the item I of the RULM scale was scored as 2 – for this item the maximum score is 1. Additional sensitivity analyses were performed to assess the impact of using the maximum score of 1 instead of 2 for these 49 data points (28 patients). The results of these sensitivity analyses showed consistency with the main analysis.

Baseline demographic and clinical characteristics appear balanced in the overall population enrolled in SUNFISH Part 2, between the control and treatment groups.

Numbers analysed

PART 2

The applicant states that all efficacy analyses were based on the ITT population. 115/120 randomised patients in the risdiplam group and 59/60 patient in the PBO group were included in the primary analysis. The six patients were excluded from the primary analysis due to missing MFM32 total scores at baseline: 5 patients randomised to risdiplam had between 2 and 13 items missing and 1 patient randomised to placebo had 3 items missing. The MFM32 missing data rules were based on input from an expert who is a part of the MFM group. The ambulant patient randomised to risdiplam was also one of the six patients excluded from the primary analysis because of missing MFM32 total score at baseline. A sensitivity analysis was conducted by imputing missing MFM32 item scores at baseline, based on the mean of the completed items in the same Domain for the same patient. The results were consistent with the results of the primary analysis. Efficacy results presented as a single p value represent the unadjusted p.

Outcomes and estimation

PART 2

Table 30: Study BP39055 (SUNFISH) Part 2: Summary of Key Efficacy Results

Endpoint	Risdiplam (N = 120)	Placebo (N = 60)
Primary Endpoint		
Change from baseline in MFM32 total score[1] at Month 12, LS Mean (SE)	1.36 (0.38) (95% CI: 0.61, 2.11)	−0.19 (0.52) (95% CI: −1.22, 0.84)
Difference from Placebo Estimate (SE) p-value[2]	1.55 (0.64) (95% CI: 0.30, 2.81) 0.0156	
Key Secondary Endpoints		
Proportion of patients with a change from baseline in MFM32 total score[1] of 3 or more at Month 12	44 (38.3%) (95% CI: 28.9, 47.6)	14 (23.7%) (95% CI: 12.0, 35.4)
Odds ratio for overall response p-value[3,4]	2.35 (95% CI: 1.01, 5.44) unadjusted p=0.0469; adjusted p=0.0469	
Change from baseline in RULM total score[5] at Month 12, LS Mean (SE)	1.61 (0.31) (95% CI: 1.00, 2.22)	0.02 (0.43) (95% CI: −0.83, 0.87)
Difference from Placebo p-value[2,4]	1.59 (0.52) (95% CI: 0.55, 2.62) unadjusted p=0.0028; adjusted p=0.0469	
Change from baseline in the caregiver-reported SMAIS total score[6] at Month 12, LS Mean (SE)	1.65 (0.5) (95% CI: 0.66, 2.63)	−0.91 (0.67) (95% CI: −2.23, 0.42)
Difference from Placebo p-value[2,4]	2.55 (0.82) (95% CI: 0.93, 4.17) unadjusted p=0.0022; adjusted p=0.3902	
Proportion of patients with a change from baseline MFM32 total score[1]≥0 at Month 12	80 (69.6%) (95% CI: 60.7, 78.4)	32 (54.2%) (95% CI: 40.7, 67.8)

LS=least-squares; MFM32= Motor Function Measure 32-Item; RULM= Revised Upper Limb Module; SE=standard error; SMAIS=Spinal Muscular Atrophy Independence Scale

1. Based on the missing data rule for MFM32, 6 patients were excluded from the analysis (risdiplam n=115; placebo n=59).
2. Data analyzed using a mixed model repeated measures with baseline total score, treatment, visit, age group, treatment-by-visit interaction, and baseline-by-visit interaction.
3. Data analyzed using logistic regression with baseline total score, treatment and age group.
4. The adjusted p-value was obtained for the endpoints included in the hierarchical testing and was derived based on all the p-values from endpoints in order of the hierarchy up to the current endpoint. Unadjusted p-value was tested at the 5% significance level.

5. Based on the missing data rule for RULM, 3 patients were excluded from the analysis (risdiplam n=119; placebo control n=58).
6. Based on the missing data rule for SMAIS, 4 patients were excluded from the analysis (risdiplam n=116; placebo control n=60).

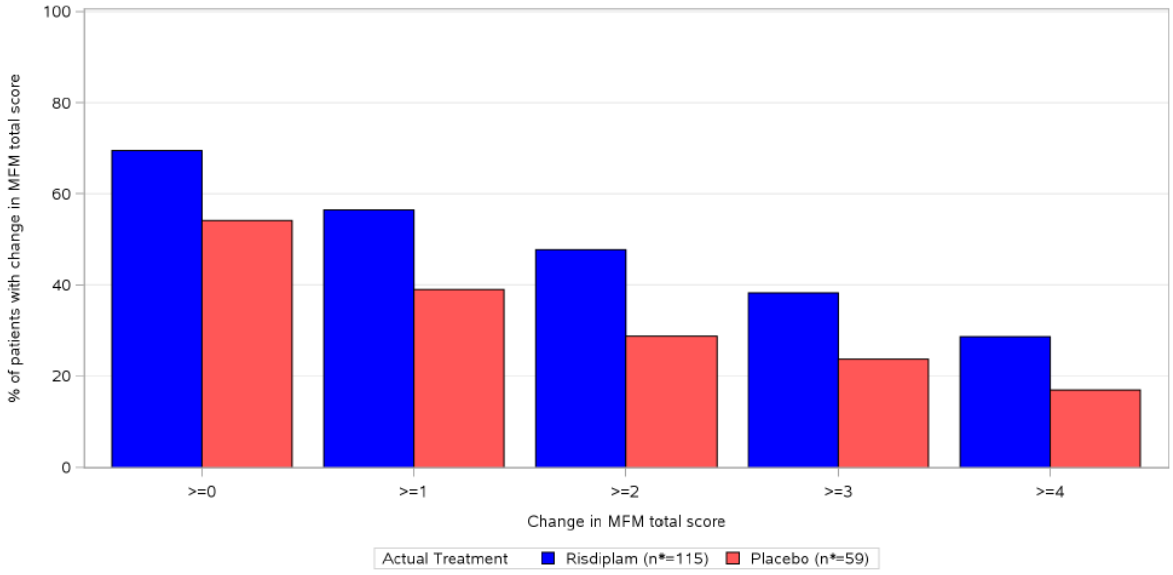
Motor Function

Motor Function Measure 32 (MFM32)

Risdiplam treatment was associated with improvement in patients' motor function as compared to placebo, as demonstrated by the changes on the primary endpoint. The primary endpoint in Part 2 of Study BP39055 (SUNFISH) was the change from baseline in the MFM32 total score at Month 12, which was both clinically meaningful and statistically significantly different from patients receiving placebo (least square difference in the mean [95% CI] changes from baseline: 1.55 [0.30, 2.81]; p=0.0156). Change from baseline in MFM32 total score showed an improvement in the risdiplam group [change from baseline, LS means: 1.36 (95% CI: 0.61-2.11)], compared to a worsening observed in the PBO group [-0.19 (95% CI:-1.22, 0.84)].

The proportion of patients with a marked improvement in MFM32 total score ≥3 points was the second endpoint in the statistical hierarchy, and was achieved by 38.3% in the risdiplam arm and 23.7% in the placebo arm (odds ratio [95% CI]: 2.35 [1.01, 5.44]; unadjusted p=0.0469, adjusted p=0.0469). An improvement on the MFM32 of ≥3 points represents an improvement for patients, such as the full acquisition of a new function or ability or significant improvement in performance of several functions.

Figure 42: Proportion of Patients Achieving Change from Baseline in MFM32 Total Score at Month 12 (Placebo-Controlled Period) (Part 2; ITT Population)



n* is the number of patients with valid baseline total score. Percentages are calculated using that as denominator.
Clinical Cutoff Date: 06SEP2019

Program: root/clinical_studies/RO7034067/CDPT7916/BP39055/data_analysis/CSR_part2/prod/program/ah_g_ef_mfm32_bar_prop.sas
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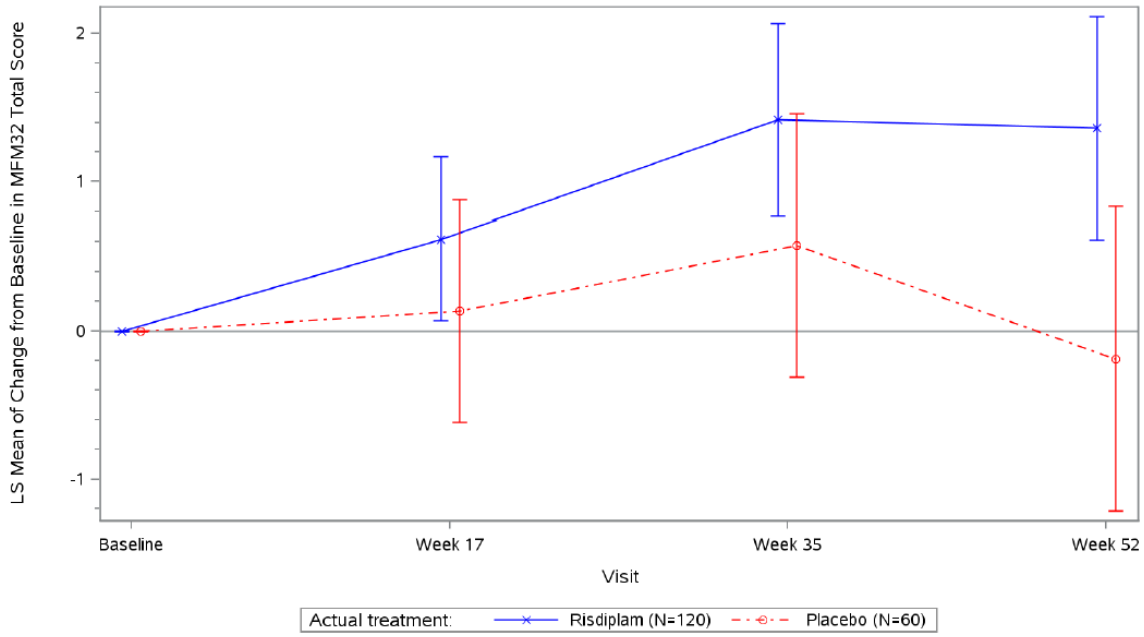
The improvement in MFM32 total score with risdiplam treatment observed at Month 12 seems to detach from the natural history of the disease, where motor function as measured by the MFM is seen to decline over time. In an observational, retrospective, multicentre cohort study that assessed the ability of the Motor Function Measure (MFM-32) to detect changes in the progression of spinal muscular atrophy in 12 untreated patients with SMA type 2 and 19 untreated patients with SMA type 3 patients aged 5.7 to 59 years, the overall slope of decline over time using the MFM32 total score was in the range of –0.9 (± SD 1.5) points/year for Type 2 SMA patients and –0.6 (± SD 4) points/year for Type 3 patients (Vuillerot et al. 2013).

Figure 43: Least-Squares Mean Change from Baseline and 95% Confidence Interval in MFM32 Total Score at Each Timepoint up to Month 12 (Placebo-Controlled Period) (Part 2; ITT Population)



A tipping point analysis was performed for the primary hypothetical efficacy estimand to determine the delta required to be applied for those patients (n=3) in the risdiplam arm with missing MFM32 total scores, due to withdrawal from the study, in order to overturn the primary analysis results. A delta of -7.75 (representing the tipping point) was required to overturn the primary results, suggesting that only a large decline in MFM32 total score for these 3 patients in the risdiplam arm would change the conclusion of the primary analysis. 3 out of 174 (1.7%) patients included in the primary analysis for Study BP39055 (SUNFISH) had a reduction ≥-7.75 in the Motor Function Measure-32 (MFM32) total score from baseline to Month 12. These were 2 patients randomised to risdiplam (with a reduction of –13.54 and –11.46, respectively) and 1 patient randomised to placebo (with a reduction of –10.42).

The applicant provided updated efficacy data at 24 months from Study BP39055 (SUNFISH) Part 2, through an interim summary with a clinical cutoff date (CCOD) of 30-September-2020. The complete set of analyses from this CCOD were still ongoing at the time of writing. The complete Statistical Analysis Plan (SAP)-specified statistical analyses will be presented in an update Clinical Study Report (CSR). Both Part 1 and Part 2 of Study BP39055 remain ongoing. At the CCOD of 30 September 2020, 10/60 patients (17%) in the group initially randomised to placebo and 17/120 patients (15%) in the group of patients initially randomised to risdiplam (n=120), are excluded from the 24 months MFM32 analyses. The most frequent reason for missing data at Month 24 assessment was due to restriction measures during the COVID-19 pandemic (6 patients initially randomised to PBO and 4 patients initially randomised to risdiplam missed the Month 24 assessment due to the COVID-19 pandemic). As acknowledged by the applicant, missed visits may have had an impact on the efficacy results.

As regards to the change from baseline in MFM32 total score (primary endpoint at 12 months), in patients treated with risdiplam for 24 months, the mean (95% CI) improvement from baseline in MFM32 total score seen at Month 12 (1.65 [0.77, 2.53]) was maintained at Month 24 (1.83 [0.74, 2.92]). In those patients initially assigned to placebo (mean change from baseline at 12 months during PBO: 0.00 [95% CI: -0.94, 0.94]) after switching to risdiplam at Month 12, the mean (95% CI) change from baseline in MFM32 total score was 0.31 (-0.65, 1.28) after 12 months of treatment, thus a smaller effect (with a 95% CI including zero, absence of effect) was observed in this group in comparison to patients initially randomised to risdiplam. In patients initially randomised to risdiplam,

after 12 months of risdiplam treatment, the proportion of patients with Change from Baseline in MFM32 Total Scores ≥3 was 32.2%, and the proportion achieving a change from baseline ≥0 was 58.3%.

According to the primary efficacy estimand based on a hypothetical treatment strategy assuming no prohibited medications intended for treatment of SMA, the only patient that received prohibited treatment (nusinersen, Spinraza) prior to withdrawal of the study was excluded from the primary analysis. This patient has also been included in the sensitivity analysis of the primary endpoint applying a treatment policy strategy. This is because the statistical analysis was performed using a mixed model repeated measures (MMRM) which includes all available data for each patient: the patient received nusinersen after taking risdiplam for 13 weeks and later discontinued from the study following the Week 17 visit. The patient completed the Motor Function Measure-32 (MFM32) at baseline and Week 17.

- **Revised Upper Limb Module (RULM)**

The change from baseline in the RULM total score at Month 12 was a secondary endpoint in Study BP39055 (SUNFISH) and the third endpoint in the statistical hierarchy. The improvement in upper limb function seen in patients treated with risdiplam at Month 12, as assessed by the RULM, was statistically significantly different from patients receiving placebo (least square difference in the mean [95% CI] changes from baseline: 1.59 [0.55, 2.62]; unadjusted p=0.0028; adjusted p=0.0469).

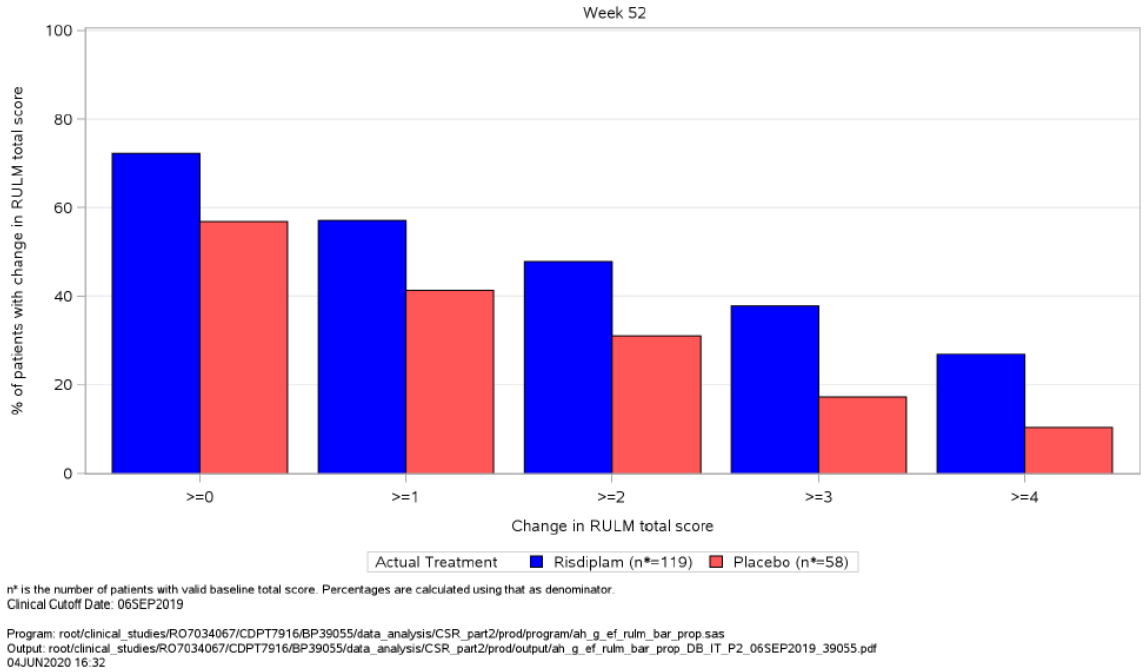
The proportion of patients with an improvement in RULM total score ≥2 points was 47.9% in the risdiplam arm and 31.0% in the placebo arm (odds ratio [95% CI]: 2.18 [1.05, 4.54]; p=0.0369).

The proportion of patients with a change from baseline in RULM total score of any threshold ≥0, representing stabilisation or improvement in this measure, was greater in those receiving risdiplam than in those receiving placebo at all post-baseline scheduled assessment visits up to Month 12. At Month 12, the proportion of patients with a change in RULM total score ≥0 points was 72.3% in the risdiplam arm and 56.9% in the placebo arm, representing a clinically meaningful difference between arms (odds ratio [95% CI]: 1.93 [0.98, 3.79]; p=0.0555).

The proportion of patients achieving a change from baseline in RULM total score ≥3 was greater in the risdiplam arm (37.8%) than in the placebo arm (17.2%) at Month 12 (odds ratio [95% CI]: 3.27 [1.40, 7.63]; p=0.0061). Likewise, the proportion of patients achieving a change from baseline in the RULM total score ≥4 was greater in those receiving risdiplam (26.9%) than those receiving placebo (10.3%) (odds ratio [95% CI]: 3.58 [1.29, 9.99]; p=0.0147).

A longitudinal study (Pera et al, 2019), previously reported that over 12 months, the mean change in RULM score was −0.4 (SD: 2.93) in Type 2 and Type 3 patients aged 2.7 to 49.7 years. Approximately 2/3 of the whole cohort had changes within ±2 points, with type 3 patients remaining stable more often (73%) than type 2 (63%).

Figure 44: Proportion of Patients Achieving Change from Baseline in RULM Total Score at Month 12 (Placebo-Controlled Period) (Part 2; ITT Population)



n* is the number of patients with valid baseline total score. Percentages are calculated using that as denominator.
Clinical Cutoff Date: 06SEP2019

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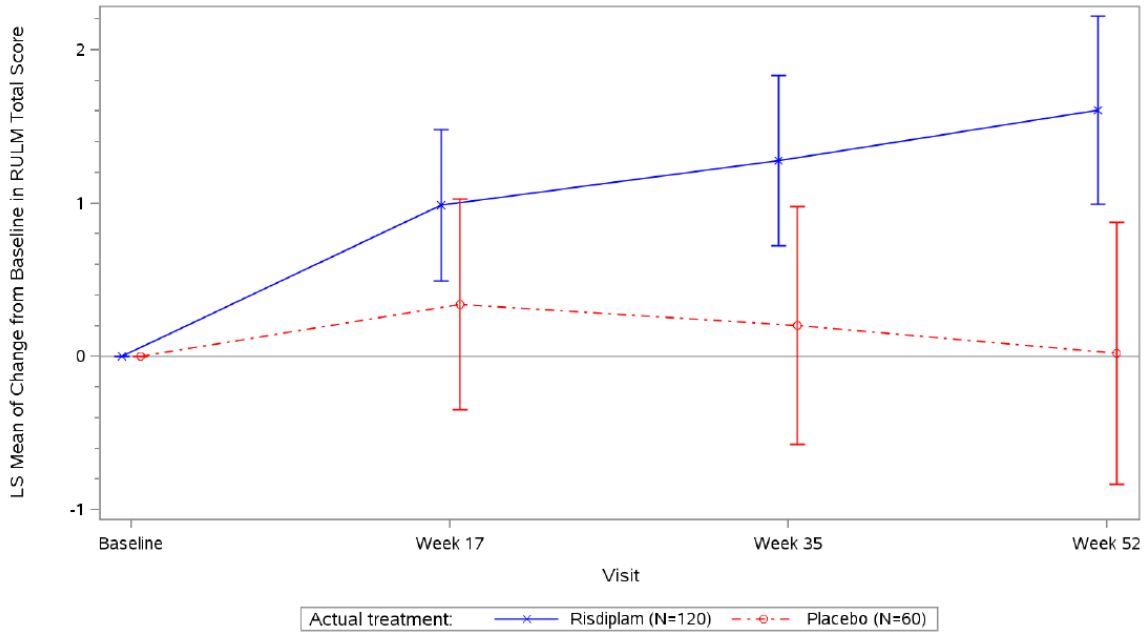
Figure 45: Least-Squares Mean Change from Baseline and 95% Confidence Interval in RULM Total Score at Each Timepoint up to Month 12 (Placebo-Controlled Period) (Part 2; ITT Population)



In the initial submission, only very limited data are available for the primary endpoint, beyond 12 months (n=8 patients, observed at week 78, all in the risdiplam group). Differently from what observed at 12 months, at 18 months (week 78) the mean change from baseline shows a worsening trend (mean change from baseline: -0.65 (95% CI -2.98, 1.67).

The proportion of responders at 24 months for the endpoints RULM and HFMSE and subgroup analysis were provided during the MAA review in response to a question.

Hammersmith Functional Motor Scale Expanded (HFMSE)

The change from baseline in the HFMSE total score at Month 12 was a secondary endpoint in Study BP39055 (SUNFISH). There was a numerically greater improvement in motor function as assessed by the HFMSE seen in patients treated with risdiplam compared to patients receiving placebo at Month 12, however, the treatment difference was not significant at this time point (least square difference in the mean [95% CI] changes from baseline: 0.58 [-0.53, 1.69]; unadjusted p=0.3015; adjusted p=0.3902). The small change seen in HFMSE was expected for the enrolled population, with significant fixed SMA-related disabilities and very low motor function scores at baseline (e.g., 41% had HFMSE baseline scores below 10, illustrating substantial weakness). Improvement observed in the HFMSE with risdiplam (+0.95 change from baseline at Month 12) seems to detach from the natural history.

Natural history data from Type 2 and Type 3 patients aged 2-45 years collected using the HFMSE shows a change of 0.08 points over the course of 12 months, a decline of -0.24 points after 24 months, and a decline of -2.31 points after 36 months, on average (Kaufmann et al. 2012). Another study of Type 2 and Type 3 patients aged 2.5 to 55 years, including ambulant and non-ambulant individuals, demonstrated that the overall slope of decline in the HFSME total score over a 12-month period is -0.57 in non-ambulant patients (Mercuri et al. 2016). The change in HFMSE varied across age groups: +0.04 in children <5 years, -0.96 in children and adolescents aged ≥5 to <15 years, and -0.35 in adolescents ≥15 years (Mercuri et al. 2016).

In a recent study (Mercuri et al 2019) in a cohort of 28 untreated patients with type II SMA, the rate of progression measured as annual changes was apparently higher in the group with highest baseline HFMSE scores and lower in the patients with low scores at baseline because they had fewer points to lose. This study confirmed that, despite the variability in changes and the possibility of improvement in the first years of life, all patients with type II SMA show a clear and progressive decline on the long-term follow-up, regardless of their scores at baseline.

Respiratory Outcomes

Forced Vital Capacity

FVC was assessed in patients aged ≥6 years at screening. There was no clinically relevant or statistically significant difference in the mean change from baseline in FVC (best percentage of predicted) between risdiplam (mean [SD]: −5.16% [1.40%]) and placebo (mean [SD]: −3.11% [1.94%]) at Month 12 (least square difference in the mean [95% CI] changes from baseline: −2.05% [−6.67%, 2.56%]; unadjusted p=0.3804; adjusted p=0.3902)

The absolute value analysis showed that there was no clinically significant change in FVC in either the risdiplam or placebo arm (least square difference in the mean [95% CI] changes from baseline: −0.01 [−0.11, 0.08]; p=0.7651)

Patient/Caregiver-Reported Outcomes

SMA Independence Scale (SMAIS)

Complementary evidence of the benefit of risdiplam treatment seen in the key motor function assessments was also observed by the SMAIS. Change from baseline in the 22-item upper limb total score of the patient- and caregiver-reported SMAIS at Month 12 were secondary endpoints in Sunfish.

Numerical improvements in SMAIS total scores with risdiplam compared to placebo were observed in both the caregiver observer-reported assessment (least square difference in the mean [95% CI] changes from baseline: 2.55 [0.93, 4.17]; unadjusted p=0.0022; adjusted p=0.3902) and the patient self-reported assessment (least square difference in the mean [95% CI] changes from baseline: 1.45 [−0.68, 3.57]; p=0.1778).

Table 31: Summary of Caregiver- and Patient-Reported SMA Independence Scale Scores in Part 2 of Study BP39055 (SUNFISH) at Month 12 (ITT Population)

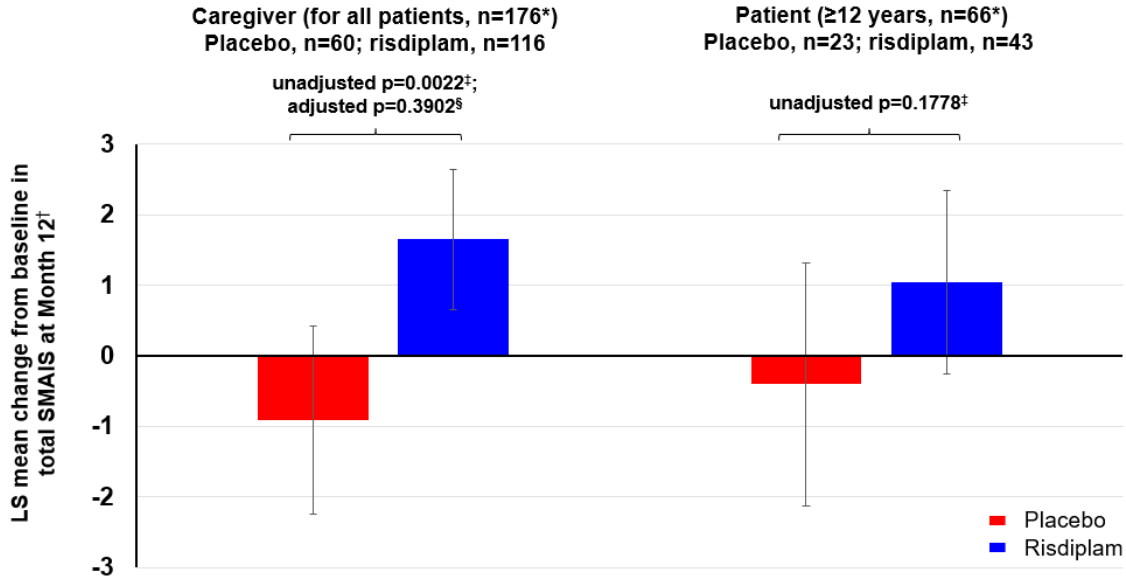
Endpoint	Risdiplam (N=120)	Placebo (N=60)
Caregiver-Reported SMAIS	**n=116**	**n=60**
Change from baseline in caregiver SMAIS total score, LS means (SE) (95% CI)	1.65 (0.50) (0.66, 2.63)	−0.91 (0.67) (−2.23, 0.42)
Difference from placebo, estimate (SE)	**2.55 (0.82)**	
(95% CI)	(0.93, 4.17)	
p-value [a]	unadjusted p=0.0022; adjusted p=0.3902	
Patient-Reported SMAIS [b]	**n=43**	**n=23**
Change from baseline in patient SMAIS total score, LS means (SE) (95% CI)	1.04 (0.65) (−0.26, 2.35)	−0.40 (0.86) (−2.13, 1.32)
Difference from placebo, estimate (SE)	**1.45 (1.06)**	
(95% CI)	(−0.68, 3.57)	
p-value	unadjusted p=0.1778	

SMAIS=SMA Independence Scale.

[a] Unadjusted p-value: each endpoint is tested at 5% significance level. Adjusted p-value: derived based on all the (unadjusted) p-values from endpoints in order of the hierarchy up to the current endpoint.

b Patient-reported SMAIS was assessed in patients aged ≥12 years only.

Figure 46: Caregiver- and Patient-Reported SMA Independence Scale Scores in Part 2 of Study BP39055 (SUNFISH) at Month 12 (ITT Population)



LS=least squares; SMAIS=SMA Independence Scale.

* N is the number of patients with valid results at baseline.

† +/- 95% confidence interval.

‡ Unadjusted p-value: each endpoint is tested at 5% significance level.

§ Adjusted p-value: derived based on all the (unadjusted) p-values from endpoints in order of the hierarchy up to the current endpoint.

Analysis performed across trials (pooled analyses and meta-analysis)

Due to the different age ranges of patients included in the two pivotal studies (as a consequence of the different age of onset of symptoms across the different SMA types), each study utilises different assessment scales for motor function and, hence, efficacy data have not been pooled across the pivotal studies.

Subgroup analysis

Table 32: Change from Baseline in MFM32 Total Score >=0 and >=3 at Month 12 by Age Category (Placebo-Controlled Period) (Part 2; ITT Population)

	Percentage of Patients	
Change in MFM32 total score ≥3		
Age Category	Risdiplam	Placebo
2–5 years (N=55)	78.1%	52.9%
6–11 years (N=57)	28.2%	16.7%
12–17 years (N=46)	20.0%	6.3%
18–25 years (N=22)	14.3%	12.5%
Change in MFM32 total score ε0		
Age Category	Risdiplam	Placebo
2–5 years (N=55)	87.5%	70.6%
6–11 years (N=57)	64.1%	50.0%
12–17 years (N=46)	63.3%	50.0%
18–25 years (N=22)	57.1%	37.5%

Efficacy by SMA Type

Risdiplam efficacy was observed in patients with both Type 2 and Type 3 SMA; this was confirmed by improvements in the MFM32 and the RULM at Month 12 in both of these subgroups as compared to placebo.

In total, 128 (71.1%) Type 2 patients and 52 (28.9%) Type 3 patients were included in Study BP39055 (SUNFISH) Part 2. Of these, 84 (70.0%) Type 2 patients and 36 (30.0%) Type 3 patients received risdiplam, and 44 (73.3%) Type 2 patients and 16 (26.7%) Type 3 patients received placebo.

As measured by the difference in change from baseline in MFM32 total score with risdiplam compared to placebo at Month 12, for both SMA Type 2 patients (mean treatment difference [95% CI]: 1.54 [0.06, 3.02]) and SMA Type 3 patients (mean treatment difference [95% CI]: 1.49 [–0.94, 3.93]), risdiplam showed treatment benefit.

Similarly, this treatment benefit in both SMA types was also demonstrated in the RULM. The difference in change from baseline in RULM total score with risdiplam compared to placebo at Month 12 in both SMA Type 2 patients (mean treatment difference [95% CI]: 1.19 [–0.03, 2.42]) and SMA Type 3 patients (mean treatment difference [95% CI]: 2.36 [0.42, 4.29]) shows evidence of gains in upper limb function with risdiplam.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 33: Summary of efficacy for trial FIREFISH Part 2

Title: FIREFISH Part 2 *FIREFISH*			
Study identifier	Protocol BP39056, A Two-Part Seamless, Open-Label, Multi-Center Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam in Infants with Type 1 Spinal Muscular Atrophy. Report No. 1100385. **Part 2**		
Design	Study BP39056 is an open-label, single arm, multicentre clinical study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in patients with Type 1 SMA.		
	Duration of main phase: Duration of Extension phase:		First Patient Enrolled in Part 2: 13 Mar 2018; Last Patient Enrolled in Part 2: 19 Nov 2018 Ongoing
Hypothesis	Superiority		
Treatments groups	Single arm vs natural history of the disease		Part 2: 40 planned; 41 actual
Endpoints and definitions	Primary endpoint	Proportion of patients sitting without support for 5 seconds (BSID-III) at Month 12 (90%CI)	Proportion of patients sitting without support for 5 seconds as defined by Item 22 of the gross motor scale of the Bayley Scales of Infant and Toddler Development Third Edition [BSID-III]at Month 12 (90% CI)
	Alternative definition of independent sitting Sensitivity Analysis of the Primary Endpoint	Sitting without support defined by the HINE-2	Proportion of patients sitting defined by the HINE-2 categories of "Stable sit" or "Pivots (rotates)" at Month 12 (90% CI)

	Alternative definition of independent Sitting	Sitting without support for 30 seconds (item 26 of the BSID-III gross motor scale) at 12 months	Proportion of patients sitting without support for 30 seconds as defined by Item 26 of the gross motor scale of the Bayley Scales of Infant and Toddler Development Third Edition [BSID-III] at Month 12 (90% CI)
	Secondary endpoint	Motor Function	Proportion of patients who achieve a score of 40 or higher in the CHOP-INTEND at Month 12 (90% CI)
	Secondary endpoint	Motor Function	Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12 (90% CI)
	Secondary endpoint	Development Milestones	Proportion of motor milestone responders as assessed by the HINE-2 at Month 12 (90% CI)
	Secondary endpoint	Survival and Ventilation-Free Survival	Proportion of patients alive without permanent ventilation at Month 12 (90% CI)
Other secondary & exploratory endpoints without adjustment for multiplicity			
	Secondary endpoint	Development Milestones	Proportion of patients able to support weight or stand with support as assessed by the HINE-2 at Month 12 (90% CI)
	Secondary endpoint	Development Milestones	Proportion of patients able to bounce while assessing the walking item of the HINE-2 at Month 12 (90% CI)
	Secondary endpoint	Survival and Ventilation-Free Survival	Proportion of patients alive at Month 12 (90% CI)
	Secondary endpoint	Nutrition	Proportion of patients with the ability to feed orally at Month 12 (90% CI)
	Exploratory endpoint	Nutrition	Proportion of patients with the ability to swallow at Month 12 (90% CI)
	Exploratory endpoint	Healthcare Utilisation	Number of hospitalisations per patient-year at Month 12 (90% CI)

	Exploratory endpoint	Healthcare Utilisation	Proportion of patients with no hospitalisations at Month 12 (90% CI)
Clinical Cut off Date	14 Nov 2019 (date when the last patient in Part 2 completed the 12-month assessment)		

Results and Analysis

Analysis description	**Primary and Secondary Analysis**			
Analysis population and time point description	ITT population: primary analysis population for all efficacy analyses, with the exception of weight-for-age and length/height-for-age percentiles, which were analysed based on the safety population. All patients received treatment with risdiplam and will be compared with natural history data used to define a Performance Criterion.			
Descriptive statistics and estimate variability	Treatment group	Risdiplam	Natural History/ Performance Criterion	p-value
	Number of subject	41		
Primary Efficacy Endpoints	Proportion of patients sitting without support for 5 seconds (item 22 of the BSID-III gross motor scale) at Month 12 (90%CI)	12/ 41 29.3% (17.8% - 43.1%)	5%	<0.0001
Alternative Definition of Sitting without Support: Sensitivity Analysis of the Primary Endpoint	Proportion of patients sitting defined by the HINE-2 categories of "Stable sit" or "Pivots (rotates)" at Month 12 (90% CI)	10/ 41 24.4% (13.9%, 37.9%)	0/24 (De Sanctis et al, 2016)	-
Alternative Definition of Sitting without Support:	Proportion of patients sitting without support for 30 seconds (item 26 of the BSID-III gross motor scale) at Month 12 (90% CI)	7/ 41 17.1% (8.30%, 29.69%)		-

Secondary Efficacy Endpoints - Motor Function	Proportion of patients who achieve a CHOP-INTEND score of 40 or higher at Month 12 (90% CI)	23/41 56.1% (42.1%, 69.4%)	0/ 16 Kolb et al, 2017 (NeuroNEXT SMA Infant Biomarker Study) Perf crit: 17%	<0.0001
	Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12 (90% CI)	37/41 90.2% (79.1%, 96.6%)	0/ 16 Kolb et al, 2017 (NeuroNEXT SMA Infant Biomarker Study) Perf crit: 17%	<0.0001
Secondary endpoint Development Milestone	Proportion of motor milestone responders as assessed by the HINE-2 at Month 12 (90% CI)	32/41 78.0% (64.8%, 88.0%)	0/24 De Sanctis et al 2016 Perf Crit: 12%	<0.0001
Secondary Efficacy Endpoints - Survival and Ventilation Free Survival	Proportion of patients alive without permanent ventilation at Month 12 (90% CI)	35/ 41 85.4% (73.4%, 92.2%)	6/16 NeuroNext SMA Infant Biomarker Study Perf Crit:42%	<0.0001
Other secondary and exploratory endpoints without adjustment for multiplicity				
	Proportion of patients able to support weight or stand with support as assessed by the HINE-2 at Month 12 (90% CI)	9/ 41 22.0% (12.0%, 35.2%) [2=stand with support; 7= support weight]	0/24 (De Sanctis et al, 2016)	-

	Proportion of patients able to bounce while assessing the walking item of the HINE-2 at Month 12 (90% CI)	1/41 2.4% (0.1%, 11.1%)	0/24 (De Sanctis et al, 2016)	-
	Proportion of patients alive at Month 12 (90% CI)	38/41 92.7% (82.2%, 97.1%)	8/16 NeuroNext SMA Infant Biomarker Study Perf Crit: 60%	0.0005
Secondary Efficacy Endpoints - Nutrition	Proportion of patients with the ability to feed orally at Month 12 (90% CI)	34/41 82.9% (70.3%, 91.7%)	NA	
Exploratory endpoint - Nutrition	Proportion of patients with the ability to swallow at Month 12 (90% CI)	36/41 87.8% (76.1%, 95.1%)	NA	
Exploratory Efficacy Endpoints - Healthcare Utilisation	Number of hospitalisations per patient-year at Month 12 (90% CI)	1.30 (1.02, 1.65)	NA	
	Proportion of patients with no hospitalisations at Month 12 (90% CI)	20/41 48.8% (35.1%, 62.6%)	NA	

Table 34
Summary of efficacy for trial SUNFISH Part 2

Title: SUNFISH Part 2	
Study identifier	Primary CSR Study BP39055, (SUNFISH) A TWO-PART SEAMLESS, MULTI-CENTER RANDOMIZED, PLACEBOCONTROLLED, DOUBLE BLIND STUDY TO INVESTIGATE THE SAFETY, TOLERABILITY, PHARMACOKINETICS, PHARMACODYNAMICS AND EFFICACY OF RO7034067 IN TYPE 2 AND 3 SPINAL MUSCULAR ATROPHY PATIENTS. Report No. 1099250 February, 2020. **Part 2**

Design	Part 2 of Study BP39055 was designed to investigate the efficacy and safety of risdiplam over a 24-month treatment period, in patients aged 2-25 years with Type 2 and non-ambulant Type 3 SMA.		
	Duration of main phase:		First patient randomised: 09 October 2017. LPLV for primary analysis: 06 September 2019.
Hypothesis	Superiority		
Treatments groups	Risdiplam		N=120
	Placebo		N=60
Endpoints and definitions	Primary endpoint	Proportion of patients sitting without support for at least 5 seconds (BSID-III) (90% CI)	To evaluate the efficacy of risdiplam compared with placebo in terms of motor function in patients with Type 2 SMA and non-ambulant Type 3 SMA, as assessed by the change from baseline in the total score of the Motor Function Measure (MFM32) at 12 months.
	Secondary endpoint	Responder analyses of the MFM32.	To investigate the efficacy of 12-month treatment with risdiplam in terms of motor function as assessed by responder analyses of the MFM32.
	Secondary endpoint	Revised Upper Limb Module (RULM)	To investigate the efficacy of 12-month treatment with risdiplam in terms of motor function as assessed by Revised Upper Limb Module (RULM)
	Secondary endpoint	Hammersmith Functional Motor Scale Expanded (HFMSE),	To investigate the efficacy of 12-month treatment with risdiplam in terms of motor function as assessed by the Hammersmith Functional Motor Scale Expanded (HFMSE)

	Exploratory endpoint	MFM32 at 24 months	Change from baseline in MFM32 total score in patients treated with risdiplam for 24 months
Clinical Cut-off Date	06 September 2019 (date when the last patient in Part 2 completed the 12-month assessment) 30 September 2020 (24-month clinical cut off date)		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The intent-to-treat (ITT) population defined as all randomised patients in Part 2 is the primary analysis population for all efficacy analyses.			
Descriptive statistics and estimate variability	Treatment group	Risdiplam	Placebo	Total
	Number of subjects	**120**	**60**	180
	MFM32 total score N Median (min-max)	**115** 46.88 (16.7 - 71.9)	**59** 47.92 (17.7 - 71.9)	174
	Change from baseline in MFM32 total score, LS means (SE) (95% CI)	1.36 (0.38) (0.61, 2.11)	-0.19 (0.52) (-1.22, 0.84)	
	MFM32 - Proportion with a change from baseline MFM32 total score>=3 (95% CI)	44 (38.3%) (28.94, 47.58)	14 (23.7%) (12.03, 35.43)	58
	MFM32 - Proportion with a change from baseline MFM32 total score>=0 (95% CI)	80 (69.6%) (60.72, 78.41)	32 (54.2%) (40.68, 67.80)	112

	RULM total score N Median (min-max)	**119** 19.00 (3.0 - 36.0)	**59** 20.00 (9.0 - 38.0)	178
	RULM - Change from baseline in RULM total score, LS means (SE) (95% CI)	1.61 (0.31) (1.00, 2.22)	0.02 (0.43) (-0.83, 0.87)	
	HFMSE total score N Median (min-max)	**120** 14.00 (0.0 - 48.0)	**60** 13.00 (2.0 - 43.0)	180
	HFMSE - Change from baseline in HFMSE total score, LS means (SE) (95% CI)	0.95 (0.33) (0.29, 1.61)	0.37 (0.46) (-0.54, 1.28)	

Effect estimate per comparison	Primary endpoint: **Motor Function Measure 32 (MFM32)**	Comparison groups	Between Risdiplam and Placebo
		Difference from placebo, estimate (SE) (95% CI)	1.55 (0.64)
		Confidence interval (95%)	(0.30, 2.81)
		P-value	0.0156
	Secondary endpoint: **Motor Function Measure 32 (MFM32) - Proportion with a change from baseline MFM32 total score>=3**	Comparison groups	Between Risdiplam and Placebo
		Odds ratio for overall response	2.35
		Confidence interval (95%)	(1.01, 5.44)
		P-value unadjusted: P-value adjusted:	0.0469 0.0469
	Secondary endpoint: **Motor Function Measure 32 (MFM32) - Proportion with**	Comparison groups	Between Risdiplam and Placebo
		Odds ratio for overall response	2.00
		Confidence interval (95%)	(1.02, 3.93)

	a change from baseline MFM32 total score>=0		
		P-value unadjusted:	0.0430
	Secondary endpoint:	Comparison groups	Between Risdiplam and Placebo
	Revised Upper Limb Module (RULM)	Difference from placebo, estimate (SE) (95% CI)	1.59 (0.52)
		Confidence interval (95%)	(0.55, 2.62)
		P-value unadjusted:	0.0028
		P-value adjusted:	0.0469
	Secondary endpoint:	Comparison groups	Between Risdiplam and Placebo
	Hammersmith Functional Motor Scale Expanded (HFMSE)	Difference from placebo, estimate (SE) (95% CI)	0.58 (0.56)
		Confidence interval (95%)	(-0.53, 1.69)
		P-value unadjusted:	0.3015
		P-value adjusted:	0.3902
Descriptive statistics and estimate variability	Exploratory Endpoint: MFM32 at 24 months	The mean change from baseline for MFM32 at 24 months was 1.83 (95% CI: 0.74, 2.92)	

Supportive study(ies)

SMA type 1

There was concordance between Part 1 and Part 2 results, despite the fact that in Part 2 more sites from different continents contributed to the enrolment of more patients than Part 1, and that in Part 1 patients received two different doses of risdiplam. Key efficacy results from Part 1 and Part 2 at Month 12 are summarised below:

Table 35: Concordance between Study BP39056 (FIREFISH) Part 1 and Part 2, Proportion of Patients at Month 12

Endpoint	Part 1 (N=21)	Part 2 (N=41)
Sitting without support for at least 5 seconds (BSID-III) (90% CI)	33.3% (16.8%, 53.6%)	29.3% (17.8%, 43.1%)
Standing (HINE-2): Supports weight or stands with support [a] (90% CI)	4.8% (0.2%, 20.7%)	22.0% (12.0%, 35.2%)
Walking (HINE-2): Bouncing (90% CI)	0% (0.0%, 13.3%)	2.4% (0.1%, 11.1%)
CHOP-INTEND score ≥40 (90% CI)	52.4% (32.8%, 71.4%)	56.1% (42.1%, 69.4%)
CHOP-INTEND change from baseline ≥4 points (90% CI)	85.7% (67.1%, 96.0%)	90.2% (79.1%, 96.6%)
HINE-2 motor milestone responders [b] (90% CI)	66.7% (46.4%, 83.2%)	78.0% (64.8%, 88.0%)
Alive without permanent ventilation [c] (90% CI)	90.5% (72.6%, 96.9%)	85.4% (73.4%, 92.2%)
Alive (90% CI)	90.5% (72.6%, 96.9%)	92.7% (82.2%, 97.1%)
Able to feed orally [d] (90% CI)	85.7% (67.1%, 96.0%)	82.9% (70.3%, 91.7%)
Able to swallow (90% CI)	85.7% (67.1%, 96.0%)	87.8% (76.1%, 95.1%)

Endpoint	Part 1 (N=21)	Part 2 (N=41)
Number of hospitalizations [e] per patient-year (90% CI)	1.17 (0.80, 1.65)	1.30 (1.02, 1.65)
Proportion of patients with no hospitalizations [e] (90% CI)	38.1% (20.6%, 58.3%)	48.8% (35.1%, 62.6%)

BSID-III=Bayley's Scale of Infant and Toddler Development - Third Edition; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2=Hammersmith Infant Neurological Examination; NA=not available.

[a] In Part 1, 1 patient (4.8%) could support weight. In Part 2, 7 patients (17.1%) could support weight and 2 patients (4.9%) could stand with support.

[b] An improvement in a motor milestone was defined as a ≥2-point increase in the ability to kick (or maximal score) or a ≥1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening was defined as a ≥2-point decrease in ability to kick (or lowest score) or a ≥1-point decrease in head control, rolling, sitting, crawling, standing, or walking. Voluntary grasp was excluded from the definition. An infant was classified as a responder if more motor milestones showed improvement than showed worsening.

[c] Permanent ventilation defined as tracheostomy or ≥16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event.

[d] Includes patients who were fed exclusively orally and those who were fed orally in combination with a feeding tube at Month 12. In Part 1, 15 patients (71.4%) were fed exclusively by mouth, and 3 patients (14.3%) were fed via a combination of oral and tube feeding. In Part 2, 28 patients (68.3%) were fed exclusively by mouth, and 6 patients (14.6%) were fed via a combination of oral and tube feeding.

[e] Hospitalizations include all hospital admissions that spanned at least two days.

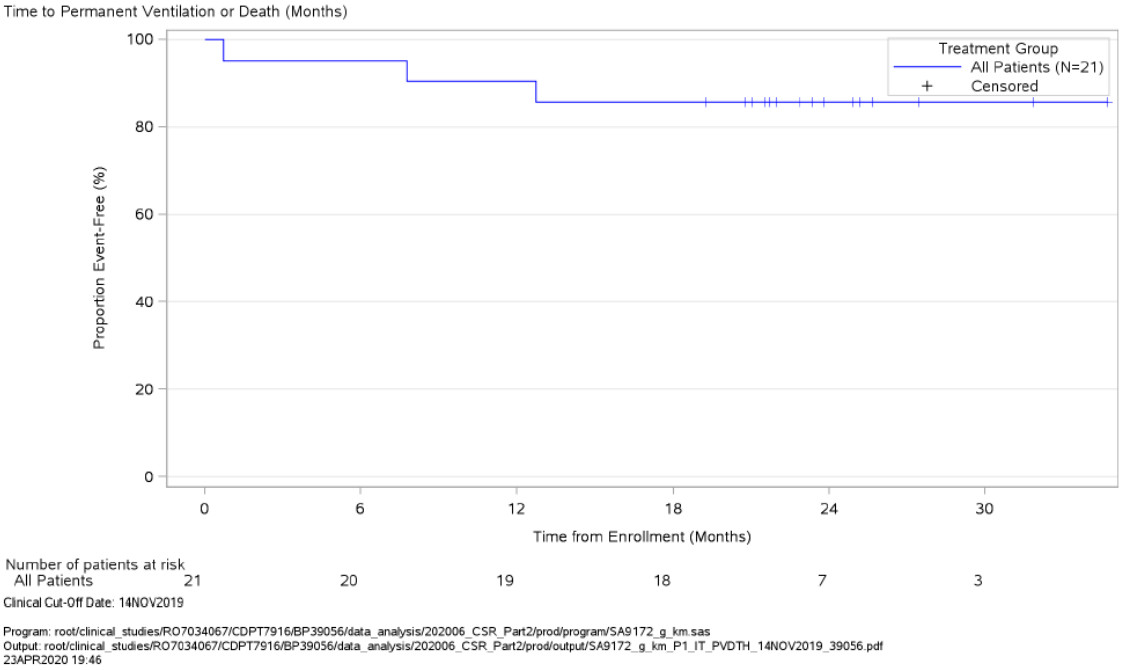
Source: Study BP39056 (FIREFISH) Primary CSR 1100385 Table 11 and Study BP39056 (FIREFISH) Interim CSR 1087161 Table 10

The results observed in Part 1 of the study would meet the threshold of achievement that was pre-defined for these endpoints in Part 2, because the lower limit of the two-sided 90% CI in each case is above the performance criterion defined for each endpoint in the Part 2 SAP.

18-months survival, Part 1 of Study BP39056 (FIREFISH)

At data cut-off (CCOD: 14 November 2019), the maximum exposure for an individual patient in Part 1 of Study BP39056 (FIREFISH) was 34.6 months (range of 0.6 to 34.6 months). 18 out of 21 patients (85.7%) were alive at Month 18 without requiring permanent ventilation. The 3 patients who died during Part 1 of the study were aged from 175 to 211 days at enrolment, and none of them required permanent ventilation. One additional patient withdrew from study treatment due to non-safety related reasons on Day 585 (the patient was censored at this timepoint). Approximately 3.5 months after treatment discontinuation, the patient presented SMA-related complications and passed away. After a minimum of 24 months of treatment, 81% (17/21) of patients were alive and event-free and reached an age of 28 months or older (median 32 months; range 28 to 45 months), see Figure below.

Figure 47: Kaplan-Meier Plot of Time to Death or Permanent Ventilation in Study BP39056 (FIREFISH) (ITT Population, Part 1 Patients)



Later onset SMA: Type 2 and non-ambulant Type 3

SUNFISH Part 1: 24 months endpoints

Table 36: Part 1: MFM32 Results at 12 and 24 Months of Risdiplam Treatment (Part 1; MFM Population)

Endpoint	Patients Ages 2–11 Years (n=31)	Patients Ages 12–25 Years (n=20)	All Patients All Ages (2–25 years) (n=51)
MFM32 Total Score (excluding patients who completed the MFM20)[a]			
Baseline, Mean (SD)	44.4 (11.9)	40.9 (18.2)	42.9 (15.0)
Month 12	**n=24**	**n=19**	**n=43**
Change from baseline, Mean (SD)	3.47 (3.77)	1.64 (3.43)	2.66 (3.70)
Proportion of patients (95% CI) who achieved change from baseline of ≥3	70.8% (48.91%, 87.38%)	42.1% (20.25%, 66.50%)	58.1% (42.13%, 72.99%)
Proportion of patients (95% CI) who achieved change from baseline of ≥0	91.7% (73.00%, 98.97%)	68.4% (43.35%, 87.42%)	81.4% (66.60%, 91.61%)
Month 24	**n=24**	**n=19**	**n=43**
Change from baseline, Mean (SD)	3.69 (4.67)	1.54 (4.99)	2.74 (4.88)
Proportion of patients who achieved a change from baseline of ≥3	66.7% (44.68%, 84.37%)	47.4% (24.45%, 71.14%)	58.1% (42.13%, 72.99%)
Proportion of patients (95% CI) who achieved change from baseline of ≥0	91.7% (73.00%, 98.97%)	68.4% (43.45%, 87.42%)	81.4% (66.60%, 91.61%)

MFM=Motor Function Measure

Notes: Baseline is the last measurement prior to patients first dose of risdiplam.

CCOD: 15 January 2020.

[a] MFM32 results are based on patients who completed the MFM32 at baseline and subsequent time points (i.e., patients who performed MFM20 at any time point are excluded).

Sources: t_ef_mfm32r_MP_P1; t_ef_mfm32r_prop_MP_P1

Table 37: Part 1: RULM, HFMSE, and FVC at 12 and 24 Months of Risdiplam Treatment (Part 1; ITT Population)

Endpoint	Patients Ages 2–11 Years (n=31)	Patients Ages 12–25 Years (n=20)	All Patients All Ages (2–25 years) (n=51)
RULM Total Score			
Baseline, Mean (SD)	18.2 (7.8)	19.0 (9.1)	18.5 (8.2)
Month 12	**n=31**	**n=19**	**n=50**
Change from baseline, Mean (SD)	2.13 (3.35)	1.05 (1.81)	1.72 (2.89)
Proportion of patients who achieve improvement (i.e., a change from baseline ≥2)	54.8% (36.03%, 72.88%)	42.1% (20.25%, 66.50%)	50.0% (35.53%, 64.47%)
Proportion of patients who achieved a change from baseline ≥0	83.9% (66.27%, 94.55%)	84.2% (60.42%, 96.62%)	84.0% (70.89%, 92.83%)
Month 24	**n=31**	**n=19**	**n=50**
Change from baseline, Mean (SD)	2.94 (3.84)	1.74 (2.38)	2.48 (3.38)
Proportion of patients who achieved a change from baseline ≥2	58.1% (39.08%, 75.45%)	57.9% (33.50%, 79.75%)	58.0% (43.21%, 71.81%)
Proportion of patients who achieved a change from baseline ≥0	80.6% (62.53%, 92.55%)	84.2% (60.42%, 96.62%)	82.0% (68.56%, 91.42%)
HFMSE Total Score			
Baseline, Mean (SD)	20.4 (16.9)	13.0 (16.1)	17.5 (16.8)
Month 12	**n=31**	**n=19**	**n=50**
Change from baseline, Mean (SD)	0.84 (3.97)	0.05 (3.46)	0.54 (3.76)
Proportion of patients who achieve improvement (i.e., a change from baseline ≥2)	48.4% (30.15%, 66.94%)	31.6% (12.58%, 56.55%)	42.0% (28.19%, 56.79%)
Proportion of patients who achieved a change from baseline ≥0	67.7% (48.63%, 83.32%)	73.7% (48.80%, 90.85%)	70.0% (55.39%, 82.14%)
Month 24	**n=31**	**n=19**	**n=50**
Change from baseline, Mean (SD)	1.39 (4.09)	-0.68 (4.53)	0.60 (4.34)
Proportion of patients who achieved a change from baseline ≥2	45.2% (27.32%, 63.97%)	26.3% (9.15%, 51.20%)	38.0% (24.65%, 52.83%)
Proportion of patients who achieved a change from baseline ≥0	67.7% (48.63%, 83.32%)	68.4% (43.45%, 87.42%)	68.0% (53.30%, 80.48%)
FVC (best percentage predicted value)			
Baseline, Mean (SD)	74.00% (33.18%)	47.53% (28.68%)	58.28% (32.84%)
Month 12	**n=13**	**n=18**	**n=31**
Change from baseline, Mean (SD)	-1.77% (14.17%)	0.83% (8.33%)	-0.26% (11.02%)
Month 24	**n=12**	**n=18**	**n=30**
Change from baseline, Mean (SD)	-6.42% (15.55%)	0.28% (7.04%)	-2.40% (11.48%)

FVC=forced vital capacity; HFMSE=Hammersmith Functional Motor Scale Expanded; RULM=Revised Upper Limb Module.

Notes: Baseline is the last measurement prior to patients first dose of risdiplam.

CCOD: 15 January 2020.

Sources: t_ef_rulmr_IT_P1; t_ef_rulmr_prop_IT_P1; t_ef_hfmser_IT_P1; t_ef_hfmser_prop_IT_P1; t_ef_resp_FVC_IT_P1.

SUNFISH Part 1: comparison with external sources

Part 1 of Study BP39055 (SUNFISH) does not have a placebo control group beyond the initial minimum 12-week dose-selection period. Data available from the NatHis-SMA Study (Study BP29540: a prospective, longitudinal and interventional study of the natural history of patients with Type 2 and 3 SMA) and the placebo arm of Study WN29836 (a previous Phase 2 SMA study for a discontinued development compound, olesoxime) have been used as an external control comparator to enable formal comparisons for the Motor Function Measure (MFM) endpoint, the primary endpoint of Part 2.

Patients in the 3 studies received a similar standard of care and there was overlap in the sites that

participated in each of the studies. Furthermore, the baseline characteristics of the patients in these studies were similar.

Patients in the NatHis-SMA Study

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

Roche performed an interim analysis of the data from the NatHis-SMA Study collected at Month 12 and a final analysis at Month 24.

Placebo Control Group in the Olesoxime Study WN29836

Study WN29836 (NCT01302600) was a Phase 2, parallel-group, placebo-controlled, randomised, double-blind, adaptive, multicentre, and multinational study designed to assess the efficacy and safety of olesoxime 10 mg/kg daily over a period of 2 years in patients aged 3 to 25 years with Type 2 or non-ambulatory Type 3 SMA from sites in Belgium, France, Germany, Italy, the Netherlands, Poland, and the United Kingdom.

The study was originally sponsored by Trophos S.A. and subsequently wholly acquired by Roche and included 165 patients, of which 57 were randomised to placebo (Bertini et al. 2017). Olesoxime development has since been discontinued.

The placebo arm of this study was utilised as a second data source for generating the external comparator population for the comparative analysis with risdiplam-treated patients in Part 1 of Study BP39055 (SUNFISH) after 12 and 24 months.

Statistical Methods:

In order to compare the MFM results from Part 1 of Study BP39055 (SUNFISH) with data from the two external control groups described above, the inverse probability of treatment weighting (IPTW) approach based on propensity scores was used. The individual patient data from the external control groups were weighted using key prognostic factors (age at enrolment, SMA type, SMN2 copy number, ambulatory status, scoliosis, MFM total score at baseline, and MFM scale). This allowed a comparison of the treated and untreated groups with similar prognostic factors. The main analyses were performed comparing the risdiplam group (treated) with the pooled external control group (untreated).

ENDPOINTS ASSESSED IN THE COMPARISON OF STUDY BP39055 (SUNFISH) WITH EXTERNAL CONTROL DATA:

In the comparison of Study BP39055 (SUNFISH) Part 1 with external control data, analyses were based on efficacy as assessed by the MFM. The MFM scale was not assessed in the same way in Study BP39055 (SUNFISH) Part 1, the NatHis-SMA study, and Study WN29836, the MFM total score was derived based on the MFM32 total score for patients aged ≥6 years and the MFM20 total score for patients age <6 years (both transformed to 0-100 scale).

More specifically, all patients in Study BP39055 (SUNFISH Part 1) were to be assessed using the MFM32 regardless of age. Patients under the age of 6 years in the NatHis-SMA study and the placebo arm of Study WN29836 were assessed using the MFM20 and patients aged 6 years and over were to perform MFM32.

The MFM20 scale consists of 20 items and the MFM32 scale consists of 32 items. The MFM20 total score and MFM32 total score were calculated according to the user manual. The MFM20 total score was calculated by summing the 20 item scores and transforming this onto a 0-100 scale (i.e., sum of 20 item scores divided by 60 and multiplied by 100) and the MFM32 total score was calculated by summing the 32 item scores and transforming this onto 0-100 scale (i.e., sum of 32 item scores divided by 96 and multiplied by 100). One raw point on the MFM20 scale translates to 1.66 in the MFM20 total score and one raw point on the MFM32 scale translates to 1.04 in the MFM32 total score.

Using the MFM20 total score for those aged under 6 years and the MFM32 total score for those aged 6 years or above, the resulting score was defined as the 'MFM total score'. To make the studies more comparable, the change from baseline in the MFM total score was derived based on MFM32 for all patients aged 6 years or above and MFM20 for all patients aged less than 6 years old; for visits where the MFM32 was used in patients aged less than 6 years, the 12 additional items which are not included in the MFM20 did not count towards the scoring algorithm.

Key efficacy endpoints assessed in the comparison with external control data included:

- Change from baseline in MFM total score at Month 12 and Month 24

- Proportion of patients with a change from baseline in MFM total score ≥3 points at Month 24

- Proportion of patients with a change from baseline in MFM total score ≥0 points at Month 24.

Only patients with an MFM assessment at baseline and at least one post-baseline assessment at Month 12 or Month 24 were included in the analysis. The patients meeting these criteria from the two external control studies formed the external comparator population.

The change from baseline in the MFM total score at Month 12 and Month 24 were analysed based on the mixed model repeated measure (MMRM) model. The proportion of patients who achieved an improvement of ≥0 and ≥3 on the MFM total score was analysed at Month 24 using logistic regression models. This responder analysis was based on patients with valid assessments, which included only patients with MFM total scores at both baseline and Month 24.

Sensitivity responder analyses were performed by considering patients as non-responders if patients withdrew or had a missing MFM total score at Month 24. Lastly, a sensitivity analysis was performed comparing the results from Part 1 of Study BP39055 (SUNFISH) against each of the external control groups separately. Both weighted and unweighted analyses were conducted for each of the three comparisons. The weighting approach used gave more weight to a patient in the external control group who had a more similar covariate profile to a patient in Study BP39055 (SUNFISH). The outcome results for each individual were then multiplied by their corresponding weights for the weighted analyses.

Study Populations

Patients Included in the Analysis

A total of 123 patients from the NatHis-SMA Study and the placebo arm of Study WN29836 had a baseline MFM total score and at least one post-baseline MFM total score at Month 12 or Month 24 and, thus, were eligible for inclusion in the analysis. Of these, 14 patients were excluded from the external control population, 12 due to missing prognostic factors and 2 with an SMN2 gene copy number of 2 (as Study BP39055 [SUNFISH] Part 1 included no patients with copy number of 2 in the comparison with the external control). Therefore, a total of 109 patients (patients eligible for weighting) were included in the external control arm of the analysis.

A total of 48 patients from Part 1 of Study BP39055 (SUNFISH) were included in the analysis. One patient had withdrawn from the study prior to the Month 12 visit and was excluded from this analysis.

Two additional patients were excluded after trimming due to no overlap of distributions in the propensity scores.

Baseline Characteristics

Table 38: Baseline Characteristics of Patients with Type 2 and 3 SMA in Study BP39055 (SUNFISH), the NatHis-SMA Study, and the Placebo-Control Arm of Study WN29836: Weighted Analysis (Patients after Weighting)

	Risdiplam (N=48)	External Control (N=109)		
	BP39055 (wN=48.0)	Nat His (wN=28.7)	WN29836 (wN=20.6)	Total External Control (wN=49.3)
Age (years) at Enrollment				
n	48.0	28.7	20.6	49.3
Mean (SD)	9.27 (6.14)	8.60 (6.87)	10.43 (5.45)	9.36 (6.32)
Median	7.00	7.00	9.00	7.00
Min - Max	2.0 - 24.0	2.0 - 28.0	3.0 - 22.0	2.0 - 28.0
Age Group				
n	48.0	28.7	20.6	49.3
2 - 5	17.0 (35.4%)	13.1 (45.5%)	3.9 (18.8%)	16.9 (34.3%)
6 - 11	13.0 (27.1%)	7.6 (26.5%)	8.7 (42.4%)	16.3 (33.2%)
12 - 18	14.0 (29.2%)	5.2 (18.2%)	6.3 (30.5%)	11.5 (23.3%)
>18	4.0 (8.3%)	2.8 (9.8%)	1.7 (8.2%)	4.5 (9.1%)
Gender				
n	48.0	28.7	20.6	49.3
Male	23.0 (47.9%)	13.8 (48.1%)	10.4 (50.6%)	24.2 (49.1%)
Female	25.0 (52.1%)	14.9 (51.9%)	10.2 (49.4%)	25.1 (50.9%)
Race				
n	48.0	28.7	20.6	49.3
Asian	1.0 (2.1%)	0	0	0
White	43.0 (89.6%)	0	0	0
Unknown	4.0 (8.3%)	28.7 (100%)	20.6 (100%)	49.3 (100%)
SMA Type (ambulatory status)				
n	48.0	28.7	20.6	49.3
TYPE II (non-ambulatory)	35.0 (72.9%)	20.3 (70.7%)	15.2 (73.8%)	35.5 (72.0%)
TYPE III (ambulatory)	7.0 (14.6%)	6.9 (24.1%)	0	6.9 (14.1%)
TYPE III (non-ambulatory)	6.0 (12.5%)	1.5 (5.1%)	5.4 (26.2%)	6.9 (13.9%)
SMN2 copy number				
n	48.0	28.7	20.6	49.3
3	44.0 (91.7%)	25.9 (90.2%)	19.6 (95.1%)	45.5 (92.3%)
4	4.0 (8.3%)	2.8 (9.8%)	1.0 (4.9%)	3.8 (7.7%)
MFM Total Score				
MFM20				
n	17.0	13.1	3.9	16.9
Mean (SD)	53.92 (13.63)	57.24 (17.65)	48.79 (16.22)	55.31 (17.22)
Median	51.67	53.33	55.00	53.33
Min - Max	33.3 - 78.3	28.3 - 95.0	25.0 - 68.3	25.0 - 95.0
MFM32				
n	31.0	15.6	16.7	32.4
Mean (SD)	44.39 (15.38)	42.68 (22.91)	44.86 (11.79)	43.81 (17.77)
Median	42.71	34.38	44.79	40.63
Min - Max	12.5 - 81.3	18.8 - 94.8	24.0 - 68.8	18.8 - 94.8
Scoliosis				
n	48.0	28.7	20.6	49.3
Yes	27.0 (56.3%)	16.5 (57.6%)	13.4 (64.9%)	29.9 (60.6%)
No	21.0 (43.8%)	12.2 (42.4%)	7.2 (35.1%)	19.4 (39.4%)

wN, n = sum of weights.

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Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_efficacy_24M/prod/output/t_dm_wgt_MTP.out
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Efficacy Outcomes: Weighted Analyses for Comparison of the MFM Total Score of Study BP39055 (SUNFISH) with an External Control

Table 39: Comparison of the MMRM Analysis of the Change from Baseline in MFM Total Score at Month 12 and Month 24 in Patients from Part 1 of Study BP39055 (SUNFISH) and an External Control: Weighted Analysis (Patients after Weighting)

Endpoint	Study BP39055 (wN=48.0)	External Control [a] (wN=49.3)
Baseline, Mean (SD)	47.76 (15.35)	47.76 (18.26)
Month 12		
Change from baseline in MFM total score, LS means (SE) (95% CI)	2.12 (0.76) (0.61, 3.62)	−0.56 (0.77) (−2.08, 0.95)
Difference from external control, estimate (SE) (95% CI) p-value	**2.68 (0.63)** (1.44, 3.93) <0.0001	
Month 24		
Change from baseline in MFM total score, LS means (SE) (95% CI)	1.99 (0.84) (0.33, 3.65)	−2.00 (0.88) (−3.73, −0.27)
Difference from external control, estimate (SE) (95% CI) p-value	**3.99 (0.84)** (2.34, 5.65) <0.0001	

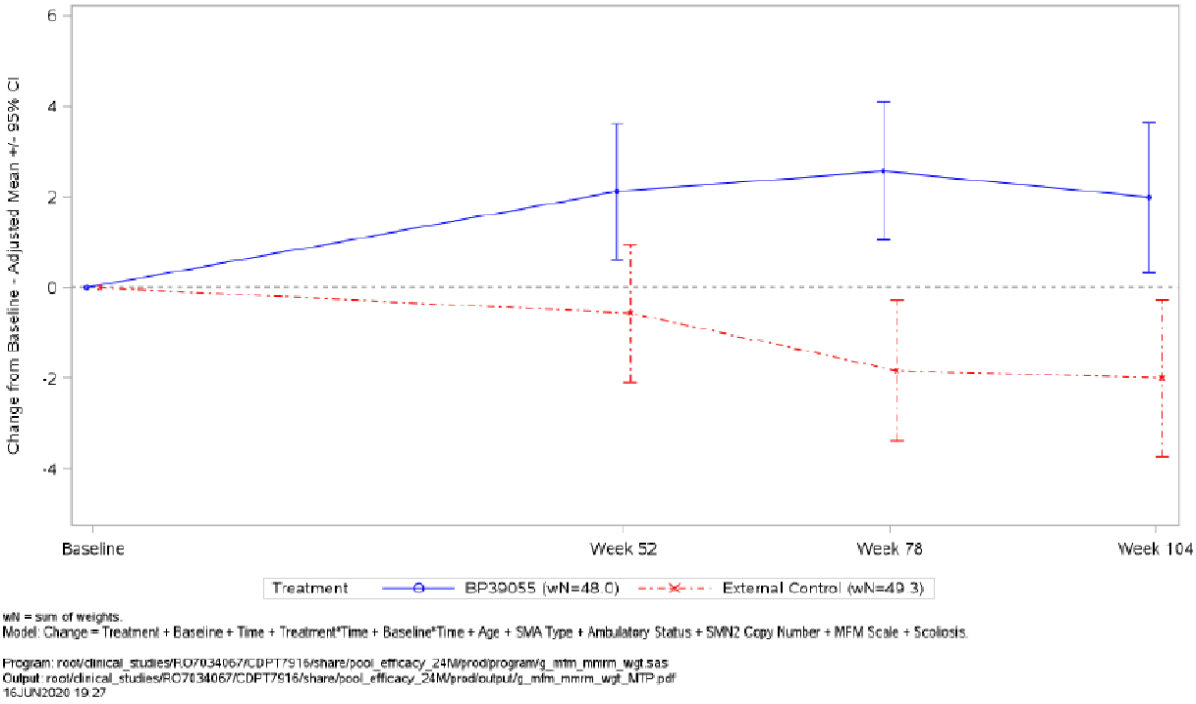
Source: t_mfm_mmrm_wgt_MTP

wN=weighted N; LS=least squares; MFM=Motor Function Measure.

The statistical model included treatment group (treated and untreated), age at enrollment, SMA type, *SMN2* copy number, ambulatory status, scoliosis, MFM scale, total score at baseline, time, treatment group*time interaction, and total score at baseline*time interaction.

[a] External control data include the NatHis-SMA Study (BP29540) and the placebo-control group of the olesoxime Phase 2 Study WN29836.

Figure 48: Least-Squares Mean Change from Baseline and 95% Confidence Interval in MFM Total Score at Each Timepoint up to Month 24 in Patients from Part 1 of Study BP39055 (SUNFISH) and an External Control: Weighted Analysis (Patients after Weighting)



wN = sum of weights.
Model: Change = Treatment + Baseline + Time + Treatment*Time + Baseline*Time + Age + SMA Type + Ambulatory Status + SMN2 Copy Number + MFM Scale + Scoliosis

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Prolonged exposure to risdiplam was associated with improvement and stabilisation in patients' motor function. At Month 24, more than half (54.2%) of patients in Part 1 of Study BP39055 (SUNFISH) achieved an improvement from baseline in MFM total score of ≥3 compared with only 16.8% in the external control group (odds ratio [95% CI]: 6.63 [2.06, 21.33]; p=0.0015). The majority of patients (81.3%) achieved a change from baseline ≥0 in the MFM, representing stabilisation or improvement in this measure, compared to 44.4% of those from the external control group (odds ratio [95% CI]: 5.63 [1.93, 16.40]; p=0.0016).

Table 40: Change from Baseline ≥3 and ≥0 in MFM Total Score at Month 24 in Patients from Part 1 of Study BP39055 (SUNFISH) and an External Control: Weighted Analysis (Patients after Weighting)

	BP39055 (wN=48.0)	External Control (wN=49.3)
Responder: Change from Baseline >= 3		
Responders	26.0/48.0 (54.2%)	5.7/34.0 (16.8%)
95% CI	(39.03, 69.30)	(2.73, 30.79)
Odds Ratio (95% CI)	6.63 (2.06, 21.33)	
p-value (Wald)	0.0015	
Responder: Change from Baseline >= 0		
Responders	39.0/48.0 (81.3%)	15.1/34.0 (44.4%)
95% CI	(69.17, 93.33)	(26.19, 62.54)
Odds Ratio (95% CI)	5.63 (1.93, 16.40)	
p-value (Wald)	0.0016	

Patients with both baseline and week 104 results are included in the analysis.
wN, number of responder and denominator = sum of weights.
Logistic regression model: Change = Treatment + Baseline + Age + SMA Type + Ambulatory Status + SMN2 copy number + MFM Scale + Scoliosis.

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Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_efficacy_24M/prod/output/t_mfm_resp_wgt_MTP.out
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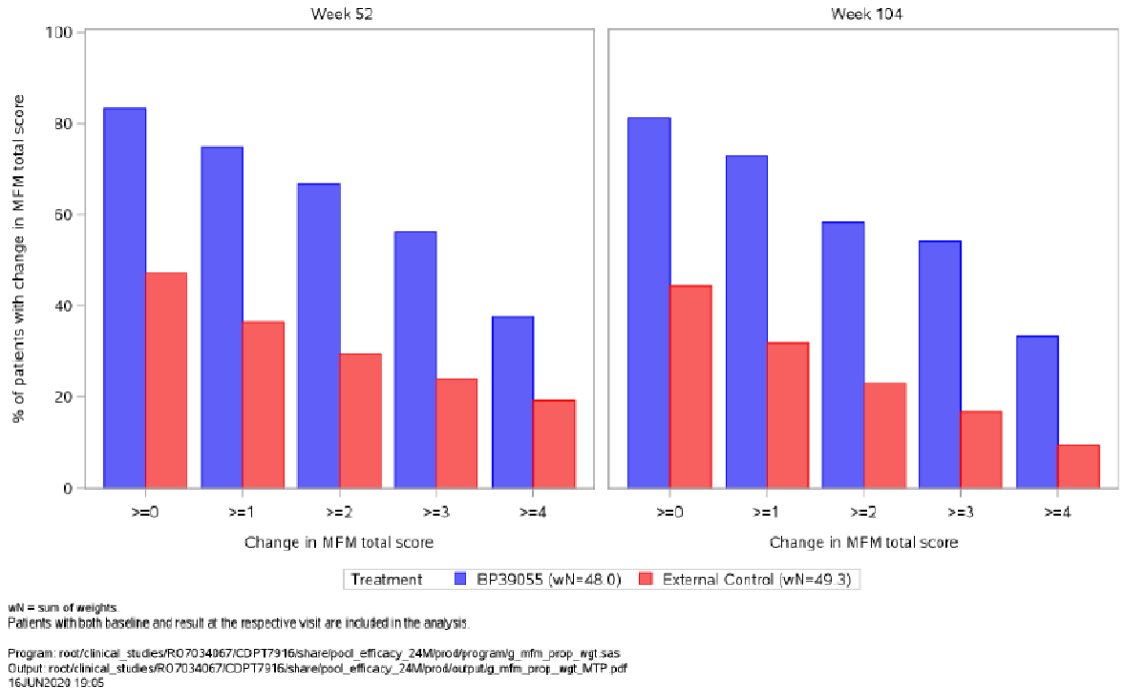
Note: The sum of weights used for the weighted analysis at Month 12 is different to the sum of weights used at Month 24. This is because more patients had dropped out of the external control group by Month 24 compared with Month 12. Conversely, only one patient discontinued from Part 1 of Study BP39055 (SUNFISH) by Month 24.

Figure 49: Proportion of Patients with Change from Baseline in MFM Total Score at Month 12 and Month 24 in Patients from Part 1 of Study BP39055 (SUNFISH) and an External Control: Weighted Analysis (Patients after Weighting)



wN = sum of weights.
Patients with both baseline and result at the respective visit are included in the analysis.

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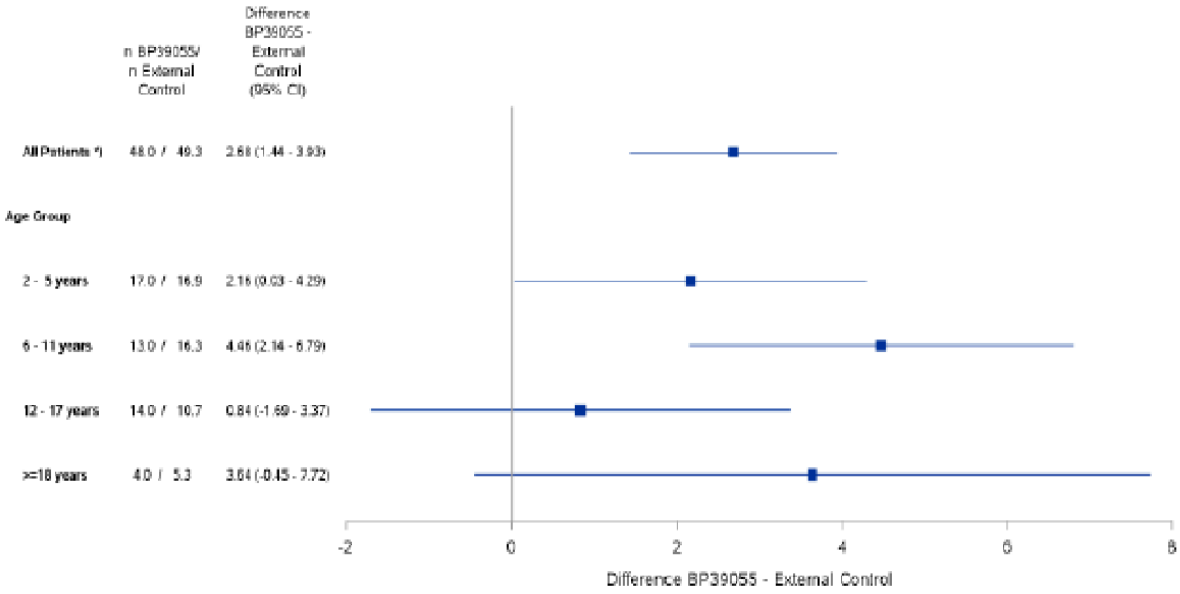
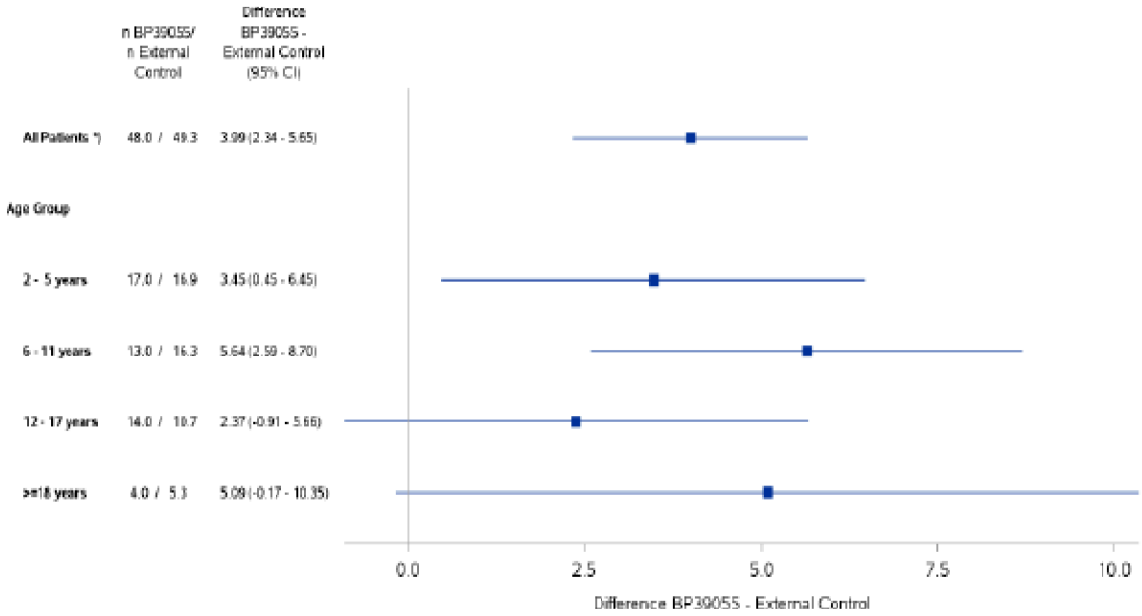
Figure 50: Forest Plot of Difference in Change from Baseline to Month 12 in MFM Total Score by Age Group (2-5, 6-11, 12-17 and 18-25 years) in Patients from Part 1 of Study BP39055 (SUNFISH) and an External Control: Weighted Analysis (Patients after Weighting)



n = sum of weights.
*) Model: Change = Treatment + Baseline + Time + Treatment*Time + Baseline*Time + Age + SMA Type + Ambulatory Status + SMN2 copy number + MFM Scale + Scoliosis.
Model: Change = Treatment + Baseline + Time + Treatment*Time + Baseline*Time + Age Category + SMA Type + Ambulatory Status + SMN2 copy number + Scoliosis + Age Category*Treatment + Age Category*Treatment*Time.
Program: root/clinical_studies/RO7034067/CDPT7916/share/pool_efficacy_24M/prod/prcgram/g_mfm_mmrm_for1_wgt.sas
Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_efficacy_24M/prod/output/g_mfm_mmrm_for1_wgt_WS2_MTP.pdf 16JUN2020 19:32

Figure 51: Forest Plot of Difference in Change from Baseline to Month 24 in MFM Total Score by Age Group (2-5, 6-11, 12-17 and 18-25 years) in Patients from Part 1 of Study BP39055 (SUNFISH) and an External Control: Weighted Analysis (Patients after Weighting)



n = sum of weights.
*) Model: Change = Treatment + Baseline + Time + Treatment*Time + Baseline*Time + Age + SMA Type + Ambulatory Status + SMN2 copy number + MFM Scale + Scoliosis.
Model: Change = Treatment + Baseline + Time + Treatment*Time + Baseline*Time + Age Category + SMA Type + Ambulatory Status + SMN2 copy number + Scoliosis + Age Category*Treatment + Age Category*Treatment*Time.
Program: root/clinical_studies/RO7034067/CDPT7916/share/pool_efficacy_24M/prod/program/g_mfm_mmrm_for1_wgt.sas
Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_efficacy_24M/prod/output/g_mfm_mmrm_for1_wgt_W104_MTP.pdf 16JUN2020 19:33

Results from the unweighted analysis are consistent to those described above for the weighted analysis, and are described in the Study BP39055 (SUNFISH) Part 1 - Comparison with External Control Summary Report in Module 5.

Results from the separate weighted analysis comparisons of 1) Part 1 of Study BP39055 (SUNFISH) with the observational NatHis-SMA Study and 2) Part 1 of Study BP39055 (SUNFISH) with the placebo arm of Study WN29836 were generally in agreement with the above results, supporting the robustness of the conclusions. Detailed results of these individual analyses are available in the Study BP39055 (SUNFISH) Part 1 - Comparison with External Control Summary Report.

Study BP39054(JEWELFISH)

This 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, which has since been discontinued) in which treatment with risdiplam is evaluated over a 24-month period. Study enrolment 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). Due to the limited treatment duration for most patients in this ongoing study at the CCOD (median treatment duration at the CCOD of 31 January 2020 was 3.0 months), efficacy results from Study BP39054 (JEWELFISH) are yet not available.

Post-authorisation efficacy study (PAES) in patients with 1 to 4 copies of the SMN2 gene

The applicant responded to the CHMP's request to discuss the conduct of a non-interventional post-authorisation efficacy study (PAES) in patients with 1 to 4 copies of the SMN2 gene.

The design of the PAES requires careful consideration to ensure the generation of meaningful data for the Agency and prescribers. The study is intended to address the CHMP's proposed overall objective to further characterise and contextualise the outcomes of patients with a genetic confirmation of diagnosis of SMA, including long-term safety and efficacy of Evrysdi.

The applicant proposed a prospective observational study in approximately 300 patients with SMA, both symptomatic and pre-symptomatic, that will use data from existing disease registries supplemented by a study specific registry collecting additional efficacy and safety data for a minimum follow-up of 5 years. Data from EU countries will be the primary source for this study.

A clinical trial in pre-symptomatic SMA infants with any SMN2 copy number is currently ongoing (Study BN40703 [RAINBOWFISH]). In this study, the total follow-up duration will be at least 5 years for each infant, which will provide long-term efficacy and safety data of risdiplam in pre-symptomatic patients. Data from this study will be supplemented by the PAES.

The applicant's considerations and proposed outline of the PAES are detailed below.

Proposed Study Objectives

As the main objective of the study, the applicant proposes to 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 with similar SMN2 copy numbers.

The PAES will focus on further characterizing:

- outcomes in patients treated with risdiplam at a pre-symptomatic stage,
- patients with 4 *SMN2* copies,
- long-term efficacy and safety outcomes in SMA patients.

Study Design and Data Sources

The applicant agreed with the study design proposed by CHMP, i.e. a multinational, multicentric, prospective observational study. Given the availability of licensed SMN-targeted treatments and the devastating disease course in most cases if patients are left untreated, a single arm study, where results will be compared with natural history data, is considered to be the most appropriate.

With regards to data sources, a hybrid approach is proposed: data will be obtained from existing registries and supplemented by an additional study specific registry collecting fit-for-purpose data in order to obtain meaningful information in a timely fashion.

There are well established SMA disease registries with participating EU member states which represent an important source of information on patients, treatments, standard of care and outcomes over time. These registries include but are not limited to:

- **Translational Research in Europe for the Assessment and Treatment of Neuromuscular Disorders (TREAT-NMD)**: an EU-funded network of excellence for genetic neuromuscular diseases with a particular focus on SMA that collects data from national/regional registries (TREAT-NMD).
- **The international Spinal Muscular Atrophy consortium (iSMAc)**: an academic collaboration linking 3 national networks (Italy, United States and the United Kingdom), collecting prospective

data focused on the natural history in infants, children and adults affected by SMA. Data from the iSMAc registry are contributing to the real-world assessment of the contemporary natural history and response to emerging therapies in a broadly based population of patients with SMA (Mercuri et al. 2019).

- **SMArtCARE**: a platform collecting real-world longitudinal data on all available SMA patients independent of their actual treatment regime as a disease-specific SMA registry. For this purpose, SMArtCARE provides an online platform for SMA patients seen by health-care providers in Germany, Austria and Switzerland. All data are collected during routine patient visits. Items for data collection are aligned with the international consensus for SMA registries (Pechmann et al. 2019).

Data sources landscaping will be conducted by the applicant across the EU in order to explore any additional relevant sources for patient enrolment and data collection for the PAES.

Suitable registries will be identified to meet the regulatory needs for the PAES based on the availability of appropriate outcome measures, the possibility of including additional variables, the quality of data and the possibility of accessing individual patient-level data (need for collaboration agreements).

Given that SMA is a rare disease, other registries that collect data outside of the EU (e.g. US- or Canada-based) may be considered in the evaluation of suitable data sources. However, the predominant population of the study is planned to be EU-based.

Proposed Population and Sample Size

It is estimated that the study will enrol approximately 300 patients treated with risdiplam with a diagnosis of SMA, including both symptomatic and pre-symptomatic patients. The final sample size will be determined based on outcome measures, statistical considerations, availability of risdiplam (national reimbursement policies and timelines), local clinical guidelines and preferred treatments by patients/families and physicians.

The study will collect longitudinal data in a broad population of risdiplam treated patients genetically diagnosed with SMA and with up to 4 SMN2 copies in a real-life environment. To ensure a representative overall population, the study will include both pre-symptomatic, newly diagnosed patients and patients with more advanced disease.

Outcome Measures

The proposed PAES aims to demonstrate maintenance or achievement of motor milestones and motor function with risdiplam treatment that are clinically meaningful and deviate from the natural history of the disease. The Applicant plans to use a different set of outcome measures for different age groups and clinical presentation, as their disease evolution is also expected to be different. The choice of outcome measures will also be determined by how widely available their use is in a real-world setting and their inclusion in the core dataset of the registries selected for inclusion in the PAES.

The following outcome measures are considered for evaluation:

- Survival and ventilation-free survival (all patients)
- CHOP-INTEND in patients up to 2 years of age
- Motor milestones (WHO motor milestones)
- MFM32 (if already available in the core dataset of included registries)
- HFMSE scale in patients from 2 years of age
- RULM scale in patients from 2 years of age
- Timed function tests (for high functioning patients, e.g. ambulatory)

In addition, in pre-symptomatic patients treated with risdiplam, it will be important to clinically identify the timing of initiation of SMA symptoms (e.g. proximal skeletal muscle weakness) in order to show deviation from the expected phenotype.

Additional data will be collected longitudinally in line with local clinical practices in the participating sites in both pre-symptomatic and symptomatic patients, including but not limited to: demographics, genetic test results, date of SMA symptom onset/diagnosis, past medical history, respiratory support, nutritional support, growth parameters, orthopaedic problems (e.g. scoliosis, contractures), previous surgeries and safety.

Statistical Analysis

The analysis population will consist of all enrolled patients.

Consistent with the observational nature of this registry, no formal a priori hypothesis testing will be performed.

The outcome measures will be summarised using descriptive statistics. Continuous data will be summarised using the number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarised using counts and percentages. Event-free survival will be evaluated using Kaplan-Meier methods.

Subgroup analysis will be performed by SMN2 copy number.

Efficacy outcome measures will be compared to and put in context with natural history. In addition, a comparison will be made between pre-symptomatic and symptomatic patients receiving risdiplam following appropriate matching on relevant variables (e.g. SMN2 copy number).

With the goal to provide meaningful data that can be analysed on an ongoing basis, an initial interim analysis will be conducted once all patients have been enrolled and have completed one year of follow-up. Subsequent interim analyses will be conducted yearly thereafter. The final analysis will be conducted when all enrolled patients have completed the study.

Further details, including methods for dealing with missing data, will be pre-specified in a statistical analysis plan.

Study Duration and Expected Milestones

The duration of the study should take into account the disease epidemiology and correlation between SMN2 copy number and expected SMA phenotype. This correlation is important in order to predict the likely disease evolution and plan for adequate study duration to be able to detect a divergence from this trajectory, especially when patients are treated with risdiplam at a pre-symptomatic stage.

Specifically, the majority of patients with 1 to 2 SMN2 copies (96% of those with 1 SMN2 copy and 79% of those with 2 SMN2 copies) are expected to present with Type 1 SMA. From patients with 3 SMN2 copies, 54% will develop SMA Type 2, 31% Type 3, and 15% Type 1. Finally, when considering patients with 4 SMN2 copies, 82% will develop Type 3 SMA and 11% Type 2 (Calucho et al. 2018) 1. The usual age of onset of symptoms of different SMA subtypes is also relevant when estimating the required duration of the study, i.e. patients with Type 1 SMA present with symptoms between birth and 6 months, patients with Type 2 between 7 and 18 months, patients with Type 3a between 18 and 36 months, and patients with Type 3b above 3 years.

Based on the above, the applicant proposes a study duration of 8 years, i.e. a 2 to 3-year enrolment

[1] In patients with 4 *SMN2* copies, from the Calucho et al. (2018) paper we reference the literature compilation/worldwide series (n=2834) results as in the Spanish cohort, patients of Type 3 and Type 4 SMA are grouped together. The percentage "82%" is derived from Figure 2b and Supplementary Fig.S2, excluding patients with 4 *SMN2* copies who had Type 4 SMA (n=21).

period followed by a minimum 5-year follow-up. This study duration will provide adequate time to observe effects in the majority of patients enrolled.

The protocol will be submitted within 6 months of CHMP Opinion. Following initiation of the study, an update on recruitment status will provided yearly.

The first interim study report will be provided once all patients have been enrolled and have completed one year of follow-up, and subsequent interim reports will be submitted yearly thereafter until study completion. Based on the proposed study duration, the estimated date for submission of the final study report is 2030.

2.5.3. Discussion on clinical efficacy

SMA type 1: FIREFISH STUDY

Design and conduct of clinical studies

Study BP39056 (FIREFISH) is an open label, two-part, multi-centre, single arm study, conducted in infants with Type 1 SMA. Inclusion criteria allowed enrolment of infants aged 1 to 7 months, however, the youngest patient actually enrolled was 2.2 months old. Thus, no data are currently available in infants below 2 months of age.

The study consists of a dose-finding Part 1 and a confirmatory Part 2, at the dose selected based on data obtained in Part 1. 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). Both Parts 1 and 2 of Study BP39056 (FIREFISH) share the same inclusion/exclusion criteria; however, the 21 patients enrolled in Part 1 did not enrol in Part 2 of the study. Therefore, Parts 1 and 2 can be considered as two independent studies. The Part 1 open label extension (OLE) phase and Part 2 of the study are ongoing.

FIREFISH Part 1: A total of 21 patients with Type 1 SMA were enrolled into Part 1 of Study BP39056 (FIREFISH). Two cohorts (Cohort 1 and 2) were defined based on the target exposure. The dose administered in Cohort 2 was the same as the pivotal dose used in Part 2 of the study (target exposure of mean AUC0- 24h,ss ≤2000 ng·h/mL), after some initial dose adjustments. At enrolment, the median age of all patients in Part 1 was 6.7 months, thus on the older end of the permitted age (range: 3.3-6.9 months); 15 of 21 patients (71.4%) were older than 5 months. Only 6 infants aged 3.3-5 months were enrolled, with higher exposure observed in 3 of these infants, and no data were available in infants < 3 months. Therefore, as for Part 1, a dose-escalation approach was chosen for Part 2, with a lower starting dose for the younger age groups and dose adjustment upon review of the individual PK data. PK samples were obtained from each infant and, based on the actual observed PK in each infant, the dose was increased to 0.2 mg/kg for all Part 2 patients (which occurred in general for most infants within 2 months of treatment start). 0.2mg/ kg is the recommended dose in the proposed SmPC between 2 months to < 2 years of age.

FIREFISH Part 2: The pivotal trial for SMA Type 1, is **Part 2 of Study BP39056 (FIREFISH),** a single-arm study of risdiplam in 41 symptomatic infants with Type 1 SMA treated for 24 months, followed by an OLE. The primary analysis of Part 2 was conducted once the last patient in Part 2 completed the 12-month assessment [clinical cut-off date (CCOD) of 14 November 2019]. Part 2 of the study is ongoing. All patients reached 24 months of treatment in November 2020. The applicant states that database snapshot is planned in January 2021. The applicant plans to finalise the Clinical Study Report presenting this data in April 2021. Results of 24 months endpoints should be provided as soon as available.

At the time of study start there were no approved disease-specific treatment options. Thus, the open-label design of the study may be acceptable, as FIREFISH enrolled a paediatric population with Type 1 SMA, the most severe form of the disease (thus representing the SMA population with the highest medical need) and the natural history of Type 1 SMA is well known, with patients never achieving sitting without support. Nevertheless, the possibility of bias remains because of the open-label nature of the study.

The applicant pre-defined performance criteria for success to be applied in the FIREFISH Part 2 study, based on natural history data on primary and secondary endpoints, i.e., a threshold of achievement for risdiplam-treated patients to be assessed against. CHMP previously agreed through SA that matching on an individual basis may be difficult in this limited and heterogeneous patient population. Therefore, the approach for generating performance criteria with a 90% upper and lower limit of the confidence interval may be the next best option, but the applicant was encouraged to continue developing the best possible understanding and description of the disease course relevant to the population included in the trial. Data from the retrospective chart review of infants with Type 1 SMA who have similar clinical characteristics to the infants included in FIREFISH Study BP39056, and who received care at the same sites (Roche study no. BP39859 ANCHOVY) was foreseen to provide additional context for the results of FIREFISH Study BP39056 and have been provided. The pre-defined performance criteria for Study BP39056 (FIREFISH) are aligned with survival data observed in Study BP39859 (ANCHOVY). The ventilation free survival and survival data observed in Study BP39056 (FIREFISH) show a marked difference from those from the untreated patients in Study BP39859 (ANCHOVY), which further supports the benefit of risdiplam in Type-1 SMA patients. As regards to HINE-2, the large amount of missing data limits the interpretation of the ANCHOVY data. Only 9 patients had a sitting assessment at age 12 months (15.0%), 5 patients at 18 months (8.3%) and 3 patients at 36 months (5.0%). Sitting without support was not achieved by any patient at any time point, up to age 36 months.

The population in the NeuroNEXT SMA infant biomarker study (Kolb et al., 2016; Kolb et al., 2017), that includes 16 infants with 2 copies of the SMN2 gene, was judged by the applicant to be most similar to the expected population in Study BP39056. Whenever possible, the performance criterion derived (for the secondary endpoints) from this study was selected as the benchmark to be used for hypothesis testing. When data for an endpoint was not available from the NeuroNEXT SMA infant biomarker study, the benchmark was derived from the study conducted by De Sanctis et al. (2016), that includes 24 infants classified as Type 1B.Through CHMP SA, the plan to assess and analyse the primary endpoint at 12 months was agreed. Long-term treatment with risdiplam will be evaluated in the ongoing open-label extension phase of clinical trials until a total treatment duration of at least 5 years. At the time of CHMP scientific advice the applicant assured that long term follow-up was planned and will be ensured, either by establishing a patient treatment registry or by utilizing existing disease registries (still under consideration at the time of SA).

Primary endpoint: The proportion of infants that are able to sit without support at 12 months of treatment is a relevant primary endpoint, because sitting is a milestone that infants with SMA type I never achieve in their natural course of disease. The operational definition of a responder i.e. sitting without support for 5 seconds (as assessed by item 22 of the gross motor scale of BSID-III) was agreed by CHMP at the time of SA. CHMP requested that this milestone should be persistent and stated that a positive result on the primary endpoint -supported by an effect in the other secondary endpoints- indicates an effect on disease progression.

Sitting without support is assessed through two items in the BSID-III Gross Motor Scale: item 22 assesses sitting without support for at least 5 seconds (primary endpoint chosen for this study); item 26 assesses sitting without support for at least 30 seconds (listed among secondary endpoints at Month 24 in this study). "Sitting alone without support for at least 30 seconds" (Bayley Scales Gross

Motor Subset item #26) has been previously used in pivotal SMA trials (Zolgensma).

The applicant has been requested to discuss the clinical relevance of sitting without support for 5 seconds; furthermore, the applicant was requested to clarify how the persistence of the milestone "sitting without support" has been assessed in FIREFISH trial. Overall, it is understood that sitting is an important milestone and provides a step towards cognitive improvement also, expanding horizons and releasing the upper limbs. The 5 secs without support is correlated to 30 secs with or without support, and to some extent those achieving 5 secs were more likely to reach 30 secs with or without support after one more year. Even though in natural history studies sitting without support is never achieved in SMA type I patients, data from randomised controlled trials showed that by using different definitions of sitting without support within the same trial, different proportions of treated patients reach the endpoint.

In the study protocol, the pre-defined performance criterion for the primary endpoint was 5%. Further discussion has been requested on how the 5% criteria was chosen.

The applicant clarified that the 5% threshold for the primary endpoint was not derived from a specific real-world data source in the same way the performance criteria for other endpoints were derived. Natural history of the disease shows that infants with Type 1 SMA never achieve sitting without support (Zerres and Davies 1999; Cobben et al. 2008; Finkel et al. 2014; De Sanctis et al. 2016). However, according to the methodology used by the applicant to define the performance criterion for each endpoint, based on available data from natural history studies, the upper limit of the 90% CI performance criterion took into consideration the sample size of the selected natural history study. For instance, for the alternative definition of sitting without support according to HINE, sitting without support after 12 months of follow up was not reached by any of the 24 type I SMA infants in a retrospective multicentric study of type I SMA infants (De Sanctis et al., 2016). Based on this natural history study, the upper limit of the 90% CI would have been 12%%. Thus, the applicant position who considers the 5% threshold a conservative benchmark for this milestone is not agreed upon. Overall, taking into consideration the alternative definition of sitting without support assessed in the study as secondary endpoints, the results observed with risdiplam for the milestone sitting without support, differ from the natural history data, even though the magnitude of effect is not so significant [sitting without support, as assessed by the HINE-2 categories of 'Stable sit' and 'Pivots (rotates)': 24.4% risdiplam (90% CI: 13.9%, 37.9%) vs upper limit of the 90% CI calculated from DeSanctis et al, 2016:12%].

Further discussion was requested on possible scenarios for the primary endpoint set at 30 seconds, also through a performance criterion. The applicant states that natural history studies conducted in Type 1 SMA have not utilised item 26 of the BSID-III gross motor scale to assess the achievement of sitting without support in untreated patients. However, the applicant emphasises that it is consistently reported in natural history studies that infants and children with Type 1 SMA, by definition, will never sit independently. In the applicant's view this means that they will never achieve any duration of sitting without support, regardless of the scale used to assess this hallmark. Even though the applicant's argumentation may be partially followed (i.e. in natural history studies sitting without support is never achieved in SMA type I patients), data from randomised controlled trials showed that by using different definitions of sitting without support within the same trial, different proportions of treated patients reach the endpoint.

The results of the sensitivity analysis still differ from natural history results.

Secondary endpoints: The proposed definition of motor-milestone responders according to results on the **Hammersmith Infant Neurological Examination (HINE-2)** [improvement in at least one category and more categories with improvement than categories with worsening] is considered a reasonable secondary endpoint and is the same definition used as coprimary endpoint (together with

time to death or permanent ventilation) for Spinraza (nusinersen), approved for SMA in 2017 (pivotal trial ENDEAR, Finckel et al 2017).

The motor milestone "sitting without support" (primary endpoint when assessed through item 22 of the BSID-III) was assessed also through the Hammersmith Infant Neurological Examination Module 2 (HINE-2) (secondary endpoint). In this scale the milestone "sitting" is graded in 5 categories [from 0, corresponding to inability to sit, to 4 (pivots, rotates)]. The results of the primary analysis are thus supported by the results of sensitivity analyses performed using a different scale, with an alternative definition of sitting without support [HINE-2 categories 3: 'Stable sit' and 4:'Pivots (rotates)'].

The **CHOP INTEND** is an acceptable neuromuscular evaluation for use as a secondary endpoint.

Population enrolled: A total of 41 patients with Type 1 SMA were enrolled into Part 2 of pivotal Study BP39056 (FIREFISH) across 14 different sites in 10 countries. At the time of the CCOD, 38 of 41 patients (92.7%) in Part 2 were still ongoing in the study; these 38 patients were older than 14 months of age. Three patients (7.3%) died due to SMA related respiratory complications within the first three months following enrolment. Of the 41 patients enrolled in Part 2, 22 (53.7%) were female and 19 (46.3%) were male. At enrolment, the median age of all patients was 5.3 months (range: 2.2-6.9 months); 22 of 41 patients (53.7%) were older than 5 months. The median age at diagnosis was 2.8 months (range: 0.9-6.1 months) and the age at onset of symptoms ranged from 1.0 to 3.0 months. In accordance with the inclusion criteria, all patients had a genetic diagnosis of SMA (SMN1) and had two SMN2 gene copies. At baseline, the median BSID-III Gross Motor Scale score was 2.0 (range: 0.0-8.0), the median CHOP-INTEND score was 22.0 points (range: 8.0-37.0) and the median HINE-2 score was 1.0 point (range 0.0-5.0). Overall, patients enrolled in FIREFISH part II are considered representative of the SMA type I patient population, apart from the exclusion of patients with the most severe forms as well as not clinically stable patients (the study excluded patients who required invasive ventilation or tracheostomy, hypoxemic patients and patients recently hospitalised for a pulmonary event).

Efficacy data and additional analyses

FIREFISH Part2:

Primary endpoint: The proportion of patients achieving the primary endpoint (sitting without support for ≥5 seconds at 12 months) is higher (12/41, 29.3%) compared to the proportion of patients sitting without support for ≥30 seconds at 12 months (7/41, 17.1%).

As regards to the results of sensitivity analyses performed using an alternative definition of sitting without support, at 12 months of treatment, 10 of 41 patients (24.4%; 90% CI: 13.9%, 37.9%) in Part 2 were sitting without support, as assessed by the HINE-2 categories of 'Stable sit' and 'Pivots (rotates). The HINE has been assessed in a retrospective multicentric study of 33 type I SMA infants (De Sanctis et al., 2016), that has been used by the applicant to derive a benchmark for development milestones, including sitting without support. None of the 24 subjects in the study by De Sanctis et al, 2016 achieved the endpoint "sitting without support at 12 months"; the performance criteria (upper limit of the 90% CI) was 12%. Thus the results observed with risdiplam for this endpoint differ from the natural history data, even though the magnitude of effect is not so significant [24.4% risdiplam (90% CI: 13.9%, 37.9%) vs performance criterion 12%].

Secondary endpoints:

CHOP-INTEND: The proportion of patients achieving a CHOP-INTEND total score of 40 or higher at 12 months [23/41 patients (56.1%; 90% CI: 42.1%, 69.4%)], as well as the proportion of patients achieving an increase of at least 4 points from baseline at 12 months [37/41 patients (90.2%; 90% CI: 79.1%, 96.6%)] was significantly higher than the pre-defined performance criterion of 17% based on natural history data ($p<0.0001$) (NeuroNEXT SMA Infant Biomarker Study (Kolb et al., 2017)).

Hammersmith Infant Neurological Examination Module 2 (HINE-2), Motor Milestone Responders: The proportion of milestone responders as assessed by the HINE-2 at 12 months (32/41 patients, 78.0%; 90% CI: 64.8%, 88.0%) was significantly higher than the pre-defined performance criterion of 12% based on natural history data (p<0.0001) (De Sanctis et al, 2016).

Survival and Ventilation-Free Survival: At 12 months 3/41 (7%) patients died and a further 3/41 patients met the endpoint of permanent ventilation. Thus, at 12 months, 35/41 patients [85.4% (35/41; 90% CI: 73.4%, 92.2%)] were alive without permanent ventilation, a proportion significantly higher than the pre-defined performance criterion of 42% based on natural history data (NeuroNEXT SMA Infant Biomarker Study, p<0.0001). The median time to death or permanent ventilation was not estimable as few patients had an event. At 12 months 38/41 (92.7%, 90% CI: 82.2%, 97.1%) patients were alive, a proportion significantly higher in comparison to the performance criteria of 60% (NeuroNEXT SMA Infant Biomarker Study, p=0.0005). Conversely, the proportion of infants without permanent ventilation at Month 12 was 92.7% (90% CI: 81.2%, 97.0%) and was not significantly different from the pre-defined performance criterion of 89% based on natural history data (p=0.2595). With regards to survival, as of 1 December 2020, the applicant confirms there have been no further deaths or study discontinuations in Part 2 of this study since the Month 12 analysis (CCOD: 14 November 2019), which represents at least 24 months of data.

Subgroup analysis: As regards to the subgroup analysis of the primary endpoint by sex, only 1/19 males (5.3%, 90% CI: 0.27-22.64) achieved the primary endpoint, compared to 11/22 females (50%, 90% CI: 31.13-68.87). It is acknowledged that, given the small numbers of patients in each subgroup, the results should be interpreted with caution; nevertheless, subgroup analysis of the primary endpoint by sex in Part 1 of Study FIREFISH have been requested, in order to assess whether a similar trend was observed and a discussion on possible reasons for the observed differences on the primary endpoint by sex has been requested. Despite the comprehensive analysis of baseline characteristics, PK/PD and efficacy endpoints, the applicant did not find an explanation for the observed differences related to gender in the Study BP39056 (FIREFISH) Part 2 primary endpoint results. The totality of the Study BP39056 (FIREFISH) survival data (Part 1 and Part 2) suggests that there is no gender difference in survival. Taking into consideration the trial's limited sample size in the context of a rare disease and the fact that the study was not powered to demonstrate efficacy among subgroups, no firm conclusions can be drawn on the potential effect of gender on the obtained results.

FIREFISH Part1: After at least 12 months of risdiplam treatment in Part 1 of the study 7/21 patients (33.3%), all in cohort 2, achieved sitting without support for 5 seconds or more, as assessed by Item 22 of the BSID-III gross motor scale. As of the CCOD, 3 patients (14.3%) in Part 1 had died and the remaining 18/21 patients (85.7%) were alive without permanent ventilation. Of the 3 deaths, two occurred before Month 12 and one after (on Days 21, 236, and 387, respectively). The results observed in Part 1 of the study would meet the threshold of achievement that was pre-defined for these endpoints in Part 2.

The results from FIREFISH Part 1 at 24 months showed that enrolled patients continued to improve with prolonged risdiplam therapy. Patients achieved additional motor milestones from Month 12 to Month 24 [proportion of patients sitting without support for 5 seconds or more (Item 22 BSID-III): 33%v s 52%; sitting without support for 30 seconds (Item 26 BSID-III): 19% vs 24%; Sitting HINE 2 (stable sit or pivots): 28.6% vs 42.9%], and a high proportion of patients remained event free (alive without permanent ventilation at Month 24). The presented data differ from natural history studies.

To allow contextualisation, the applicant has been requested to compare results of risdiplam development plan in infantile symptomatic SMA to those with nusinersen and onasemnogene abeparvovec, the approved medication that covers similar indication. The applicant responds that the population in STRIVE (onasemnogene abeparvovec) and FIREFISH studies were so different due to

inclusion / exclusion criteria that no comparison can be performed. One of them was the maximal age at the time of starting treatment. Another was the fact that for STRIVE, presymptomatic patients were also allowed. Median age at treatment for STRIVE was 3.5 months as compared to 5.3 for FIREFISH Part 2. On average, STRIVE pts had higher basal performance 32.0 mean CHOP-INTEND score than the FIREFISH (mean of 21.7). These differences are considered significant. Since the MAA does not have individual data for STRIVE, a patient-to-patient comparison cannot be performed. Moreover, STRIVE excluded patients with AAV antibodies and with recent infections, so part of the differences would be expected. Also, given the fact that onasemnogene abeparvovec is a single administration only product, which attains (and hopefully sustains) the attained response after a restricted interval in time while risdiplam is a chronic use product, the nusinersen / risdiplam comparison is the most relevant.

Comparison of nusinersen to risdiplam: the severity of disease at baseline was slightly worse in Study BP39056 (FIREFISH) for both part patient populations, as shown in the differences in baseline CHOP-INTEND and HINE-2 scores, which is in line with the inclusion criteria for FIREFISH of disease diagnosed until 3 mths of age as compared to ENDEAR 6 mths. ENDEAR study was assessed at the interim analysis, and the survival outcome may have been underestimated if some of the pts were under ventilation and later recovered and the motor milestones might have been higher and more frequently reached if the pts had been followed for a sufficient period. This may explain the better nominal results of FIREFISH as compared to ENDEAR in the endpoints that were similarly assessed in both studies: % of HINE 2 responders is roughly 1.3 to 1.5x higher with risdiplam (FIREFISH Part 1 and 2) than with nusinersen, and the % of infants alive is 1.5 to 1.6x higher with risdiplam than with nusinersen. Event free survival and time to death or permanent ventilation also follow a similar pattern.

Later onset SMA: Type 2 and non-ambulant Type 3

Design and conduct of clinical studies

Study BP39055 (SUNFISH) is a two-part, multi-centre, randomised, placebo-controlled, double-blind study to investigate the 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 based on the data obtained in Part 1. In Part 1 of the study, a total of 51 patients were enrolled. 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 open-label treatment phase. Part 1 patients did not enrol in Part 2 of the study. The open-label treatment phases of Part 1 and Part 2 remain ongoing.

SUNFISH Trial Part 2:

The pivotal trial for later onset SMA, is **Part 2 of Study BP39055 (SUNFISH),** a double-blind, randomised, placebo controlled study, that -according to inclusion criteria- enrolled 2-25 years of age patients with clinical symptoms attributable to Type 2 or Type 3 SMA non-ambulant (i.e. not having the ability to walk unassisted for 10 m or more) and genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the SMN1 gene. A 2:1 (risdiplam: placebo) randomisation ratio was applied in Study BP39055 (SUNFISH) to help support recruitment and retention, in light of the availability of nusinersen.

The Motor Function Measure 32 (MFM 32) was agreed as a primary endpoint at the time of CHMP Scientific Advice (SA). The items assessed in the MFM32 capture a broad range of motor abilities, including items relating to distal fine motor movements of the hands and gross motor function activities such as standing. However, in light of the fact that MFM 20 is usually used before 5 years of age and MFM 32 was initially validated in children aged > 6, further discussion was requested on to

whether the results observed in the 2-5 years age subgroup (showing a larger effect in comparison to older ages) might have been influenced by any development-related improvement. A further analysis was requested in the 2-5 years age group, excluding from the scoring algorithm the 12 additional items which are not included in the MFM20 (this is the approach used by the applicant to compare the results of the Part1 SUNFISH Study with an external control group, where MFM 20 was used for patients <6 years of age). The applicant's argumentation that -given that Study BP39055 (SUNFISH) Part 2 was a placebo-controlled study- although the MFM32 results in the youngest age group (2-<6 years) may have been influenced by functional gains driven by general development of these children, the placebo arm enrolled in Part 2 of the study allows for a comparison with the treated group and evaluation of this potential effect, is acknowledged. The results show an improvement both in the risdiplam treated group [mean change from baseline of 5.34 (95% CI: 3.97, 6.71)] and in the PBO group [mean change from baseline of 2.20 (95% CI: 0.33, 4.08)], and an overall estimate of the difference of risdiplam from placebo of 3.14 (95% CI: 0.81, 5.46) demonstrating the benefit of risdiplam in this age group. Given that the overall findings of risdiplam studies appear to support the early initiation of treatment with risdiplam, the request to perform a sensitivity analysis of the primary endpoint excluding children under the age of 6, to understand how this would impact results was not further pursued.

Among secondary endpoints, there were: Revised Upper Limb Module (RULM), a validated SMA-specific outcome measure that assesses upper limb functional abilities, and the Hammersmith Functional Motor Scale Expanded (HFMSE) that, similarly to the chosen primary endpoint, assesses motor function and for which there is significant longitudinal experience in patients with SMA.

Population enrolled: Most of the patients enrolled had Type 2 SMA (71%, 128/180) and most patients had 3 copies of the SMN2 gene (>80%). Median patient age at screening was 9.0 years in both groups, with 37.8% (68 patients) 12 years or older at screening. Only 22 patients were in the age category 18-25 years (risdiplam: n=14; placebo: n= 8). The median age of onset of initial SMA symptoms, as reported by the parents or patients, was 12.4 months (range 0-135 months). One hundred and twenty patients (66.7%) had scoliosis at screening (risdiplam: 63%, placebo: 73%). 3 patients (2.5%) in the risdiplam group required BiPAP support >16 hours/ day, compared to no patients in PBO. Randomisation in Study BP39055 (SUNFISH) was stratified by age group only (2-5, 6-11, 12-17, or 18-25 years at randomisation).

The median motor function scores for the different scales at baseline were comparable across the risdiplam and placebo arms. The range (min-max) of total scores at baseline for MFM32, RULM, and HFMSE was broad (i.e. MFM32: 17-72 points; RULM: 3-38 points; HFMSE: 0-48 points), reflecting the heterogeneity of the enrolled population. The proportion of patients with a HFMSE score below 10 at baseline was high: 41.1% across the study population, with a similar proportion in each treatment arm (RIS: 40.8%; PLB: 41.7%).

The primary analysis was conducted once the last patient in Part 2 completed 12 months of treatment (CCOD: 6 September 2019). Only four patients discontinued the study during the placebo-controlled period, in order to switch to other treatment [3 patients (2.5%) in the risdiplam arm, and 1 patient (1.7%) in the placebo arm].

Patients who received placebo during the double-blind period of the study were then switched in a blinded manner to the study sites to treatment with risdiplam when they completed 12 months of treatment and continued on risdiplam until Month 24. Considering the slow progression of Type 2 and Type 3 SMA, 12 months is a relatively short study duration.

In SUNFISH Part 2, risdiplam was administered orally at 5 mg once daily for patients with body weight ≥20 kg and 0.25 mg/kg once daily for patients with body weight <20 kg, that correspond to

recommended dosing regimen in the proposed SmPC in patients ≥ 2 months of age.

The patient population enrolled in FIREFISH and SUNFISH trial is not representative of the broad indication sought by the applicant. Available data do not allow a benefit/ risk assessment in severely affected (both infantile and later onset) SMA patients, in ambulant type 3 and in all type 4 patients. The applicant was requested to discuss the need to restrict the indication to the patient population enrolled in risdiplam pivotal trials, in light of the overall available results. Early onset SMA patients were not under mechanical ventilation at BL. While some had tracheostomy and invasive ventilation, these did not reach primary endpoint, in spite of reaching improvement in CHOP INTEND. For presymptomatic children RAINBOWFISH trial is ongoing and efficacy data is not available at the moment; notwithstanding, data on safety warns about possible hepatic risk of risdiplam in this very young population. Therefore, the applicant proposal that the indication will be limited to symptomatic patients above 2 mths of age is agreed. Regarding late onset SMA, no data has been obtained in type 4 patients, and extrapolation from type 3 is hampered by the limitation of main trial to non ambulant patients. Also, risdiplam has not been studied in any patient with 5 or more SMN copies, which precludes information on the magnitude of effect of risdiplam in these patients.

Among SUNFISH Part 2 exclusion criteria, there was concomitant or previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy either in a clinical study or as part of medical care. The discussion on the need to include or exclude from the indication patients that previously received treatment with Zolgensma or Spinraza, also in light of updated data from the JEWELFISH study provided only limited data. Unfortunately, no specific data was provided regarding efficacy of risdiplam after treatment with nusinersen. While in terms of safety there does not seem to exist any special issue, data supporting the use of risdiplam after previous treatment with nusinersen is not available, in spite of the number of treated patients. As for Zolgensma, safety data does not raise new concerns over the known safety profile of naïve SMA patients. However, only 14 patients previously received Zolgensma (5 treated with risdiplam for ≤6 months, 9 receiving risdiplam between 6 and 12 months). These data appear insufficient to allow an adequate assessment of possible safety risks of risdiplam treatment, following previous treatment with Zolgensma. Moreover, no specific recommendations can be made upon the interval between Zolgensma administration or nusinersen stop and risdiplam initiation.

The actual number of patients randomised to and enrolled in Part 2 (n=180) was higher than the target sample size (n=168) and the applicant has been requested to discuss on the impact that this may have had on the statistical significance of the study results. Screening/enrolment into the study was competitive and managed via a study portal. The study portal was used to allow the Sponsor to have control and oversight of the enrolment process. There was overenrolment at the end of study inclusion. Ten of the last 12 enrolled pts were from the 3 Canadian sites. Screen failure always remained stable (14-16%). A sensitivity analysis was provided using a mixed model repeated measures analysis on the primary endpoint of the change from baseline in MFM32 total score at Month 12 of Part 2 of Study BP39055 (SUNFISH) including only the first 168 enrolled patients. The corresponding values in the primary analysis including all the 180 patients enrolled were the following: the least square means (lsmeans) (SE) change from baseline in MFM32 total score at Month 12 was 1.36 (0.38) in patients receiving risdiplam and -0.19 (0.52) in patients receiving placebo. Least square difference in mean [95% CI] change from baseline in MFM32 at Month 12: 1.55 [0.30, 2.81]; p=0.0156). Thus the sensitivity analysis on the primary endpoint including only the first 168 enrolled patients determined a decrease in the difference from PBO and in the level of statistical significance, although difference from PBO remained statistically significant.

The FDA statistical review indicated that the positive SUNFISH study results were dependent on the data from the sites in Poland. The applicant was requested to discuss possible reasons for the observed

greater magnitude of effect in sites from Poland. It is worth to mention that Poland was the country that enrolled the highest number of patients (n=32/180, 17.8%).

As requested, the applicant provided analysis of the primary endpoint, the change from baseline in the Motor Function Measure-32 (MFM32) total score at Month 12 of Study BP39055 (SUNFISH) Part 2 by country and the analysis of the secondary endpoints, the proportion of patients with a change from baseline in the MFM32 ≥3 and the change from baseline in the Revised Upper Limb Module (RULM) at Month 12 by country. For MFM32 total score, the greatest improvement from baseline with risdiplam compared with placebo was observed in Italy (mean treatment difference [95% CI]: 7.06 [2.37, 11.76]) followed by Poland (mean treatment difference [95% CI]: 5.75 [2.78, 8.71]). Although the magnitude of improvement is greater in both these countries compared with the overall population (mean treatment difference [95% CI]: 1.55 [0.30, 2.81]), the results in all countries have overlapping 95% confidence intervals. It is true that Poland is among the countries with a stronger treatment effect, but it is not an isolated outlier and there is variation across countries. The results from Poland are within the range of what we see across all countries and are consistent with the assumption that this is a chance finding. For ≥3 points in MFM32, the greatest improvement from baseline with risdiplam compared with placebo was observed in Italy followed by Canada, Serbia, United States then Poland. The results in Poland (odds ratio [95% CI]: 2.98 [0.84, 10.55]) are consistent with the overall population (odds ratio [95% CI: 2.35 [1.01, 5.44].

SUNFISH Trial Part 1:

Exploratory efficacy analyses were also conducted in the dose-finding Part 1 of the SUNFISH study. Patients in Part 1 did not roll over into Part 2 of the study. 51 type 2 (73%) and type 3 (27%) SMA patients, mostly non-ambulatory (86.3%), with a median age at screening of 7.0 years (range: 2-24 years) were enrolled in Part 1 of the SUNFISH trial. After the first 12 weeks of placebo- controlled treatment, all patients received the pivotal dose. In the absence of a placebo control arm, the applicant conducted a retrospective analysis in order to compare patients with Type 2 and 3 SMA from Part 1 of Study BP39055 (SUNFISH) who received risdiplam for at least 24 months with patients from two external control sources, the NatHis-SMA Study (a longitudinal natural history study) and the placebo arm of Study WN29836 (a phase 2 Study with Olesoxime).

For the retrospective comparison -given that the MFM scale was not assessed in the same way in SUNFISH Study and in the external control sources- the MFM total score was derived based on the MFM32 total score for patients aged ≥6 years and the MFM20 total score for patients age <6 years.

Efficacy data and additional analyses

SUNFISH Trial Part 2

Primary endpoint: The primary endpoint showed a statistically significant difference from PBO in the change from baseline in MFM-32 total score: difference from PBO estimate 1.55 (95%CI: 0.30, 2.81), p=0.0156. Change from baseline in MFM32 total score showed an improvement in the risdiplam group [change from baseline, LS means: 1.36 (95% CI: 0.61-2.11)], compared to a worsening observed in the PBO group [-0.19 (95% CI:-1.22, 0.84)].

Even though the difference was statistically significant, the absolute difference from PBO is relatively modest (1.6-point difference on a 100-point scale) and the magnitude of effect observed was lower than expected in the assumptions for sample size calculations (minimum detectable treatment difference: approximately 2.03; true treatment difference 3).

Only very limited data are available for the primary endpoint, beyond 12 months (n=8 patients, observed at week 78, all in the risdiplam group). Differently from what observed at 12 months, at 18 months (week 78) the mean change from baseline shows a worsening trend (mean change from baseline: -0.65 (95% CI -2.98, 1.67). Ideally, results of the primary endpoint at 24 months are thus needed. From available data, in patients initially randomised to risdiplam, the favourable effects

observed in motor function through mean change from baseline in MFM32 and RULM scores after 12 months were maintained after 24 months. As regards to change from baseline in the HFMSE total score (secondary endpoint with no statistically significant difference from PBO at 12 months), in patients treated with risdiplam for 24 months, a numerical improvement was observed by Month 24.

The pre-specified responder analysis of MFM32 (proportion of patients with a change from baseline in MFM32 total score ≥3 at Month 12: 38.3% risdiplam vs 23.7% PBO) lends support to the clinical relevance of the observed effect, even though the results appear to be on the verge of statistical significance (with a p-value of 0.0469, rounded 0.05). The proportion of patients who achieved stabilisation or improvement (i.e., a change from baseline ≥0) on the total MFM score at Month 12 (endpoint not included in the hierarchy, thus without adjustment for multiplicity) was 69.6% in patients receiving risdiplam and 54.2% in those receiving placebo at Month 12 (odds ratio [95% CI]: 2.00 [1.02, 3.93]; p=0.0430). The proportion of MFM-32 responders (i.e. patients with Change from Baseline in MFM32 Total Scores ≥3 (32.2% vs 38.3%) and the proportion of patients who achieved stabilisation or improvement (i.e., a change from baseline ≥0 on the total MFM32 score (58.3% vs 69.6%) decreased at 24 months in comparison to what observed at 12 months.

Results on the Clinical Global Impression of Change (CGI-C) outcome at 24 months, as well as proportion of responders at 24 months for the endpoints RULM and HFMSE and subgroup analysis have not been included in the Summary Report provided.

In SUNFISH trial Part 2, the results on the subgroup analysis by age of the primary endpoint (Change from Baseline in MFM32 Total Score at Month 12), showed absence of effect in the subgroup 19-25 years of age. The applicant highlights several aspects to justify: a) baseline characteristics of adult patients: among the 22 adult non-ambulant patients (aged 18 to 25 years) randomised to receive risdiplam (14 patients) or placebo (8 patients), the median age of onset of initial symptoms was 17.6 months and they had an extensive duration of disease, up to 23 years, by the time of receiving the first dose of study treatment (risdiplam or placebo). There were 12 (54.5%) Type 2 SMA patients and 10 (45.5%) Type 3 patients in the adult group, with more Type 2 patients within the risdiplam group (57.1%). As expected, with increased age there was an accumulation of SMA-related disabilities: all but one of the adult patients had scoliosis and 35.7% of the patients who received risdiplam and 50% of the patients who received placebo had severe scoliosis (Cobb angle >40°). 71.4% and 50.0% of risdiplam and placebo patients, respectively had undergone surgery for scoliosis. At baseline, the median MFM32 (39 vs 46), RULM (17 vs 19) and HFMSE scores (5 vs 10) were lower in the risdiplam arm compared to placebo, indicating weaker motor function ability. b) the lack of power for subgroup analyses. And c) descriptive efficacy results in the adult subgroup: a numerically higher proportion of patients showed stabilisation in MFM32 score from baseline (change from baseline MFM32 total score ≥0) and stabilisation or improvement in RULM score from baseline (change from baseline RULM ≥0 or ≥2) among the small subgroup of adult patients treated with risdiplam in comparison with the small subgroup of adult patients assigned to placebo.

The applicant has been requested to clarify how MFM32 domain 1 (standing position and transfer) has been included for non-ambulant patients in SUNFISH Part 2. It was justified in two fold: first, an ambulant patient was erroneously included to the study due to misunderstanding of the criteria by a study site; second, the standing and transfer domain 1 assesses several levels of difficulty, and progression could be observed in some patients which might have attained some motor skills in spite of being non ambulant. Notwithstanding, most pts scored zero at this domain at BL, and improved scores afterwards. This also confirmed that MFM32 is a tool able to detect treatment response.

The applicant has been requested to provide a post hoc sensitivity analysis and comment to what degree presence of relevant genetic factors besides number of SMN copies are expected to affect observed results. No specific genetic testing for possible splicing-affecting mutations or single-

nucleotide polymorphisms (SNPs) was performed. Only the number of SMN2 copies was studied. This is unfortunate, as it further highlights the lack of sufficient data to allow adequate extrapolation of response to risdiplam in SMA type 4 patients. Moreover, as the applicant states, the published evidence on specific polymorphisms such as .859G>C and the A-44G in intron 6 in the SMN2 gene shows that these are rare in EU population, and might only affect up to 10% of SMA type 3 pts. Therefore other non studied features are likely to impact prognosis, particularly in LO-SMA.

Secondary endpoints:

Several concerns were raised regarding maintenance of effect and magnitude of response between M12 and 24 according to disease severity (HFMSE total score ≥ 10 or < 10 at baseline). The applicant provided the requested subgroup analyses for MFM-32 endpoints (mean change from baseline and responders analysis) at 12 months and at 24 months.

Revised Upper Limb Module (RULM): A statistically significant difference from PBO was observed in mean change from baseline at Month 12 in the RULM total score, with a directionally consistent decline in the RULM observed in the placebo arm from Week 17 to Month 12, and an improvement observed in the risdiplam group. Patients with a less severe disease (HFMSE ≥10) at baseline achieved greater improvements in the RULM total scores with risdiplam treatment after 12 months (mean change from baseline: 2.81[95% CI 1.94, 3.68]) and 24 months of treatment (mean change from baseline: 3.63 [95% CI 2.56, 4.69]), compared with the subgroup of patients with HFMSE <10 (at 12 months: 0.64 [-0.55, 1.84]; at 24 months: 1.49 [0.14, 2.84]). Further responders' analyses have been requested in order to better evaluate the clinical relevance of the observed effect on RULM. The % of patients receiving risdiplam with a change from Baseline of ≥3 (37.8 vs 17.2%) and ≥4 (26.9 vs 10.3%) in RULM total score at 12 months was greater in those receiving risdiplam than those on PBO.

Hammersmith Functional Motor Scale Expanded (HFMSE): The difference from PBO in changes from baseline at 12 months in HFMSE (either assessed as mean change in total score or proportions of responders) was not significantly different between patients receiving risdiplam and patients receiving PBO. In the applicants view the small changes observed on this endpoint are likely a consequence of the low motor function scores at baseline [41.1% of patients had a HFMSE score below 10 at baseline (RIS: 40.8%; PLB: 41.7%)], making it more difficult for patients to show changes on the HFMSE. However, the subgroup analyses according to disease severity defined as HFMSE total score ≥ 10 or < 10 at baseline, did not show differences in the effect of risdiplam at 12 months between patients with a less severe disease (HFMSE ≥10) (mean change from baseline: 1.16 [95% CI 0.23, 2.10]) and patients with HFMSE <10 (mean change from baseline: 1.24 [95% CI 0.17, 2.31]). After 24 months of treatment, a greater improvement in the HFMSE total score was observed in those with less severe disease at baseline (HFMSE ≥10), even though with overlapping confidence intervals (mean change from baseline: 2.45 [95% CI 0.94,3.96]) compared with the subgroup of patients with HFMSE <10 (mean change from baseline: 1.69 [0.49, 2.89]).

RULM and HFMSE responder analysis at 24 months (defined as % of patients with change from baseline ≥ 0 and ≥2) showed that the results observed at 12 months were maintained at 24 months.

A subgroup analysis was performed to assess the efficacy by mth 24.

Table 41:Subgroup Analysis of MFM32, RULM, HFMSE and Caregiver-reported SMAIS at Month 24 by Age (All Exposure to Risdiplam Treatment Period) (ITT Patients; BP39055 Part 2)

	Age 2-5 (N=37)		Age 6-11 (N=39)		Age 12-17 (N=30)		Age 18-25 (N=14)	
Visit	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**
Change from baseline in MFM32 total score								
Baseline								
n	32		39		30		14	
Mean (SD)	45.02 (11.00)		47.36 (14.04)		45.97 (10.80)		40.25 (10.75)	
95% CI	(41.05, 48.98)		(42.80, 51.91)		(41.94, 50.00)		(34.04, 46.46)	
Month 24								
n	28	28	35	35	29	29	11	11
Mean (SD)	52.53 (10.24)	6.55 (5.56)	47.23 (14.10)	0.36 (5.60)	46.19 (12.06)	-0.18 (3.41)	38.73 (11.03)	-0.19 (3.12)
95% CI	(48.56, 56.50)	(4.39, 8.70)	(42.39, 52.08)	(-1.57, 2.28)	(41.61, 50.78)	(-1.48, 1.12)	(31.32, 46.14)	(-2.28, 1.91)
Proportion of patients with a change from baseline in MFM32 total score of 3 or more								
Baseline								
n	32		39		30		14	
Month 24								
n	28		35		29		11	
Percentage	65.6%		20.5%		20.0%		14.3%	
95% CI	(46.8, 81.4)		(9.3, 36.5)		(7.7, 38.6)		(1.8, 42.8)	
Visit	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**
Change from baseline in RULM total score								
Baseline								
n	37		38		30		14	
Mean (SD)	18.11 (6.88)		20.11 (7.36)		21.37 (7.29)		18.21 (6.59)	
95% CI	(15.81, 20.40)		(17.69, 22.52)		(18.64, 24.09)		(14.41, 22.02)	
Month 24								
n	32	32	34	34	29	29	10	10
Mean (SD)	24.88 (6.68)	6.16 (4.49)	21.85 (8.56)	2.35 (3.83)	21.55 (8.17)	0.03 (2.73)	18.70 (8.29)	1.50 (2.88)

95% CI	(22.47, 27.28)	(4.54, 7.77)	(18.87, 24.84)	(1.02, 3.69)	(18.45, 24.66)	(-1.00, 1.07)	(12.77, 24.63)	(-0.56, 3.56)
Change from baseline in HFMSE total score								
Baseline								
n	37		39		30		14	
Mean (SD)	19.05 (11.10)		17.90 (13.38)		13.07 (12.84)		9.79 (9.45)	
95% CI	(15.35, 22.75)		(13.56, 22.24)		(8.27, 17.86)		(4.33, 15.24)	
Month 24								
n	32	32	35	35	29	29	10	10
Mean (SD)	26.13 (13.13)	5.97 (5.83)	18.29 (13.72)	0.46 (5.19)	14.34 (13.35)	0.90 (2.43)	9.70 (10.73)	-0.50 (3.50)
95% CI	(21.39, 30.86)	(3.87, 8.07)	(13.57, 23.00)	(-1.32, 2.24)	(9.27, 19.42)	(-0.03, 1.82)	(2.02, 17.38)	(-3.01, 2.01)
Change from baseline in SMAIS caregiver 22-item upper limb total score								
Baseline								
n	36		37		30		13	
Mean (SD)	24.17 (7.10)		24.65 (7.61)		28.77 (9.03)		27.00 (10.24)	
95% CI	(21.77, 26.57)		(22.11, 27.19)		(25.40, 32.14)		(20.81, 33.19)	
Month 24								
n	32	31	36	34	28	28	10	10
Mean (SD)	28.38 (7.81)	3.68 (5.68)	28.08 (9.74)	3.50 (5.73)	30.61 (9.56)	1.32 (3.59)	27.20 (9.62)	1.10 (4.56)
95% CI	(25.56, 31.19)	(1.59, 5.76)	(24.79, 31.38)	(1.50, 5.50)	(26.90, 34.31)	(-0.07, 2.71)	(20.32, 34.08)	(-2.16, 4.36)

MFM32=Motor Function Measure 32. RULM=Revised Upper Limb Module. HFMSE=Hammersmith Functional Motor Scale Expanded. SMAIS=SMA Independence Scale.

Baseline is the last measurement prior to the patient's first dose of risdiplam.

n=Valid results after applying the missing item rule.

The total number of patients with a valid baseline (Day -1 or screening) total score in each corresponding scale were used as the denominator to calculate the percentages at each time point.

Clinical cut-off date: 30 Sep2020.

Subgroup analysis by age at 24 months confirmed (as observed at 12 month) that a larger effect on endpoints assessing motor function (MFM-32, RULM and HFMSE endpoints) was observed in the 2-5 years age subgroup, in comparison to the older age groups.

A further subgroup analysis was performed by SMN2 gene copy number.

Table 42: Subgroup Analysis of MFM32, RULM, HFMSE and Caregiver-reported SMAIS at Month 24 by *SMN2* Gene Copy Number (All Exposure to Risdiplam Treatment Period) (ITT Patients; BP39055 Part 2)

	2 SMN2 Copies (N=3)		3 SMN2 Copies (N=107)		4 SMN2 Copies (N=10)	
Visit	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**
Change from baseline in MFM32 total score						
Baseline						
n	3		103		9	
Mean (SD)	34.03 (14.18)		44.71 (11.74)		58.10 (6.27)	
95% CI	(-1.20, 69.26)		(42.42, 47.01)		(53.28, 62.92)	
Month 24						
n	3	3	91	91	9	9
Mean (SD)	32.99 (17.19)	-1.04 (3.13)	46.84 (12.33)	2.05 (5.76)	58.68 (7.14)	0.58 (4.14)
95% CI	(-9.72, 75.69)	(-8.80, 6.72)	(44.27, 49.41)	(0.85, 3.25)	(53.19, 64.17)	(-2.60, 3.76)
Proportion of patients with a change from baseline in MFM32 total score of 3 or more						
Baseline						
n	3		103		9	
Month 24						
n	3		91		9	
Percentage	0		34.0%		22.2%	
95% CI	NA		(24.9, 44.0)		(2.8, 60.0)	
Change from baseline in RULM total score						
Baseline						
n	3		106		10	
Mean (SD)	13.67 (6.03)		19.01 (6.87)		27.40 (5.19)	
95% CI	(-1.31, 28.64)		(17.69, 20.33)		(23.69, 31.11)	
Month 24						
n	3	3	92	92	10	10
Mean (SD)	13.67 (8.33)	0.00 (2.65)	21.85 (7.65)	2.90 (4.55)	30.00 (6.24)	2.60 (2.91)
95% CI	(-7.02, 34.35)	(-6.57, 6.57)	(20.26, 23.43)	(1.96, 3.84)	(25.54, 34.46)	(0.52, 4.68)
Change from baseline in HFMSE total score						

	2 SMN2 Copies (N=3)		3 SMN2 Copies (N=107)		4 SMN2 Copies (N=10)	
Visit	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**
Change from baseline in RULM total score						
Baseline						
n	3		106		10	
Mean (SD)	13.67 (6.03)		19.01 (6.87)		27.40 (5.19)	
95% CI	(-1.31, 28.64)		(17.69, 20.33)		(23.69, 31.11)	
Month 24						
n	3	3	92	92	10	10
Mean (SD)	13.67 (8.33)	0.00 (2.65)	21.85 (7.65)	2.90 (4.55)	30.00 (6.24)	2.60 (2.91)
95% CI	(-7.02, 34.35)	(-6.57, 6.57)	(20.26, 23.43)	(1.96, 3.84)	(25.54, 34.46)	(0.52, 4.68)
Change from baseline in HFMSE total score						
Baseline						
n	3		107		10	
Mean (SD)	9.67 (13.28)		14.97 (11.96)		30.10 (9.01)	
95% CI	(-23.32, 42.65)		(12.68, 17.26)		(23.65, 36.55)	
Month 24						
n	3	3	93	93	10	10
Mean (SD)	8.00 (11.27)	-1.67 (2.08)	17.56 (13.20)	2.17 (4.65)	33.20 (15.12)	3.10 (9.88)
95% CI	(-19.99, 35.99)	(-6.84, 3.50)	(14.84, 20.28)	(1.22, 3.13)	(22.38, 44.02)	(-3.97, 10.17)

Table 43: Subgroup Analysis of MFM32, RULM, HFMSE and Caregiver-reported SMAIS at Month 24 by SMN2 Gene Copy Number (All Exposure to Risdiplam Treatment Period) (ITT Patients; BP39055 Part 2) (cont.)

	2 SMN2 Copies (N=3)		3 SMN2 Copies (N=107)		4 SMN2 Copies (N=10)	
Visit	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**
Change from baseline in SMAIS caregiver 22-item upper limb total score						
Baseline						
n	3		104		9	
Mean (SD)	20.67 (3.21)		25.03 (7.79)		36.78 (7.01)	
95% CI	(12.68, 28.65)		(23.51, 26.54)		(31.39, 42.17)	
Month 24						
n	3	3	93	91	10	9
Mean (SD)	20.00 (5.57)	-0.67 (3.21)	28.08 (8.72)	2.81 (5.32)	37.70 (7.56)	3.00 (3.77)
95% CI	(6.17, 33.83)	(-8.65, 7.32)	(26.28, 29.87)	(1.71, 3.92)	(32.29, 43.11)	(0.10, 5.90)

Note: Unknown SMN2 copies (N=3) is not included in this table.

MFM32=Motor Function Measure 32. RULM=Revised Upper Limb Module. HFMSE=Hammersmith Functional Motor Scale Expanded. SMAIS=SMA Independence Scale. Baseline is the last measurement prior to the patient's first dose of risdiplam. n=Valid results after applying the missing item rule.

The total number of patients with a valid baseline (Day -1 or screening) total score in each corresponding scale were used as the denominator to calculate the percentages at each time point.

Clinical cut-off date: 30Sep2020.

In summary, there is evidence of a small effect on the upper limbs and overall muscle response and dexterity in the second year of treatment. In spite of the small number in the subgroup of patients with 4 SMN2 copies (N=10), limiting the interpretability of the results, the magnitude of effect is similar, in the subgroup with 3 and 4 SMN2 copy number.

As regards to disease severity, both at Month 12 and at month 24, the proportion of patients achieving improvement (change from baseline total score ≥2) in the RULM and HFMSE, was greater in those with less severe disease (HFMSE ≥10) at baseline in comparison to patients with more severe disease at baseline (HFMSE <10). As regards to RULM a similar trend was observed also for proportion of patients achieving stabilisation (change ≥0); conversely, as regards to HFMSE, the proportion of patients achieving stabilisation (change ≥0) was similar between patients with baseline HFMSE ≥10 and <10.

FVC: Spirometry was performed to assess respiratory function in patients who were ≥6 years of age at screening. No relevant difference from PBO was observed in FVC at 12 months.

SMA Independence Scale (SMAIS): Changes in caregiver-reported and patient-reported SMAIS total score (a new caregiver and PRO scale developed with the study) numerically favoured risdiplam compared to placebo, even though the differences were not statistically significant.

Clinical Global Impression of Change (CGI-C): The difference between risdiplam (47.5%) and PBO (40%) group in the proportion of patients assessed as improved by the clinician (either minimally/ much or very much improved) at Month 12 was not statistically significant. The applicant argues that

for the patient population enrolled in SUNFISH Study Part 2, that includes older patients with progressed disease, functional stabilisation (≥0 change from baseline in MFM-32) is an important treatment benefit. However, in Part 2 of the SUNFISH trial, according to clinician's impression of a patient's change in global health from baseline (CGI-C), a similar proportion of patients global health either improved or did not change from baseline (assessed as either "minimally improved", "much improved", "very much improved" or "no change" by the clinician) in the risdiplam arm (85.8%) compared to the placebo arm (83.3%) at Month 12 (difference from PBO: 1.21 (95% CI: 0.52, 2.83; p=0.6636). The applicant considers that the reason why the CGI-C failed to adequately discriminate patients in terms of their level of improvement may be due to the one-year recall period, lack of sensitivity to change in the outcome measure, and the broad nature of this item and the response options focused on global health.

The applicant emphasises that the results from a caregiver-reported measure, the SMA Independence Scale (SMAIS)- a new tool which has been validated along the development plan- used approximately every 3 months in the study and with a seven-day recall period, demonstrated numerical improvements with risdiplam compared to placebo at Month 12. Numerical improvements were also observed in the patient-reported SMAIS (ages 12-25 years) with risdiplam compared to placebo at Month 12.

Table 44: Reference source not found. (cont.)

	North America (N=16)		**Europe (N=81)**		**China (N=11)**		**Japan (N=10)**	
Visit	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**	**Value at Visit**	**Change from Baseline**
Change from baseline in SMAIS caregiver 22-item upper limb total score								
Baseline								
n	13		80		11		10	
Mean (SD)	24.31 (7.73)		26.64 (8.19)		26.82 (9.11)		21.20 (8.12)	
95% CI	(19.64, 28.98)		(24.81, 28.46)		(20.70, 32.94)		(15.39, 27.01)	
Month 24								
n	13	11	71	70	11	11	10	10
Mean (SD)	26.15 (8.11)	2.64 (6.36)	30.11 (8.60)	3.10 (4.91)	27.27 (9.92)	0.45 (2.94)	22.70 (9.94)	1.50 (6.08)
95% CI	(21.25, 31.06)	(-1.64, 6.91)	(28.08, 32.15)	(1.93, 4.27)	(20.61, 33.94)	(-1.52, 2.43)	(15.59, 29.81)	(-2.85, 5.85)

Note: Rest of World (N=2) is not included in this table. MFM32=Motor Function Measure 32. RULM=Revised Upper Limb Module. HFMSE=Hammersmith Functional Motor Scale Expanded. SMAIS=SMA Independence Scale. Baseline is the last measurement prior to the patient's first dose of risdiplam. n=Valid results after applying the missing item rule. The total number of patients with a valid baseline (Day -1 or screening) total score in each corresponding scale were used as the denominator to calculate the percentages at each time point. Clinical cut-off date: 30Sep2020.

The applicant has been requested to discuss the 24 mth CGI-C data, but responded that per protocol the outcome was not collected at Month 24, and thus were unable to provide the results.

SUNFISH Part 1: comparison with external sources: The results of the weighted analyses showed a statistically significant difference between patients treated with risdiplam, showing an improvement in motor function (assessed through LS mean change from baseline in total MFM) and the untreated weighted external control group, where a decline in motor function was observed. The weighting approach used gave more weight to a patient in the external control group who had a more similar covariate profile to a patient in SUNFISH study. A statistically significant higher proportion of responders (defined as change from baseline in MFM total score of ≥3) was observed among risdiplam treated patients in comparison with untreated external controls (54.2% vs 16.8% at 24 months). These differences were observed at Month 12 and maintained at Month 24.

The applicant has been requested to discuss available data regarding pre-symptomatic patients, and discuss the benefit/risk in this population. Few SMA1 presymptomatic pts have been enrolled up to now in the Phase 2 RAINBOWFISH Study (expected to enrol 25 pts overall, 9 pts presented for IDMC available) and there is no hint on the possible effective dose for this very young population (pts enrolled aged 42 days or below). Moreover, two episodes of increased liver enzymes raise the concern of possible population sensitiveness to risdiplam, or a higher than expected administered dose. Therefore it is agreed that this population should be excluded from the indication.

PAES proposal assessment

The applicant has focused the PAES on a prospective, observational study of circa 300 patients with both symptomatic and pre-symptomatic patients. Data will be collected from possible multiple sources, from existing SMA registries plus a study specific registry. Data gathering will cover a minimum of 5 years. EU countries will be the primary source for data.

Study objectives

The proposed study objectives (outcomes in treated pre-symptomatic stage pts, pts with 4 SMN2 copies and long-term maintenance of efficacy and safety in SMA pts) are acceptable. These outcomes, however, should be compared to similar condition patients who have not been treated with risdiplam (natural history patients). The population (including both risdiplam treated and non-treated patients) should ideally come from the same registries, to decrease the risk of biases resulting from different study populations and different epochs. This aspect is especially relevant for the assessment of B/R in patients with 4 SMN2 copies: longitudinal data for both treated and non-treated patients must be available at the end of the study in this population.

Study design and data sources

A hybrid approach is proposed: data to be obtained from existing registries (including, but not limited to: TREAT-NMD, iSMAc, SMArtCARE) and a supplementary study specific registry to accommodate targeted data and deliver results within the expected timeframe. The applicant considers conducting preparation feasibility study to build the definitive PAES study.

Proposed population and sample size

300 treated patients will be enrolled. A comparable number of non treated patients, with comparable status at study entrance, follow up and data on SMN2 copies number should also be available from the same registries. Final numbers will derive from final outcome measures, statistical plan and time-to-population-availability of risdiplam within individual countries.

Outcome measures

Final outcomes target maintenance or improvement of motor milestones, ventilation and overall survival of patients. In all pts will be collected: Survival and ventilation free survival + WHO motor milestones. In pts up to two years, CHOP-INTEND will be obtained; in patients two years and above, HFMSE and RULM and MFM32 (where available) will be obtained. For highly functioning patients, timed endpoints will be collected. Overall the proposed strategy is acceptable. A balance is needed between

the number of tools to be used and the practicality of data acquisition, both from each registry base and the individual patient (taken fatigue into consideration). For the sake of benefit risk assessment on the long term, the use of the tools that have been used during the development plan is favoured. As such, consideration should be given to inclusion of HINE-2.

Statistical analysis

Descriptive statistics will be used.

Subgroup analyses will be made regarding SMN2 number of copies, symptomatic vs pre-symptomatic, and treated vs "natural history" non treated patients.

An initial interim analysis is planned the moment that all expected pts have been enrolled. Further interim analyses will have a yearly basis.

Status reports are expected annually, independently from the planned interim analysis. These status reports will allow assessment of ongoing recruitment and follow-up attrition, to confirm feasibility within the proposed timeframe, and to implement recover strategies if needed.

Study duration and expected milestones

The applicant proposes to conduct a study with 2-3 years enrolment period + 5 years of follow-up. The study is to be started upon agreement of the final plan once the feasibility is conducted (first 6 mths prior to PAES study start), and final results and plan are presented to CHMP. The estimated submission for the final study is thus in 2030. This date should mark the limit date for submission.

2.5.4. Conclusions on the clinical efficacy

The patient population enrolled in FIREFISH and SUNFISH trial is not representative of the broad indication initially sought by the applicant, as patients with a clinical diagnosis of Type 4 SMA or exhibiting 5 SMN2 copies or more have not been studied in the clinical development. Available data only allow a benefit/ risk assessment in children 2 months and above, and after the assessment of available data from all sources, efficacy has been considered sufficiently demonstrated for marketing authorisation in patients with up to 4 *SMN2* copies or with clinical types of SMA 1, 2 and 3.

Efficacy data of Evrysdi treatment when used in patients that previously received *SMN1* gene therapy is not available. There is no efficacy or safety data to support the concomitant use of risdiplam and nusinersen.

SMA type 1:

After clarifications have been received on the clinical relevance of the primary endpoint chosen (sitting without support for 5 seconds) and on how the persistence of the milestone "sitting without support" has been assessed in FIREFISH trial, its relevance was accepted.

Later onset SMA: Type 2 and non-ambulant Type 3

Even though the difference from PBO on the primary endpoint (MFM-32) in SUNFISH trial Part 2 was statistically significant, the absolute difference from PBO was relatively modest (1.6-point difference on a 100-point scale) and no statistically significant difference from PBO was observed in the secondary endpoint HFMSE. Besides the known slower progression of Type 2 and Type 3 SMA, the modest effects observed may be due to the short study duration (12 months) and also to the heterogeneity of disease progression in later onset SMA (also in untreated subjects). The results of primary and secondary endpoints at 24 months overall showed that the results observed at 12 months were generally maintained at 24 months.

The CHMP considers the following measures necessary to address issues related to efficacy:

"Post-authorisation Efficacy Study (PAES): 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."

The proposed PAES will provide data on the knowledge gaps of:

a) efficacy when risdiplam is started in pre-symptomatic patients;

b) efficacy in patients with 4 SMN2 copies;

c) maintenance of efficacy on the long term in all patients including the a) and b) populations.

The presented plan is acceptable, provided that the main aspects as described in the study proposal are fulfilled.

2.6. Clinical safety

Introduction

Risdiplam is a small molecule SMN2 (survival of motor neuron 2) splicing modifier presented with an oral formulation (powder for oral solution) and proposed for the treatment of spinal muscular atrophy (SMA). Risdiplam promotes the inclusion of exon 7 to generate full-length SMN2 mRNA, leading to the increase in the production of functional SMN protein from the SMN2 gene, both in the central nervous system and systemically, throughout the body. A rapid (within 4 weeks) and durable increase of SMN protein blood levels has been shown. The recommended once daily dose is determined by age and body weight up to a maximum of 5 mg. Treatment with a daily dose above 5 mg has not been studied. The safety data set of risdiplam submitted in support of the present MAA is based on safety data available from the two ongoing pivotal clinical studies FIREFISH and SUNFISH as well as from the ongoing supportive study JEWELFISH. Where relevant, reference is made to safety data from 5 completed studies in healthy volunteers and subjects with hepatic impairment and to placebo-controlled safety data from the double-blind period of SUNFISH.

Patient exposure

In order to provide a comprehensive assessment of the safety profile of risdiplam in All SMA population N=465) and by SMA type (Type 1 versus Type 2 and 3), the available safety data were integrated and analysed for the following 3 pools:

i) All patients with SMA;

ii) Patients with Type 1 SMA (infantile-onset);

iii)Patients with Type 2 and Type 3 SMA (later-onset).

The following ***studies*** are ***integrated for pooling***:

- **Study BP39056 (FIREFISH):** Part 1 and Part 2; n=62 patients with infantile-onset SMA (Type 1) (aged 1 to 7 months at enrolment).

This is a two-part, multicentre, single arm, open-label study. Part 1: dose-finding, included 21 patients that did not enrol in the Part 2 but entered an ongoing open-label extension (OLE) phase to continue treatment at the dose selected for Part 2. Part 2: confirmatory at the dose selected in Part 1 (pivotal dose); pivotal, single-arm study; 41 symptomatic patients treated for 24 months followed by an OLE. The clinical cut-off date (CCOD) for the safety data was 14 November 2019 when all patients in Part 2 had completed the 12-month assessment (primary analysis of efficacy) and all patients in Part 1 had been dose-escalated to the pivotal dose and completed the 12-month assessment. Updated data was CCOD 27 October 2020.

- **Study BP39055 (SUNFISH):** Part 1 and Part 2; n=231 patients with later-onset SMA (Type 2 and 3) (aged 2 to 25 years).

This is a two-part, multicentre, randomised, placebo-controlled, double-blind study. Part 1: dose-finding, included 51 patients, those 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 (pivotal dose), all patients in Part 1 received the pivotal dose as part of an open-label treatment phase. Part 1 patients did not enrol in Part 2 of the study. Part 2: confirmatory at the dose selected in Part 1; ongoing double-blind, 2:1 randomised, placebo-controlled study; 180 patients enrolled (risdiplam: n=120, placebo: n=60). Patients who received placebo during the double-blind period of the study were switched in a blinded manner to treatment with risdiplam when they completed 12 months of treatment.

Overall, safety data up to the CCOD of 15 January 2020 from 230 out of 231 patients enrolled who received risdiplam are included in the pooled safety analyses. This CCOD includes safety data up to the primary analyses for Part 2 of the study (time point at which all ongoing patients had reached at least 12-months of treatment with risdiplam or placebo), as well as safety data for Part 1 for the timepoint at which all ongoing patients had reached at least 24 months of treatment with risdiplam at the pivotal dose. Updated data was CCOD 30 September 2020.

- **Study BP39054 (JEWELFISH):** n=174 including 159 patients with later-onset SMA (Type 2 and 3) and 15 patients with infantile-onset SMA (Type 1)

This 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, which has since been discontinued) in which treatment with risdiplam is evaluated over a 24-month period. Study enrolment 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 31 January 2020 from 173 out of 174 patients enrolled are included in the analyses presented in this SCS. One interim analysis with some safety data was updated during the MAA review (CCOD 31 July 2020).

Safety data from Study BN40703 (RAINBOWFISH, CCOD 27 October 2020) was provided.

No safety data are available from Study BP39859 (ANCHOVY) because this is a non-interventional natural history study, in which safety data was not collected.

Non-integrated safety data from the following studies are also provided:

- Safety data from the 12-month double-blind placebo-controlled period from Study BP39055 (SUNFISH) Part 2 (patients with Type 2 and 3 SMA) to show double-blind placebo comparison.
- 5 studies in healthy volunteers and subjects with hepatic impairment (Studies BP39122, BP29840, NP39625, BP41361, BP40995). Of note, data from these studies were included in the assessments of abuse potential, and effects on ability to Drive and Use Machines.

Table 45: Patient Exposure

	Patients enrolled (N)	**Patients exposed (N)**	**Patients exposed to the proposed dose range (N)**	**Patients with long term safety data (>24 Months) (N)**
Placebo-controlled	155	155	155	0
Active-controlled	0	0	0	0
Open studies	476	474	470	200
Post-marketing	1989	789	789	N/A
Compassionate use	807	337	337	N/A

Cutoff dates:

BP39054 (JEWELFISH): 31 July 2020

BP39055 (SUNFISH) Part 1: 04 June 2020

BP39055 (SUNFISH) Part 2: 30 September 2020

BP39056 (FIREFISH) Part 1 & Part 2: 27 October 2020

BN40703 (RAINBOWFISH): 27 October 2020

Post-marketing: 23 November 2020

Compassionate use: 27 October 2020

A comprehensive summary of the pooling strategy is shown in the Figure below:

Table 46 - Studies Contributing Safety Data to the Analysis Population Pools

Population	No of Patients	Studies	Purpose of Pool
Integrated Data			
All Patients with SMA	N=467	BP39056 (FIREFISH) Part 1 and Part 2 BP39055 (SUNFISH) Part 1 and Part 2 BP39054 (JEWELFISH)	The All Patients with SMA pool includes all of the available unblinded safety data up to the CCOD for each study. The purpose of this pool is to assess the safety of risdiplam in patients with Type 1, 2, and 3 SMA.
Patients with Type 1 SMA	N= 77	BP39056 (FIREFISH) Part 1 and Part 2 BP39054 (JEWELFISH)	The Type 1 SMA pool includes all of the available safety data up to the CCODs for Study BP39056 (Part 1 and Part 2) and Study BP39054. The purpose of this pool is to assess the safety of risdiplam in patients with Type 1 SMA.
Patients with Type 2 and Type 3 SMA	N= 388	BP39055 (SUNFISH) Part 1 and Part 2 BP39054 (JEWELFISH)	The Type 2 and Type 3 SMA pool includes all of the available safety data up to the CCODs for Study BP39055 (Part 1 and Part 2 of the study), and Study BP39054. The purpose of this pool is to assess the safety of risdiplam in patients with Type 2 and 3 SMA.
Non-Integrated Data			
Patients with Type 2 and Type 3 SMA	N=180 (60 placebo/120 risdiplam)	BP39055 (SUNFISH) Double-Blind Period Part 2	These data are included to provide double-blind placebo-controlled safety assessment and provide the basis for preliminary ADR identification in patients with Type 2 and 3 SMA.
Healthy Volunteers	N=124 (13 placebo/111 risdiplam)	Healthy volunteer studies: BP39122, BP29840, NP39625, BP41361, Study in subjects with hepatic impairment: BP40995	These data are included to enable the most comprehensive safety profile assessment possible at this time. Data from these studies were included in the assessments of abuse liability, and effects on ability to drive and use machines, as well as the impact of mild to moderate hepatic impairment and the impact of risdiplam on the PK of midazolam.
Total Number Of Patients Exposed To Risdiplam	N=465[a]		

CCOD=clinical cutoff date; SMA=spinal muscular atrophy.
The CCOD for Part 1 and Part 2 of Study BP39056 (FIREFISH) is 14 Nov 2019. The CCOD for Part 1 and Part 2 of Study BP39055 (SUNFISH) is 15 Jan 2020. The CCOD for Study BP39054 (JEWELFISH) is 31 Jan 2020.

[a] Total number of patients exposed to risdiplam includes 465 patients in the pooled All Patients with SMA population; 2 patients who did not receive risdiplam are not included.

All Patients with SMA

In the All Patients with SMA population (n=465), the median duration of exposure to risdiplam was 12.68 months (range: 0.0–38.9). A total of 158 patients (34.0%) had been treated for up to 6 months, 69 patients (14.8%) for more than 6 months up to 12 months, 85 patients each (18.3%) for between 12 months and 18 months and 18 to 24 months, and 68 patients (14.6%) for more than 24 months. The overall exposure was 521.4 patient-years (PY). The overall exposure to the pivotal dose was 480.9 PY, corresponding to approximately 92% of the overall exposure time (PY).

All patients had received at least 78.5% of the total number of prescribed doses (dose intensity). Median dose intensity was 100%.

Patients with Type 1 SMA

In the Type 1 SMA population (n=77), the median duration of exposure was 15.24 months (range: 0.1–34.6). At the time of analysis, the majority of patients (55 patients, 71.4%) had been treated for >12 months. Exposure time was 33.6 PY in the 0–6 months treatment period, 28.9 PY in the 6–12 months period, and 19.1 PY in the >12–≤18 month period, and declined further thereafter. The overall exposure was 92.1 PY.

Median exposure to the pivotal dose of 0.2 mg/kg for patients <2 years old and 0.25 mg/kg (<20 kg body weight) or 5 mg (≥20 kg body weight) for patients ≥2 years old was 13.98 months (range: 0.1–23.6). The total exposure to the pivotal dose was 77.9 PY, corresponding to approximately 85% of the overall exposure time (PY).

Patients with Type 2 and Type 3 SMA

In the Type 2 and Type 3 SMA population (n=388), the median duration of treatment was 9.30 months (range: 0.0–38.9). At the time of analysis most patients (246 patients, 63.4%) had been treated for >6 months. Overall exposure was 429.2 PY, with an exposure time of 164.2 PY in the 0–6 months treatment period, declining progressively to 100.6 in the 6–12 months period, 87.4 PY in the 12–18 months treatment period, and 39.4 PY in the 18-24 months treatment period, with 37.6 PY exposure beyond 24 months.

Median exposure to the pivotal dose of 0.25 mg/kg for patients with body weight <20 kg or 5 mg for patients with body weight ≥20 kg was 9.13 months (range: 0.0–34.5). The total exposure to the pivotal dose was 403.0 PY, corresponding to approximately 94% of the overall exposure time.

Table 47 - Exposure to Risdiplam

	Type 1 SMA (N=77)	Type 2 and 3 SMA (N=388)	All SMA Patients (N=465)
Active Exposure Duration (months)			
n	**77**	**388**	**465**
Mean (SD)	**14.36 (8.16)**	**13.28 (10.32)**	**13.46 (9.99)**
Median	**15.24**	**9.30**	**12.68**
Range	**0.1 - 34.6**	**0.0 - 38.9**	**0.0 - 38.9**
Total Patient-Years	**92.1**	**429.2**	**521.4**
Pivotal Dose Exposure Duration (months)			
n	**74**	**388**	**462**
Mean (SD)	**12.63 (6.42)**	**12.46 (8.98)**	**12.49 (8.61)**
Median	**13.98**	**9.13**	**11.98**
Range	**0.1 - 23.6**	**0.0 - 34.5**	**0.0 - 34.5**
Total Patient-Years	**77.9**	**403.0**	**480.9**
Dose Intensity (%)			
n	**77**	**388**	**465**
Mean (SD)	**99.77 (1.00)**	**99.29 (2.11)**	**99.37 (1.97)**
Median	**100.00**	**100.00**	**100.00**
Range	**91.7 - 100.0**	**78.5 - 100.0**	**78.5 - 100.0**

Table 48 - Overall Exposure Time in Patient-Years by Treatment Period

	Type 1 (N=77)	**Type 2/3** (N=388)	**All Patients** (N=465)
Exposure time in Patient-Years (PY)			
Total	92.1	429.2	521.4
0–≤6 Months	33.6	164.2	197.8
>6–≤12 Months	28.9	100.6	129.5
>12–≤18 Months	19.1	87.4	106.4
>18–≤24 Months	7.8	39.4	47.2
>24-≤30 Months	2.1	25.7	27.8
>30–≤36 Months	0.7	11.1	11.8
>36 Months	0.0	0.8	0.8

Table 49 - Overall Exposure Time in Patient-Years by Intrinsic Factors: Race and Age

	White (N=343)	Asian (N=63)	Black or African American (N=3)	Unknown (N=54)	0–<2 years (N=67)	2-<12 years (N=189)	12–<18 years (N=119)	≥18 years (N=90)
Exposure time in Patient-Years (PY)								
Total	388.1	69.7	2.9	59.0	88.8	230.3	123.9	78.4
0–≤6 Months	145.3	28.5	1.1	22.2	30.7	83.1	48.4	35.7
>6–≤12 Months	91.9	21.2	1.0	14.9	28.5	57.4	27.0	16.6
>12–≤18 Months	77.3	15.6	0.8	12.3	19.1	50.2	23.7	13.5
>18–≤24 Months	37.2	2.7	0.0	7.2	7.8	20.6	10.6	8.2

>24–≤30 Months	24.7	1.0	0.0	2.1	2.1	13.9	8.2	3.6
>30–≤36 Months	10.9	0.7	0.0	0.3	0.7	5.1	5.2	0.9
>36 Months	0.8	0.0	0.0	0.0	0.0	0.0	0.8	0.0

The clinical cut-off date was January of 2020 for the SUNFISH and JEWLFISH studies. An update of safety data after both including and excluding JEWELFISH data, with the SUNFISH Part 2 placebo group included in the summary tables as a reference for the assessment; updated safety data of JEWELFISH was requested. Furthermore, available updated safety data, even if they are still limited, from the other ongoing studies RAINBOWFISH (Study BN40703 on pre-symptomatic infants from birth to 6 weeks who were genetically diagnosed with SMA), ANCHOVY (Study BP39859, a natural history study to assess medical record data retrospectively), and Pre-approval access (PAA)/Compassionate Use (CU) programme should also be provided as available.

Demographic Characteristics

There was a higher representation of patients with Type 2 and 3 SMA (n=388) versus Type 1 SMA (n=77) in this pooled population.

The majority of patients with Type 1 SMA were less than 2 years of age at the time of the first dose of risdiplam (87.0%), whereas patients with Type 2 and 3 SMA were generally in the 2 to <12 years old group (46.9%) and older. A total of 19.4% of patients were 18 years or older at the time of the first dose of risdiplam.

The patients were predominantly White (73.8%), while 13.5% were of Asian race. Overall, 77.2% of patients were enrolled at sites in European countries. The proportion of Asian patients was higher in the Type 1 SMA pool (23.4%) compared to the Type 2 and 3 SMA pool (11.6%).

Numerically, at baseline patients were lower than a healthy population in terms of height, weight and BMI based on WHO Child Growth Standards (World Health Organization, 2006), respectively. Indeed, the patients' mean (SD) weight, height, and BMI, were at the 35.11 (33.97), 39.18 (32.71), 37.16 (38.46) percentile compared to WHO percentiles of healthy children and young adults. However, there was broad inter-patient variability.

Baseline Disease Characteristics

Regarding type 1 SMA patients, a total of 65 patients had 2 SMN2 copies (genotyping), one patient had 3 SMN2 copies, and the number of SMN2 copies was unknown (i.e., genotyping results were not available) for 11 patients. The median age at onset of initial SMA symptoms, as reported by the parents, was 1.5 months (range: 0.0–9.0) in line with a diagnosis of Type 1 SMA. The median age at diagnosis was 3.0 months (range: 0.0–9.9).

Seven patients were assessed as having scoliosis at screening. The degree of curvature due to scoliosis was <40 in 3 patients (3.9%) and >40 in 3 patients (3.9%). For patients with Type 1 SMA, information about ambulatory status, scoliosis, hip surgery and fractures is only captured for patients enrolled in Study BP39054.

Regarding type 2/3 SMA patients, the majority (70.1%) of patients had Type 2 SMA, and the most frequent SMN2 copy number (genotyping) was 3 SMN2 copies (68.0% of patients). The median age at onset of symptoms was 12.1 months (range: 0.0–258.0) and the majority of patients (93.8%) were non-ambulatory. The median age at diagnosis was 18.0 months (range: 1.0-287.0).

A total of 125 patients (32.2%) had severe scoliosis with a curvature of >40 degrees, and 131 patients (33.8%) had scoliosis surgery before screening. Information about ambulatory status, scoliosis, hip surgery, and fractures is only captured for patients enrolled in Studies BP39054 and BP39055.

Adverse events

Overview

All patients with SMA

A total of 465 patients received risdiplam and are included in the integrated safety analyses with an overall exposure time of 521.4 PY. Overall, 393 patients (84.5%) treated with risdiplam experienced at least one AE. The AE rate was 577.50 per 100 PY (95% CI: 557.06, 598.51). The overall rate of AEs was comparable in patients with Type 1 SMA and patients with Type 2 and 3 SMA. The majority of AEs were of Grade 1 or 2 intensity reported at rates of 418.31 per 100PY (95% CI: 400.94, 436.24) for Grade 1 and 124.48 per 100PY (95% CI: 115.08, 134.43) for Grade 2. Grade 3 events were reported at a rate of 26.47 per 100PY (95% CI: 22.24, 31.27). Twenty-five Grade 4 events were reported (4.79 events per 100PY [95% CI: 3.10, 7.08]). The rate of Grade 3 and Grade 4 AEs was markedly higher in patients with Type 1 SMA, as compared to patients with Type 2 and 3 SMA, approximately 2.5-fold and 18.5-fold, respectively.

Overall, seven patients with Type 1 SMA died due to SMA-related respiratory complications (reported as not related to study medication):

Six patients died due to events with an onset date during the treatment period (1 patient experienced two Grade 5 AEs leading to death [cardiac arrest and respiratory failure]).

A seventh patient died due to cardiac arrest 3.5 months after treatment discontinuation.

Risdiplam treatment was permanently discontinued due to an AE (respiratory tract infection viral, Grade 5) in 1 patient with Type 1 SMA who discontinued risdiplam to receive palliative care 3 days prior to their death.

A total of 65 patients (14.0%) had an AE that was reported as related to study treatment. Treatment was interrupted for one patient with Type 2 or 3 SMA with an AE (diarrhoea) reported as related to study drug; the AE resolved and the patient continued treatment with risdiplam. The majority of related AEs resolved as of the CCOD. The rate of related AEs was 19.18 per 100PY (95% CI: 15.61, 23.33) and was comparable in patients with Type 1 and patients with Type 2 and 3 SMA.

During treatment with risdiplam, 103 patients (22.2%) experienced at least one SAE. The overall rate of SAEs was 37.21 per 100PY (95% CI: 32.16, 42.83). Of these, 1 patient with Type 1 SMA had an SAE of neutropenia that was reported as related to study treatment but resolved despite ongoing treatment with risdiplam, and another patient with Type 1 SMA had an SAE that led to withdrawal of study treatment (respiratory tract infection viral with fatal outcome). The rate of SAEs was approximately 3.5-fold higher in patients with Type 1 SMA (93.33 per 100PY [95% CI: 74.66, 115.27]) compared to patients with Type 2 and 3 SMA (25.16 [95% CI: 20.64, 30.38]).

One patient with Type 1 SMA who had discontinued risdiplam for non-safety related reasons experienced a total of 6 AEs that were reported during the safety follow-up period.

Patients with Type 1 SMA

A total of 77 patients with Type 1 SMA received risdiplam and are included in the integrated safety analyses with a total exposure time of 92.1 PY. Seventy-two patients (93.5%) with Type 1 SMA treated with risdiplam experienced at least one AE. The rate of AEs was 577.37 per 100PY (95% CI: 529.34, 628.58). The majority of AEs were of Grade 1 or 2 intensity, and Grade 3□5 AEs were experienced by 35 patients (45.5%). Three patients (3.9%) had an AE that led to dose interruption for one day: pneumonia (1 patient), and hypoxia (1 patient), and 9 days pyrexia (1 patient), which were all reported as unrelated to study treatment and resolved without recurrence despite ongoing

treatment with risdiplam at the same dose. One patient had an AE (respiratory tract infection viral, resulting in death) that led to withdrawal from treatment which was reported as unrelated to study treatment. Nine patients (11.7%) had an AE that was reported as related to study treatment; however, none of these related AEs led to withdrawal or interruption of study treatment and had resolved or were resolving at the CCOD. The rate of related AEs was 16.28 per 100PY (95% CI: 9.11, 26.85).

During treatment with risdiplam 42 patients (54.5%) with Type 1 SMA experienced at least one SAE at a rate of 93.33 per 100PY (95% CI: 74.66, 115.27). Of these, 1 patient had an SAE (neutropenia) that was considered to be related to study treatment and resolved without change to study treatment, and 6 patients had a total of 7 fatal SAEs associated with SMA-related respiratory complications.

Patients with Type 2 and 3 SMA

A total of 388 patients with Type 2 and Type 3 SMA received risdiplam and are included in the integrated safety analyses with total exposure time of 429.2 PY. A total of 321 patients (82.7%) with Type 2 and 3 SMA treated with risdiplam experienced at least one AE. The AE rate was 577.53 per 100PY (95% CI: 555.02, 600.72). The majority of AEs were of Grade 1 or 2 intensity, and 53 patients (13.7%) experienced a Grade 3 or 4 AE. Fifty-six patients (14.4%) had an AE that was reported as related to study treatment. One AE that was assessed as related to treatment resulted in dose interruption (diarrhoea, Day 17); the patient also experienced abdominal pain and hyperchlorhydria, which were reported by the investigator as not related to risdiplam.

Events reported as related to risdiplam resolved in most patients. The unresolved events did not worsen in intensity despite ongoing treatment with risdiplam, with the exception of 3 AEs in 2 patients: livedo reticularis and cyanosis that went from Grade 1 intensity to Grade 2 intensity and an AE of weight increased that went from Grade 1 intensity to Grade 2 intensity. A related AE that had not resolved at the time of the CCOD was reported in one patient with a Grade 1 event of INR increased; the action taken with study drug was listed as unknown. The rate of related AEs was 19.80 per 100 PY (95% CI: 15.82, 24.49).

Thirty patients with Type 2 and 3 SMA reported AEs that led to interruption of study treatment. By CCOD, all events had resolved. Events had not recurred after reinitiating treatment with risdiplam in all of these patients with the exception of two patients who had not restarted risdiplam by the time of CCOD.

During treatment with risdiplam, 61 patients (15.7%) with Type 2 and 3 SMA experienced at least one SAE at a rate of 25.16 per 100 PY (95% CI: 20.64, 30.38). One SAE (supraventricular tachycardia) was reported as related to study treatment, and none led to withdrawal of treatment. At the CCODs for this analysis, no deaths were reported among patients with Type 2 and 3 SMA.

An overview of the safety profile of risdiplam in the All Patients with SMA population is shown in the next two tables.

Table 50 - Overview of Adverse Events by Rates per 100PY

	Type 2/3 SMA BP39055 Only (N=230)[1]	Type 2/3 SMA BP39055 & BP39054 (N=388)[2]	Type 2/3 SMA BP39054 Only (N=158)[3]	BP39055 Part 2 Placebo-Controlled Group (1-year data) (N=60)[4]
Overall Total Number Of Events				
Number of AEs	2032	2479	447	354
Rate per 100PY	573.36	577.53	597.30	588.82
95% CI	(548.70, 598.84)	(555.02, 600.72)	(543.21, 655.33)	(529.07, 653.47)
Number of Fatal AEs (Grade 5)				
Number of AEs	0	0	0	0
Rate per 100PY	0.00	0.00	0.00	0.00
95% CI	NE	NE	NE	NE
Life-threatening AEs (Grade 4)				
Number of AEs	4	5	1	0
Rate per 100PY	1.13	1.16	1.34	0.00
95% CI	(0.31, 2.89)	(0.38, 2.72)	(0.03, 7.45)	NE
Moderate AEs (Grade 3)				
Number of AEs	68	92	24	14
Rate per 100PY	19.19	21.43	32.07	23.29
95% CI	(14.90, 24.32)	(17.28, 26.29)	(20.55, 47.72)	(12.73, 39.07)
Serious AEs				
Number of AEs	90	108	18	14
Rate per 100PY	25.39	25.16	24.05	23.29
95% CI	(20.42, 31.21)	(20.64, 30.38)	(14.26, 38.01)	(12.73, 39.07)
Related AEs				
Number of AEs	50	85	35	9
Rate per 100PY	14.11	19.80	46.77	14.97
95% CI	(10.47, 18.60)	(15.82, 24.49)	(32.58, 65.04)	(6.85, 28.42)

Table 51 - Overview of Adverse Events (Number of Patients with Events)

Patients	Type 1 (N=77)	Type 2/3 (N=388)	All (N=465)
Total number of patients with at least one AE	72 (93.5%)	321 (82.7%)	393 (84.5%)
Total number of AEs	532	2479	3011
Total number of deaths	7 (9.1%)	0	7 (1.5%)
Total number of patients withdrawn from study due to an AE	0	0	0
Total number of patients with at least one			
AE with fatal outcome	6 (7.8%)	0	6 (1.3%)
Serious AE	42 (54.5%)	61 (15.7%)	103 (22.2%)
Serious AE leading to withdrawal from treatment	1 (1.3%)	0	1 (0.2%)
Serious AE leading to dose modification/interruption	2 (2.6%)	13 (3.4%)	15 (3.2%)
Related Serious AE	1 (1.3%)	1 (0.3%)	2 (0.4%)
AE leading to withdrawal from treatment	1 (1.3%)	0	1 (0.2%)
AE leading to dose modification/interruption	3 (3.9%)	30 (7.7%)	33 (7.1%)
Related AE	9 (11.7%)	56 (14.4%)	65 (14.0%)
Related AE leading to withdrawal from treatment	0	0	0
Related AE leading to dose modification/interruption	0	1 (0.3%)	1 (0.2%)
Grade 3-5 AE	35 (45.5%)	53 (13.7%)	88 (18.9%)

Common Adverse events

Common AEs by SOC and preferred terms

The tables below reported the common AEs by SOC at a rate of ≥15 per 100PY and by preferred terms at a rate of ≥10 per 100PY in the three pools.

Table 52 - Adverse Events Reported at a Rate ≥15 per 100PY (in Any Group) by System Organ Class

MedDRA System Organ Class Rate per 100PY 95% CI	**Type 1** (N=77)	**Type 2/3** (N=388)	**All Patients** (N=465)
Infections and infestations	215.97 (187.00, 248.15)	170.30 (158.18, 183.11)	178.37 (167.09, 190.21)
Gastrointestinal disorders	84.65 (66.91, 105.65)	89.93 (81.18, 99.36)	88.99 (81.08, 97.47)
Nervous system disorders	5.43 (1.76, 12.66)	80.37 (72.12, 89.32)	67.13 (60.28, 74.54)
General disorders and administration site conditions	99.85 (80.49, 122.45)	46.59 (40.36, 53.52)	56.00 (49.76, 62.81)
Respiratory, thoracic and mediastinal disorders	62.95 (47.80, 81.37)	53.35 (46.66, 60.73)	55.05 (48.86, 61.80)
Skin and subcutaneous tissue disorders	41.24 (29.18, 56.61)	30.98 (25.94, 36.72)	32.80 (28.07, 38.10)
Musculoskeletal and connective tissue disorders	6.51 (2.39, 14.17)	24.93 (20.43, 30.12)	21.67 (17.86, 26.06)
Injury, poisoning and procedural complications	10.85 (5.20, 19.96)	21.20 (17.07, 26.03)	19.37 (15.78, 23.54)

Common Adverse Events by System Organ Class and Preferred Term

Table 53 - Adverse Events Reported at a Rate ≥10 per 100PY (in Any Group) by Preferred Term

Preferred Term Rate per 100PY 95% CI	**Type 1** **(**N=77)	**Type 2/3** (N=388)	**All Patients** (N=465)
Headache	0 (NE)	67.79 (60.23, 76.05)	55.81 (49.58, 62.61)
Pyrexia	91.16 (72.72, 112.87)	32.85 (27.65, 38.74)	43.15 (37.70, 49.18)
Upper respiratory tract infection	60.78 (45.91, 78.92)	37.51 (31.94, 43.77)	41.62 (36.27, 47.54)
Nasopharyngitis	21.71 (13.26, 33.52)	29.12 (24.24, 34.70)	27.81 (23.47, 32.72)
Vomiting	22.79 (14.11, 34.84)	22.83 (18.54, 27.82)	22.82 (18.91, 27.31)
Cough	8.68 (3.75, 17.11)	20.50 (16.44, 25.26)	18.41 (14.91, 22.48)
Diarrhoea	13.02 (6.73, 22.75)	16.77 (13.12, 21.12)	16.11 (12.85, 19.95)
Pneumonia	28.22 (18.43, 41.34)	9.09 (6.46, 12.42)	12.47 (9.62, 15.89)
Gastroenteritis	5.43 (1.76, 12.66)	10.02 (7.25, 13.49)	9.21 (6.79, 12.21)
Nausea	0 (NE)	10.72 (7.85, 14.29)	8.82 (6.46, 11.77)
Constipation	14.11 (7.51, 24.13)	6.99 (4.72, 9.98)	8.25 (5.97, 11.11)
Respiratory tract infection	13.02 (6.73, 22.75)	6.52 (4.33, 9.43)	7.67 (5.48, 10.45)
Rhinitis	11.94 (5.96, 21.36)	3.96 (2.31, 6.34)	5.37 (3.57, 7.76)
Teething	14.11 (7.51, 24.13)	0 (NE)	2.49 (1.33, 4.26)

Table 54 - Adverse Event Rate Adjusted for Patient-Years at Risk

Patients	Type 1	Type 2/3	All
Time on Treatment:	(N=77)	(N=388)	(N=465)
Overall			
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	532	2479	3011
Number of Adverse Events per 100 patient-years	577.37	577.53	577.50
95% CI	(529.34, 628.58)	(555.02, 600.72)	(557.06, 598.51)
0 - <= 6 Months			
Total patient-years at risk	33.6	164.2	197.8
Number of Adverse Events	222	1255	1477
Number of Adverse Events per 100 patient-years	659.77	764.53	746.71
95% CI	(575.83, 752.50)	(722.81, 808.03)	(709.11, 785.78)
>6 - <= 12 Months			
Total patient-years at risk	28.9	100.6	129.5
Number of Adverse Events	159	521	680
Number of Adverse Events per 100 patient-years	550.32	517.81	525.06
95% CI	(468.10, 642.81)	(474.30, 564.24)	(486.33, 566.05)
>12 - <= 18 Months			
Total patient-years at risk	19.1	87.4	106.4
Number of Adverse Events	112	417	529
Number of Adverse Events per 100 patient-years	587.00	477.34	497.00
95% CI	(483.33, 706.31)	(432.62, 525.43)	(455.54, 541.21)
>18 - <= 24 Months			
Total patient-years at risk	7.8	39.4	47.2
Number of Adverse Events	30	188	218
Number of Adverse Events per 100 patient-years	385.56	476.82	461.78
95% CI	(260.13, 550.41)	(411.09, 550.07)	(402.51, 527.32)

The three **SOCs** with the highest rate of AEs by 100 PY were Infections and infestations; reported by 305 patients (65.6%) at a rate of 178.37 AEs per 100PY, Gastrointestinal disorders (39.1%) at a rate of 88.99 per 100 PY, and Nervous system disorders (81 patients; 17.4%) at a rate of 67.13 per 100PY.

In patients with Type 1 SMA, there was a trend towards higher rates of AEs compared with patients with Type 2 and 3 SMA in the SOCs Infections and infestations driven by events of upper respiratory tract infection, and General disorders and administration site conditions driven by events of pyrexia.

In patients with Type 2 and 3 SMA, rates of AEs were higher in the SOCs Nervous system disorders, Musculoskeletal and connective tissue disorders, Injury, poisoning and procedural complications, and Reproductive system and breast disorders compared with patients with Type 1 SMA. The marked differences in the SOCs Musculoskeletal and connective tissue disorders and Nervous system disorders were driven by differences in events of pain in extremity (17 patients, 20 events), arthralgia (15 patients, 21 events), back pain (14 patients, 29 events), and headache (64 patients, 291 events), which were reported mainly in patients with Type 2 and 3 SMA and rely on self-reporting that is not

expected in patients with Type 1 SMA due to their young age. No AEs were reported in the Reproductive system and breast disorders SOC in patients with Type 1 SMA who have mostly not reached sexual maturity.

Other SOCs where AEs occurred frequently in Type 2 and 3 SMA pool were Gastrointestinal disorders (38.1% [n=148], 89.93 per 100PY) and Skin and subcutaneous disorders (21.4% [n=83], 30.98 per 100PY).

Differences, some of them smaller, between the two SMA pools were observed for other less frequently reported SOCs, such as Blood and lymphatic system disorders (Type 1 SMA 8.68 vs. Type 2 and 3 SMA 3.96 per 100PY), Congenital familial and genetic disorders (4.34 vs. 0.93 per 100PY), Ear and Labyrinth disorders (1.09 vs. 5.36 per 100PY), Hepatobiliary disorders (2.17 vs. 0.70 per 100PY), Immune system disorders (1.09 vs. 2.56 per 100PY), Investigations (6.51 vs. 9.55 per 100PY), Metabolism and Nutrition disorders (9.77 vs. 6.29 per 100PY), Renal and urinary disorders (1.09 vs. 5.82 per 100PY).

A discussion in light to the extent of exposure, with AE rates decreasing over time, but no differences between the two population groups, on the differences in AE rates in Type 1 and Type 2/3 SMA populations in the four imbalanced SOCs was done. In nervous system disorders the greatest difference between the two SMA populations was in the magnitude of reported AEs of headache, all of them reported in the Type 2/3 SMA population. In musculoskeletal and connective tissue disorders the greatest differences between the two SMA populations were seen in the AEs related to pain reports (in the extremity, back pain, arthralgia, myalgia, neck pain, chest pain), more reported in Type 2/3 population. In Injury, Poisoning and Procedural Complications the difference in AE rates was driven by the AEs of contusion, all of which were reported in the Type 2/3 population. In Reproductive System and Breast Disorders, all as reported in Type 2/3 population, the most frequent AE was dysmenorrhoea and metrorrhagia.

In terms of SOCs, the results of FIREFISH (Study BP39056) and SUNFISH (Study BP39055) in terms of common AEs showed consistent results with the integrated safety analysis. Concerning the AEs by **preferred terms**, overall, in All patients with SMA, the AEs reported at the highest rates per 100 PY were headache (55.81 [95% CI: 49.58, 62.61]), pyrexia (43.15 [95% CI: 37.70, 49.18]), upper respiratory tract infection (41.62 [95% CI: 36.27, 47.54]), and nasopharyngitis (27.81 [95% CI: 23.47, 32.72]). Among AEs reported at rates ε10 per 100PY, there were higher rates of headache, nausea, and cough in patients with Type 2 and 3 SMA compared with Type 1 SMA patients. A total of 90 patients (19.4%) had an AE that had not resolved by the CCOD, 6 patients (1.3%) had a fatal AE, and 7 patients (1.5%) had an AE with an unknown outcome. The differences in AE rates between Type 1 SMA and Type 2 and 3 SMA populations appeared to be driven mainly by differences in age; the higher rate of pneumonia in patients with Type 1 SMA may be associated with higher disease severity.

Adverse events reported with higher rates in patients with *Type 1 SMA* were pyrexia, upper respiratory tract infection, pneumonia, constipation, respiratory tract infection, rhinitis, and teething. Adverse events of teething were reported only in patients with Type 1 SMA.

Other frequently reported AEs (rate <10 per 100PY) were cough (7.8%, 8.68 per 100PY) and gastroenteritis (3.9%, 5.43 per 100PY). Among the AEs with a frequency of 2 patients or more, there were urinary tract infection, ear infection, lower respiratory tract infection, viral infection (5.2% each), respiratory failure (6.5%, 5 patients), rash (6.5%), eczema (5.2%), erythema (3.9%), rash maculo-papular (5.2%), dermatitis atopic (1.3%). Neutropenia occurred in 2 patients (2.6%).

Overall, the results of FIREFISH (Study BP39056) (Part 1 and Part 2) in terms of common AEs showed consistent results with the integrated analysis. Of note, in Part 1 among the AEs occurring in ≥10% of patients there were ear infection 4 patients (19.0%), eczema, and erythema reported in 3 patients

(14.3%) each; in Part 2, among the AEs occurring in ≥5% of patients in Part 2 there were also maculo-papular rash (4 patients, 9.8%), rash (3 patients, 7.3%). These AEs under the PT of rash, together with diarrhoea, are already reported in the proposed Table of ADRs in the SmPC section 4.8.

Given the lack of a control group in the studies on Type 1 SMA, it is not possible to draw definite conclusions on the actual drug relationship for most these AEs. The applicant provided explanations and justifications for not including some of the abovementioned AEs in the Table of ADRs in the SmPC section 4.8. According to the applicant, it is plausible that infection-related AEs, in particular infections of the respiratory tract, cough, and events related to respiratory failure, represent a consequence of the underlying more severe SMA phenotype. AEs like constipation, vomiting, urinary tract infections could be confounded by the underlying disease; ear infection was not included as ADR because no increase of this AE was observed over time with patient's age as alternative explanation. Pneumonia was not included as ADR because difference in serious events of pneumonia in SUNFISH Study could be explained by unexpectedly low rate of events in the placebo group and because events generally resolved despite ongoing treatment.

11 patients (14.3%) had at least one AE that had not resolved by the CCOD; the AE outcome was unknown for 3 patients (3.9%).

In Type 2 and 3 SMA pool, the most commonly reported AEs (>5% of frequency) were headache (16.5%, 67.79 per 100PY), pyrexia (19.1%, 32.85 per 100PY), upper respiratory tract infection (22.2%, 37.51 per 100PY), nasopharyngitis (18.3%, 29.12 per 100PY), vomiting (13.9%, 22.83 per 100PY), cough (11.9%, 20.50 per 100PY), diarrhoea (12.4%, 16.77 per 100PY), nausea (7.7%, 10.72 per 100PY), gastroenteritis (9.0%, 10.02 per 100PY), pneumonia (6.7%, 9.09 per 100PY), rash (6.4%), constipation (4.9%, 6.99 per 100PY), respiratory tract infection (5.2%, 6.52 per 100PY), and rhinitis (3.4%, 3.96 per 100PY).

Of note, headache and nausea were reported only in Type 2 and 3 SMA patients.

Urinary tract infections occurred with a <5% frequency (3.6%), pain in extremity (4.4%), arthralgia (3.9%), back pain (3.6%), dysmenorrhoea (2.8%).

Overall, the results of SUNFISH (Part 1 and blinded placebo-controlled Part 2) in terms of common AEs showed consistent results with the integrated analysis. Of note, in Part 1 among the AEs occurring in ≥15% of patients there were also oropharyngeal pain (21.6%) as well as pain in extremity (11.8%), back pain (7.8%), dysmenorrhoea (5.9%). In Part 2, AEs that occurred with a higher frequency in the risdiplam group compared with the placebo group were pyrexia (20.8% vs 16.7%), headache (20.0% vs. 16.7%), diarrhoea (16.7% vs. 8.3%); AE diarrhoea is already included in the proposed ADR Table of the SmPC section 4.8. Pyrexia could be confounded by concurrent infections. However, pyrexia and headache were reported with a 4.1% and 3.3% higher frequency in patients treated with risdiplam compared with placebo.

Other AEs occurring with a higher frequency in risdiplam group compared with placebo were: pneumonia (8.3% [10 patients], vs. 6.7% [4 patients]), viral upper respiratory tract infection (4.2% [5] vs. 1.7 [1]), gastroenteritis viral (3.3% [4] vs. 1.7% [1]), urinary tract infection (4.2 [5] vs. 0), cystitis (2.5% [3] vs. 0), mouth ulceration (4.2% [5] vs. 0), aphthous ulcer (2.5% [3] vs. 0), rash (7.5% [9] vs. 1.7% [1]), eczema (4.2% [5] vs. 1.7% [1]), erythema and rash maculo-papular, (2.5% [3] vs. 0), acne, dermatitis allergic, dry skin, rash erythematous (1.7% [2] vs. 0), migraine (2.5% [3] vs. 1.7% [1]), contusion (3.3% [4] vs. 0), fall and joint dislocation (2.5% [3] vs. 0), head injury, and ligament sprain (1.7 [2] vs. 0), arthralgia (5.0% [6] vs. 0), pain in extremity and scoliosis (3.3% [4] vs. 1.7% [1]), myalgia (2.5% [3] vs. 0), activated partial thromboplastin time prolonged (1.7% [2] vs. 0), C-reactive protein increased (1.7% [2] vs. 0), decreased appetite, dysmenorrhea (1.7% [2] vs. 0), seasonal allergy (3.3% [4] vs. 1.7% [1]).

Some of the AEs in the SOC Skin and subcutaneous tissue disorders, such as rash maculo-papular, erythema, dermatitis, dermatitis allergic, rash erythematous are already included in the ADR Table of the SmPC section 4.8 under the PT rash.

The applicant specified that AEs in the SOC Injury, poisoning and procedural complications such as contusion, fall, joint dislocation, head injury, and ligament sprain were considered unrelated to study treatment and all resolved except for one AE of joint dislocation which is expected to have a prolonged course. Furthermore, the applicant pointed out that although the non-fracture events occurred more frequently in patients in the risdiplam arm, the rate of fracture events was comparable across both arms.

AEs like arthralgia, pain in extremity, myalgia, and scoliosis were not included by the applicant among the ADRs in the SmPC section 4.8 because they resolved despite ongoing treatment (except for events of scoliosis), did not lead to study treatment change, and were considered related to the underlying disease. Arthralgia occurred with a relatively high frequency, in 5.0% of risdiplam patients versus none in the placebo group.

The higher rate of pneumonia and upper respiratory tract infections, in general, in Type 1 SMA patients compared to Type 2 and 3 SMA patients may be related to the higher severity of the disease observed with the Type 1 SMA phenotype.

Urinary tract infection, cystitis, mouth ulceration, aphthous ulcer, occurred only in the risdiplam arm versus none in the placebo group of SUNFISH Part 2 and the last two AEs were considered related to study treatment by the investigators.

79 patients (20.4%) had at least one AE that had not resolved by the CCOD; the AE outcome was unknown for 4 patients (1.0%).

Initially there were 7 patients in the two SMA patient populations for whom AE outcome was unknown. Additional information regarding the seven patients with unknown AE outcome at the CCOD was provided: Three resolved or resolved with sequelae, 1 (nasal congestion) was reported as not recovered/not resolved, and the outcome of 3 AEs remained unknown (1 teething, 1 hepatocellular injury and 1 drooling in a deceased patient).

In the All Patients with SMA pool, the AE rate decreased over time with continued risdiplam treatment, with the highest rate of AEs observed during 0–≤6 months of treatment (746.71 per 100PY [95% CI: 709.11, 785.78]) followed by 525.06 per 100 PY [95% CI: 486.33, 566.05]) during the >6–≤12 months period. The decline in rates was observed in both the Type 1 SMA, and Type 2 and 3 SMA populations as described in the sections below.

Adverse events by intensity

The Tables below report the overall AE rate adjusted for PY at risk by severity and over time in the three pools.

Table 55

Table 16 Adverse Event Rate Adjusted for Patient-Years at Risk by NCI-CTCAE Grade

NCI-CTCAE Grade	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	532	2479	3011
Number of Adverse Events per 100 patient-years	577.37	577.58	577.50
95% CI	(529.34, 628.58)	(555.02, 600.72)	(557.06, 598.51
CTC Grade 1			
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	331	1850	2181
Number of Adverse Events per 100 patient-years	359.23	430.99	418.31
95% CI	(321.57, 400.09)	(411.58, 451.09)	(400.94, 436.24)
CTC Grade 2			
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	128	521	649
Number of Adverse Events per 100 patient-years	138.92	121.38	124.48
95% CI	(115.89, 165.17)	(111.18, 132.26)	(115.08, 134.43)
CTC Grade 3			
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	46	92	138
Number of Adverse Events per 100 patient-years	49.92	21.43	26.47
95% CI	(36.55, 66.59)	(17.28, 26.29)	(22.24, 31.27)
CTC Grade 4			
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	20	5	25
Number of Adverse Events per 100 patient-years	21.71	1.16	4.79
95% CI	(13.26, 33.52)	(0.38, 2.72)	(3.10, 7.08)
CTC Grade 5			
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	7	0	7
Number of Adverse Events per 100 patient-years	7.60	0.00	1.34
95% CI	(3.05, 15.65)	NE	(0.54, 2.77)
CTC Grade Missing			
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	0	11	11
Number of Adverse Events per 100 patient-years	0.00	2.56	2.11
95% CI	NE	(1.28, 4.59)	(1.05,3.77)

Total patient-years at risk is the sum over all patients of the time intervals (in years) from the start of risdiplam treatment to the earliest of the last treatment date or the clinical cutoff date. 95% CI for rates was constructed using exact method.
Includes AEs with onset from first dose of risdiplam up to the clinical cutoff date, excluding AEs reported during the safety follow-up period.

Source: Modified from t_ae_rt_CTC_SMA_SE.out

Table 56

Table 17 Adverse Event Rate Adjusted for Patient-Years at Risk by NCI-CTCAE Grade over Time

	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Grade 1			
0–≤6 Months	401.21 (336.39, 474.88)	588.47 (551.94, 626.79)	556.62 (524.22, 590.49)
>6–≤12 Months	359.95 (294.11, 436.15)	381.65 (344.43, 421.80)	376.81 (344.11, 411.77)
>12–≤18 Months	377.36 (295.26, 475.22)	326.24 (289.46, 366.40)	335.40 (301.51, 372.06)
>18–≤24 Months	205.63 (117.54, 333.93)	360.15 (303.35, 424.50)	334.68 (284.53, 391.13)
Grade 2			
0–≤6 Months	142.65 (105.18, 189.14)	148.64 (130.57, 168.51)	147.62 (131.17, 165.56)
>6–≤12 Months	121.14 (84.38, 168.47)	111.31 (91.66, 133.94)	113.51 (95.90, 133.41)
>12–≤18 Months	141.51 (93.26, 205.89)	122.48 (100.38, 148.01)	125.89 (105.48, 149.10)
>18–≤24 Months	167.07 (88.96, 285.70)	96.38 (68.20, 132.29)	108.03 (80.44, 142.04)
Grade 3			
0–≤6 Months	65.38 (40.97, 98.99)	25.59 (18.44, 34.58)	32.36 (24.92, 41.32)
>6–≤12 Months	48.46 (26.49, 81.30)	20.87 (12.92, 31.90)	27.03 (18.82, 37.59)
>12–≤18 Months	47.17 (21.57, 89.54)	22.89 (13.98, 35.36)	27.25 (18.25, 39.13)
>18–≤24 Months	12.85 (0.33, 71.61)	20.29 (8.76, 39.98)	19.06 (8.72, 36.19)
Grade 4			
0–≤6 Months	38.64 (20.57, 66.07)	0.61 (0.02, 3.39)	7.08 (3.87, 11.88)
>6–≤12 Months	13.84 (3.77, 35.45)	3.98 (1.08, 10.18)	6.18 (2.67, 12.17)
>12–≤18 Months	15.72 (3.24, 45.95)	0.00 NE	2.82 (0.58, 8.24)
>18–≤24 Months	0.00 NE	0.00 NE	0.00 NE
>18–≤24 Months	0.00 NE	0.00 NE	0.00 NE
Grade 5			
0–≤6 Months	11.89 (3.24, 30.44)	0.00 NE	2.02 (0.55, 5.18)
>6–≤12 Months	13.84 (3.77, 35.45)	0.00 NE	6.18 (2.67, 12.17)
>12–≤18 Months	5.24 (0.13, 29.20)	0.00 NE	0.94 (0.02, 5.23)
>18–≤24 Months	0.00 NE	0.00 NE	0.00 NE

In the *All SMA Patient Population*, Grade ≥3 AEs were reported in 18.9% of patients at a rate of 26.47 per 100PY and were most commonly reported in the SOC Infection and Infestations and in the Type 1 SMA patients compared with the Type 2 and 3 SMA patients that instead experienced Grade 1 AEs more frequently.

Indeed, in Type 1 SMA patients, Grade 1 and 2 AEs occurred in 48.1% of patients (359.23 and 138.92 per 100PY, respectively), while Grade ≥3 AEs were reported in 45.5% of patients with a higher percentage for Grade 3 AEs (49.92, 21.71, and 7.60 per 100PY for Grade 3, 4 and 5, respectively). Grade ≥3 AEs occurred more frequently in the SOC Infections and Infestations (31.47, 7.60, and 4.34 per 100PY for Grade 3, 4, and 5, respectively). AEs of all grades declined over time particularly Grade 4 and 5 AEs.

In Type 2 and 3 SMA patients, Grade 1 and 2 AEs occurred in the majority of patients (68.8%) (430.99 and 121.38 per 100PY, respectively), while Grade 3 or 4 AEs were reported in 13.7% of patients (21.43, and 1.16 per 100PY for Grade 3 and 4, respectively). There were no Grade 5 AEs in this patient population. Grade ≥3 AEs occurred more frequently in the SOC Infections and Infestations (10.95 and 0.47 per 100PY for Grade 3 and 4, respectively). AEs of all grades declined over time particularly Grade 1 and 2 AEs while Grade 3 and 4 AEs remained relatively stable over time.

Adverse Events by Relationship to Study Treatment

The majority of AEs were reported as unrelated to study treatment. In the All Patients with SMA population, 65 patients (14.0%) had at least 1 AE that was reported as related to study treatment, and a total of 100 related AEs were reported. The rate of AEs reported as related to study treatment was 19.18 per 100PY (95% CI: 15.61, 23.33) and was comparable in both SMA populations. Overall, 3.3% of all reported AEs were reported as related. The rate of AEs reported as related to study treatment was 19.18 per 100PY (95% CI: 15.61, 23.33), and comparable between patients with Type 1 SMA and patients with Type 2 and 3 SMA.

Table 57

Adverse Events Related to Study Treatment, by SMA Type, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety - EMA Filing 2020

MedDRA System Organ Class MedDRA Preferred Term	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Total number of patients with at least one adverse event	9 (11.7%)	56 (14.4%)	65 (14.0%)
Overall total number of events	15	85	100
Gastrointestinal disorders			
Total number of patients with at least one adverse event	3 (3.9%)	23 (5.9%)	26 (5.6%)
Total number of events	3	31	34
Diarrhoea	1 (1.3%)	8 (2.1%)	9 (1.9%)
Nausea	0	7 (1.8%)	7 (1.5%)
Abdominal pain	0	3 (0.8%)	3 (0.6%)
Aphthous ulcer	0	3 (0.8%)	3 (0.6%)
Constipation	2 (2.6%)	0	2 (0.4%)
Mouth ulceration	0	2 (0.5%)	2 (0.4%)
Abdominal discomfort	0	1 (0.3%)	1 (0.2%)
Abdominal pain upper	0	1 (0.3%)	1 (0.2%)
Faeces soft	0	1 (0.3%)	1 (0.2%)
Oral mucosal erythema	0	1 (0.3%)	1 (0.2%)
Vomiting	0	1 (0.3%)	1 (0.2%)
Skin and subcutaneous tissue disorders			
Total number of patients with at least one adverse event	4 (5.2%)	14 (3.6%)	18 (3.9%)
Total number of events	5	20	25
Rash	0	5 (1.3%)	5 (1.1%)
Dry skin	0	3 (0.8%)	3 (0.6%)
Rash maculo-papular	2 (2.6%)	1 (0.3%)	3 (0.6%)
Skin discolouration	2 (2.6%)	1 (0.3%)	3 (0.6%)
Skin exfoliation	0	2 (0.5%)	2 (0.4%)
Dermatitis acneiform	0	1 (0.3%)	1 (0.2%)
Eczema	0	1 (0.3%)	1 (0.2%)
Erythema	0	1 (0.3%)	1 (0.2%)
Hyperhidrosis	0	1 (0.3%)	1 (0.2%)
Hyperkeratosis	0	1 (0.3%)	1 (0.2%)
Livedo reticularis	0	1 (0.3%)	1 (0.2%)
Macule	1 (1.3%)	0	1 (0.2%)
Palmar erythema	0	1 (0.3%)	1 (0.2%)
Pruritus	0	1 (0.3%)	1 (0.2%)

Investigations			
Total number of patients with at least one adverse event	1 (1.3%)	7 (1.8%)	8 (1.7%)
Total number of events	2	9	11
Weight increased	0	2 (0.5%)	2 (0.4%)
Amylase increased	0	1 (0.3%)	1 (0.2%)
Aspartate aminotransferase increased	1 (1.3%)	0	1 (0.2%)
Hepatic enzyme increased	0	1 (0.3%)	1 (0.2%)
International normalised ratio increased	0	1 (0.3%)	1 (0.2%)
Lipase increased	0	1 (0.3%)	1 (0.2%)
Neutrophil count decreased	1 (1.3%)	0	1 (0.2%)
Pancreatic enzymes increased	0	1 (0.3%)	1 (0.2%)
Platelet count increased	0	1 (0.3%)	1 (0.2%)
Prothrombin time prolonged	0	1 (0.3%)	1 (0.2%)
Nervous system disorders			
Total number of patients with at least one adverse event	0	7 (1.8%)	7 (1.5%)
Total number of events	0	7	7
Headache	0	5 (1.3%)	5 (1.1%)
Dizziness	0	2 (0.5%)	2 (0.4%)
Infections and infestations			
Total number of patients with at least one adverse event	1 (1.3%)	4 (1.0%)	5 (1.1%)
Total number of events	1	4	5
Upper respiratory tract infection	1 (1.3%)	2 (0.5%)	3 (0.6%)
Gastroenteritis	0	1 (0.3%)	1 (0.2%)
Gastroenteritis viral	0	1 (0.3%)	1 (0.2%)
Cardiac disorders			
Total number of patients with at least one adverse event	0	4 (1.0%)	4 (0.9%)
Total number of events	0	4	4
Cyanosis	0	1 (0.3%)	1 (0.2%)
Palpitations	0	1 (0.3%)	1 (0.2%)
Supraventricular tachycardia	0	1 (0.3%)	1 (0.2%)
Tachycardia	0	1 (0.3%)	1 (0.2%)
Blood and lymphatic system disorders			
Total number of patients with at least one adverse event	3 (3.9%)	0	3 (0.6%)
Total number of events	3	0	3
Neutropenia	2 (2.6%)	0	2 (0.4%)
Eosinophilia	1 (1.3%)	0	1 (0.2%)

General disorders and administration site conditions			
Total number of patients with at least one adverse event	0	2 (0.5%)	2 (0.4%)
Total number of events	0	2	2
Fatigue	0	1 (0.3%)	1 (0.2%)
Granuloma	0	1 (0.3%)	1 (0.2%)
Metabolism and nutrition disorders			
Total number of patients with at least one adverse event	0	2 (0.5%)	2 (0.4%)
Total number of events	0	3	3
Decreased appetite	0	1 (0.3%)	1 (0.2%)
Hypercholesterolaemia	0	1 (0.3%)	1 (0.2%)
Reproductive system and breast disorders			
Total number of patients with at least one adverse event	0	2 (0.5%)	2 (0.4%)
Total number of events	0	2	2
Amenorrhoea	0	1 (0.3%)	1 (0.2%)
Menstrual disorder	0	1 (0.3%)	1 (0.2%)
Ear and labyrinth disorders			
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.2%)
Total number of events	0	1	1
Vertigo	0	1 (0.3%)	1 (0.2%)
Eye disorders			
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.2%)
Total number of events	0	1	1
Macular cyst	0	1 (0.3%)	1 (0.2%)
Psychiatric disorders			
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.2%)
Total number of events	0	1	1
Apathy	0	1 (0.3%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders			
Total number of patients with at least one adverse event	1 (1.3%)	0	1 (0.2%)
Total number of events	1	0	1
Pulmonary hypertension	1 (1.3%)	0	1 (0.2%)

Investigator text for AEs is coded using MedDRA version 22.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of risdiplam up to the clinical cutoff date, excluding AEs reported during the safety follow-up period.

Program: root/clinical_studies/RO7034067/CDPT7916/share/pool_safety_202004_MAAFiling/prod/program/t_ae.sas
Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_safety_202004_MAAFiling/prod/output/t_ae_REL_SMA_SE.out

Table 58

Table 43 Adverse Events Related to Study Treatment (Double Blind Treatment P

MedDRA System Organ Class MedDRA Preferred Term	Risdiplam (N=120)	Placebo (N=60)
Total number of patients with at least one adverse event	16 (13.3%)	6 (10.0%)
Overall total number of events	21	9
Gastrointestinal disorders		
Total number of patients with at least one adverse event	6 (5.0%)	1 (1.7%)
Total number of events	6	1
Abdominal pain upper	1 (0.8%)	1 (1.7%)
Mouth ulceration	2 (1.7%)	0
Nausea	2 (1.7%)	0
Faeces soft	1 (0.8%)	0
Skin and subcutaneous tissue disorders		
Total number of patients with at least one adverse event	6 (5.0%)	1 (1.7%)
Total number of events	6	1
Dermatitis acneiform	1 (0.8%)	0
Dermatitis herpetiformis	0	1 (1.7%)
Dry skin	1 (0.8%)	0
Eczema	1 (0.8%)	0
Rash	1 (0.8%)	0
Rash maculo-papular	1 (0.8%)	0
Skin discolouration	1 (0.8%)	0
Infections and infestations		
Total number of patients with at least one adverse event	3 (2.5%)	1 (1.7%)
Total number of events	3	2
Upper respiratory tract infection	2 (1.7%)	0
Bronchitis	0	1 (1.7%)
Gastroenteritis viral	1 (0.8%)	0
Respiratory tract infection	0	1 (1.7%)
Nervous system disorders		
Total number of patients with at least one adverse event	2 (1.7%)	1 (1.7%)
Total number of events	2	1
Headache	2 (1.7%)	1 (1.7%)
Blood and lymphatic system disorders		
Total number of patients with at least one adverse event	0	1 (1.7%)
Total number of events	0	3
Leukopenia	0	1 (1.7%)
Neutropenia	0	1 (1.7%)
Thrombocytopenia	0	1 (1.7%)
Cardiac disorders		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Palpitations	1 (0.8%)	0
Eye disorders		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	2	0
Cataract subcapsular	1 (0.8%)	0
Posterior capsule opacification	1 (0.8%)	0
Metabolism and nutrition disorders		
Total number of patients with at least one adverse event	1 (0.8%)	0
Total number of events	1	0
Hypercholesterolaemia	1 (0.8%)	0

Psychiatric disorders			
Total number of patients with at least one adverse event	0		1 (1.7%)
Total number of events		0	1
Sleep disorder	0		1 (1.7%)

Investigator text for AEs encoded using MedDRA version 22.0. Percentages are based on N in the column headings.
Only treatment emergent AEs related to study medication are displayed. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.
Only AEs onset with onset date on or after first dose and up to the completion date of the placebo controlled period are included.
Patients are grouped by initial treatment received and/or age.
Clinical Cutoff Date: 06SEP2019

Table 59 - Adverse Event Related to Study Treatment Rate Adjusted for Patient-Years at Risk

	Type 1	Type 2/3	All Patients
Time on Treatment:	(N=77)	(N=388)	(N=465)
Overall			
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	15	85	100
Number of Adverse Events per 100 patient-years	16.28	19.80	19.18
95% CI	(9.11, 26.85)	(15.82, 24.49)	(15.61, 23.33)
0 - <= 6 Months			
Total patient-years at risk	33.6	164.2	197.8
Number of Adverse Events	13	68	81
Number of Adverse Events per 100 patient-years	38.64	41.42	40.95
95% CI	(20.57, 66.07)	(32.17, 52.52)	(32.52, 50.90)
>6 - <= 12 Months			
Total patient-years at risk	28.9	100.6	129.5
Number of Adverse Events	2	8	10
Number of Adverse Events per 100 patient-years	6.92	7.95	7.72
95% CI	(0.84, 25.01)	(3.43, 15.67)	(3.70, 14.20)
>12 - <= 18 Months			
Total patient-years at risk	19.1	87.4	106.4
Number of Adverse Events	0	5	5
Number of Adverse Events per 100 patient-years	0.00	5.72	4.70
95% CI	NE	(1.86, 13.36)	(1.53, 10.96)
>18 - <= 24 Months			
Total patient-years at risk	7.8	39.4	47.2
Number of Adverse Events	0	2	2
Number of Adverse Events per 100 patient-years	0.00	5.07	4.24
95% CI	NE	(0.61, 18.32)	(0.51, 15.30)

The most frequently reported related AE by PT was diarrhoea (9 patients, 1.9%), followed by nausea (7 patients, 1.5%), rash (5 patients, 1.1%), and headache (5 patients, 1.1%). The majority of AEs resolved. The rate of AEs reported as related to study treatment decreased approximately 5.5-fold over time, between the 0–6 months period (40.95 per 100 PY [95% CI: 32.52, 50.90]) and the 6-12 months period (7.72 per 100PY [95% CI: 3.70, 14.20]). This decrease in rate of related AEs was comparable in both SMA populations.

Patients with Type 1 SMA

In the patients with Type 1 SMA, a total of 15 treatment-related AEs were reported in 9 patients (11.7%) at a rate of 16.28 per 100PY (95% CI: 9.11, 26.85). Overall 2.8% of all reported AEs were reported as related. The rate of related AEs decreased approximately 5.5-fold between the 0-6 months (38.64 per 100 PY [95% CI: 20.57; 66.07]) and 6–12 months treatment intervals (6.92 per 100 PY [95% CI: 0.84, 25.01]). No related AEs were reported after 12 months of treatment. The most frequently reported related AEs by PT were rash maculo-papular (2 patients, 2.6%), skin discoloration (2 patients, 2.6%), constipation (2 patients, 2.6%), and neutropenia (2 patients, 2.6%).

All events reported as related to risdiplam resolved or were recovering/resolving at the time of CCOD despite ongoing treatment with risdiplam. One related AE was serious (neutropenia). As regard to the AEs of skin discoloration, investigators considered these events related to study treatment.

The results on the type of AEs considered related to treatment from FIREFISH (Study BP39056) were consistent with the integrated safety analysis. In *Part 1*, 2/21 patients experienced a total of 3 AEs that were considered by the investigator as related to study medication: macule, neutropenia, and diarrhoea that resolved. In all cases the dose of risdiplam was not changed. In *Part 2*, up to the CCOD, 7/41 patients (17.1%) (enrolled at the 2 study sites in China) experienced a total of 12 related AEs: rash maculo-papular, skin discoloration, and constipation (2, 4.9% each), eosinophilia, neutropenia, upper respiratory tract infection, neutrophil count decreased, aspartate aminotransferase increased, and pulmonary hypertension (1, 2.4% each).

Patients with Type 2 and Type 3 SMA

In the patients with Type 2 and 3 SMA, a total of 85 treatment-related AEs were reported in 56 patients (14.4%) at a rate of 19.80 per 100PY (95% CI: 15.82, 24.49). Overall, 3.4% of all reported AEs were reported as related. The most frequently reported related AEs by PT were diarrhoea (8 patients, 2.1%), nausea (7 patients, 1.8%), rash (5 patients, 1.3%), and headache (5 patients, 1.3%).

Other AEs considered as treatment-related were: aphthous ulcer and dry skin (3, 0.8% each), mouth ulceration, skin exfoliation, weight increased, dizziness, upper respiratory tract infection (2, 0.5% each). As regard to dizziness, in SUNFISH Part 2 no patient in the risdiplam arm reported dizziness versus 2 patients in the placebo arm.

Most events reported as related to risdiplam resolved despite ongoing treatment with risdiplam. Fifteen AEs reported as related in 11 patients had not resolved by CCOD.

The unresolved events did not worsen over time with the exception of 3 AEs in two patients: one patient had livedo reticularis and cyanosis that went from Grade 1 to Grade 2 intensity and another patient had weight increased that also went from Grade 1 to Grade 2.

One related AE was serious (supraventricular tachycardia).

The majority of AEs were reported as unrelated to study treatment.

The results on the type of AEs considered related to treatment from SUNFISH (Study BP39055) were consistent with the results of the integrated safety analysis. In *Part 1*, a total of 20 related AEs occurred in 10/51 (19.6%): the most frequent was rash (3 patients, 5.9%); other AEs occurred in only 1 patient each (2.0%) (erythema, hyperkeratosis, palmar erythema, skin exfoliation, abdominal pain, diarrhoea, nausea, oral mucosal erythema, dizziness, headache, tachycardia, granuloma, hepatic enzyme increase, decreased appetite, amenorrhea, nasal dryness). All AEs reported as related to study medication resolved with the exception of erythema, nasal dryness, palmar erythema, skin exfoliation, rash and headache. There was no change of treatment. During the placebo-controlled period of Part 1, 16 AEs in 13 patients (All risdiplam: 9 patients; All placebo: 4 patients) occurred. The treatment-related AEs were rash (2 patients in All risdiplam vs. 0 in All Placebo group), hyperkeratosis, diarrhoea, nausea, oral mucosal erythema, hepatic enzyme increased, decreased appetite, dizziness, granuloma (1 vs. 0); tachycardia (1 vs. 1); hyperpyrexia (0 vs. 1).

In *Part 2*, during the double-blind, placebo-controlled period, 22 patients had a total of 30 related AEs. The overall percentage of patients with at least one related AE was slightly higher in the risdiplam arm compared with the placebo arm (13.3% [16] vs. 10.0% [6]): mouth ulceration, nausea, upper respiratory tract infection, headache (2 patients each, 1.7%), abdominal pain upper, dermatitis

acneiform, , eczema, rash, rash maculo-papular, skin discoloration, gastroenteritis viral, palpitations, cataract subcapsular, posterior capsule opacification, hypercholesterolemia (1 patient each). All AEs reported as related to study medication resolved without change to study medication with the exception of dry skin in 1 patient and 2 AEs of cataract in 1 patient.

Adverse Events of Special Interest (AESI)

Patients with Type 1 SMA

At the CCOD, no AESIs had been reported. No Hy's law cases were observed.

Patients with Type 2 and Type 3 SMA

Adverse events of special interest were reported in 2 patients with Type 2 and 3 SMA:

- One patient (SUNFISH Part 1) reported 2 non-serious AESIs (dyspnoea and tongue oedema). On Study Day 480 (last dose of risdiplam on Day 479), the patient (23-year-old White female, non-ambulant) woke up during the night with a sensation of tongue oedema and dyspnoea and was diagnosed with probable allergic reaction that resolved in less than 30 minutes from onset. These AEs were assessed as unrelated to risdiplam by the investigator. Treatment with risdiplam was not changed due to these events;

- Another patient (JEWELFISH) reported 4 AESIs: cyanosis (reported term acrocyanosis), livedo reticularis, pruritus generalised, and rash. The patient (46-year-old White male, ambulant) was previously enrolled in study BP29420 (MOONFISH Study on the splicing modifier RO6885247). His medical history included scoliosis and sinus bradycardia. Treatment with risdiplam was not changed due to these events. Grade 1-2 rash and pruritus generalised occurred on Day 124 and resolved. There was no change in study drug due to these events. The Investigator considered rash and pruritus generalised, to be related to risdiplam and possibly related to disease under study. The sponsor assessed that the rash and pruritus generalised resolved under continuation of risdiplam therapy which does not speak for a causal relationship with the study medication. Grade 1-2 cyanosis (acrocyanosis) and livedo reticularis occurred on Day 132. The patient presented with an episode of cutaneous blue discoloration of the distal limbs (fingers, toes, and calf); however, no pain, swelling or fever were reported. The same day, an unspecified angiological examination revealed non-serious cyanosis and livedo reticularis (for both, initial Grade 1 and extreme Grade 2). Treatment included triamcinolone acetonide for the events. Reportedly, these symptoms occurred episodically. The events of livedo reticularis and cyanosis remained unresolved at the time of clinical cut-off day (i.e., 640 days after the event onset). There was no change in study drug due to the events. The Investigator considered cyanosis and livedo reticularis, to be related to risdiplam and possibly related to disease under study. The sponsor assessed that the episodic appearance of livedo reticularis with acrocyanosis does not speak for a causal relationship with the study drug.

No Hy's law cases were observed in patients with Type 2 and 3 SMA.

Analysis of Adverse Events by Organ System or Syndrome

Effects on Epithelial Tissues

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 due to risdiplam-induced alternative splicing of other off target genes (*FoxM1* and *MADD*). 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.

Table 60

Table 22 Adverse Events in the Skin and Subcutaneous Tissue System Organ Class

MedDRA System Organ Class MedDRA Preferred Term	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Skin and subcutaneous tissue disorders Total number of patients with at least one adverse event	27 (35.1%)	83 (21.4%)	110 (23.7%)
Total number of events	38	133	171
Rash	5 (6.5%)	25 (6.4%)	30 (6.5%)
Eczema	4 (5.2%)	8 (2.1%)	12 (2.6%)
Acne	0	10 (2.6%)	10 (2.2%)
Erythema	3 (3.9%)	7 (1.8%)	10 (2.2%)
Dry skin	0	8 (2.1%)	8 (1.7%)
Rash maculo-papular	4 (5.2%)	3 (0.8%)	7 (1.5%)
Dermatitis	2 (2.6%)	2 (0.5%)	4 (0.9%)
Dermatitis allergic	2 (2.6%)	2 (0.5%)	4 (0.9%)
Dermatitis atopic	1 (1.3%)	3 (0.8%)	4 (0.9%)
Miliaria	3 (3.9%)	1 (0.3%)	4 (0.9%)
Pruritus	0	4 (1.0%)	4 (0.9%)
Rash papular	2 (2.6%)	2 (0.5%)	4 (0.9%)
Urticaria	1 (1.3%)	3 (0.8%)	4 (0.9%)
Blister	0	3 (0.8%)	3 (0.6%)
Rash erythematous	0	3 (0.8%)	3 (0.6%)
Skin discolouration	2 (2.6%)	1 (0.3%)	3 (0.6%)
Skin exfoliation	0	3 (0.8%)	3 (0.6%)
Alopecia	0	2 (0.5%)	2 (0.4%)
Dermatitis contact	0	2 (0.5%)	2 (0.4%)
Dermatitis diaper	1 (1.3%)	1 (0.3%)	2 (0.4%)
Dyshidrotic eczema	1 (1.3%)	1 (0.3%)	2 (0.4%)
Hyperhidrosis	0	2 (0.5%)	2 (0.4%)
Macule	1 (1.3%)	1 (0.3%)	2 (0.4%)
Palmar erythema	0	2 (0.5%)	2 (0.4%)
Petechiae	2 (2.6%)	0	2 (0.4%)
Seborrhoeic dermatitis	0	2 (0.5%)	2 (0.4%)
Dandruff	0	1 (0.3%)	1 (0.2%)
Decubitus ulcer	0	1 (0.3%)	1 (0.2%)
Dermatitis acneiform	0	1 (0.3%)	1 (0.2%)
Ecchymosis	0	1 (0.3%)	1 (0.2%)
Eczema nummular	0	1 (0.3%)	1 (0.2%)
Hair growth abnormal	0	1 (0.3%)	1 (0.2%)
Hair texture abnormal	0	1 (0.3%)	1 (0.2%)
Hyperkeratosis	0	1 (0.3%)	1 (0.2%)
Hypertrichosis	0	1 (0.3%)	1 (0.2%)
Lichen planus	0	1 (0.3%)	1 (0.2%)
Livedo reticularis	0	1 (0.3%)	1 (0.2%)
Papule	0	1 (0.3%)	1 (0.2%)
Pityriasis rosea	0	1 (0.3%)	1 (0.2%)
Seborrhoea	0	1 (0.3%)	1 (0.2%)
Skin disorder	0	1 (0.3%)	1 (0.2%)
Skin erosion	0	1 (0.3%)	1 (0.2%)
Skin induration	0	1 (0.3%)	1 (0.2%)
Skin lesion	0	1 (0.3%)	1 (0.2%)
Skin odour abnormal	0	1 (0.3%)	1 (0.2%)
Urticaria aquagenic	0	1 (0.3%)	1 (0.2%)

Investigator text for AEs is coded using MedDRA version 22.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of risdiplam up to the clinical cutoff date, excluding AEs reported during the safety follow-up period.

In the All Patients with SMA population, 171 AEs in the SOC Skin and subcutaneous tissue disorders were reported in 110 patients (23.7%) at a rate of 32.80 per 100PY (95% CI: 28.07, 38.10).

Twenty-five AEs in 18 patients (3.9%) were reported as related to study treatment; all except 4 events in 2 patients (livedo reticularis, palmar erythema, erythema, and skin exfoliation) resolved despite ongoing treatment with risdiplam.

Fourteen patients (3.0%) had at least 1 AE that had not resolved by the CCODs for this analysis; these were: 5 cases of acne and one case each of: dermatitis, dermatitis atopic, dry skin, dyshidrotic eczema, erythema, hair growth abnormal, hypertrichosis, livedo reticularis, palmar erythema, seborrhoeic dermatitis, skin disorder, skin exfoliation, skin odour abnormal.

Unresolved skin events did not lead to a change in study medication and did not worsen despite ongoing treatment, with the exception of livedo reticularis, which was reported in one patient with multiple skin related AEs which were reported as related to study medication. The event of mild dry skin with onset on Day 18 resolved without change to study medication after 39 days. The events of moderate pruritus and rash with onset on Day 124 resolved without change to study medication after 7 days. On Study Day 132 the patient reported with moderate livedo reticularis associated with moderate cyanosis in fingers (coding to SOC cardiac disorders and reported verbatim as acrocyanosis) with a chronic intermittent course, unresolved at CCOD and considered possibly secondary to vascular manifestations of SMA.

An approximately 2-fold decline in the rate of AEs in the SOC Skin and subcutaneous tissue disorders was observed over time from 55.11 per 100PY (95% CI: 45.25, 66.47) in the first 6 months of treatment to 27.03 per 100PY (95% CI: 18.82, 37.59) during the >6–≤12 months period, after which the rate appeared to stabilise, at 19.73 per 100PY (95% CI: 12.21, 30.16) during the >12–≤18 months period. This decline, which is more pronounced than for overall AEs, may be in part due to patients getting older given that skin related AEs were generally declining with age in patients below 18 years of age.

In a young population such as that affected by Type 1 and Type 2 and 3 SMA, skin-related disorders can be frequent compared with older subjects. However, in the double-blind, placebo-controlled SUNFISH Part 2 there is a higher frequency (approximately 3-fold higher) of epithelial tissue-related AEs in patients receiving risdiplam compared with those receiving placebo (30.8% vs. 11.7%). AEs reported in more than 1 patient from this SOC in the risdiplam arm were rash (9 patients), eczema (5 patients), erythema (3 patients), rash maculo-papular (3 patients) and (in 2 patients each) acne, dermatitis allergic, dry skin, and rash erythematous. In the placebo arm, all AEs were single occurrences. All events were mild to moderate in intensity and none of the events were reported as a SAE or led to a change in study medication. Events were mostly reported as unrelated to study medication with the exception of 6 events in 6 patients in the risdiplam arm (dermatitis acneiform, dry skin, eczema, rash, rash maculo-papular and skin discolouration) and 1 event in one patient in the placebo arm (dermatitis herpetiformis). Events resolved in most patients with the exception of 7 patients in the risdiplam arm and 1 patient in the placebo arm. AEs which were unresolved at the CCOD are events expected to have a prolonged course: acne, dry skin, seborrheic dermatitis, dermatitis contact, dyshidrotic eczema, hair growth abnormal, pityriasis rosea, intertrigo (this last in the placebo arm), all reported as unrelated to study treatment.

Some of these AEs are already included in the ADRs Table of the SmPC section 4.8 under the PT "rash". Other AEs occurred in only 1 or 2 patients in the risdiplam arm versus none in the placebo arm (particularly skin discolouration but also eczema, skin erosion, dry skin, dermatitis atopic, hair growth abnormal, pruritus, pityriasis rosea, etc.) can be suggestive of an effect of risdiplam on skin and epithelial tissues in general.

Ophthalmology Adverse Events

In a 39-week study in cynomolgus monkeys, retinal toxicity was observed in all animals at exposures above the no-observed-adverse-effect level (NOAEL) i.e., at approximately 2-fold the exposures observed at the pivotal dose selected for patients with SMA. These consisted of **peripheral photoreceptor loss and hyper-reflective retinal pigment epithelium** which was not fully reversible as well as, at higher exposures, reversible **microcystic macular degeneration** in the macula. The expected initial clinical symptoms of such structural changes in the peripheral retina would be impaired night vision or loss of peripheral vision. Blindness was not observed in any of the monkeys even at high doses (approximately 4 times the exposures achieved at the pivotal dose in patients with SMA) after 9 months of daily administration of risdiplam. These findings were not observed in albino or pigmented rats when dosed chronically with risdiplam at exposures exceeding those administered to monkeys.

Due to this nonclinical finding, a comprehensive panel of ophthalmological assessments was performed in all clinical studies in SMA patients, including imaging to detect structural changes of the retina, and visual function testing to detect potential functional impairment in central or peripheral vision.

Duration of Ophthalmological Follow-Up

In general, over 90% of the 465 patients successfully completed their SD-OCT assessments as scheduled.

Duration of ophthalmological follow-up was:

- 386 patients at least 8 weeks
- 330 patients at least 6 months (26 weeks)
- 243 patients at least 1 year (52 weeks)
- 72 patients at least 2 years (104 weeks)
- 12 patients completed 3 years (156 weeks)

The longest duration of follow-up in patients aged 7 months or less at enrollment was 2 years and 9 months (143 weeks).

Review of Numerical Parameters Over Time

While for the younger patients, assessments relied on overall interpretation by the ophthalmologist, numerical results for the following assessments were available from the patients who were able to perform the more difficult assessments: at least 70% of patients for SD-OCT, BCVA and IOP, and approximately 50% of patients Visual field threshold perimetry:

Retinal imaging:

- SD-OCT assessment with PPole and Cross hair scans: macular volume and retinal thickness

Visual field:

- Threshold perimetry: fixation losses, threshold sensitivities across the visual field, mean deviation, and pattern standard deviation

Visual acuity:

- BCVA: LogMar score, number of optotypes
- Sloan LCVA: contrast sensitivity and total number of letters correctly read

IOP

Table 61 - Adverse Events in Eye Disorders System Organ Class

MedDRA System Organ Class MedDRA Preferred Term	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Eye disorders			
Total number of patients with at least one adverse event	5 (6.5%)	24 (6.2%)	29 (6.2%)
Total number of events	6	27	33
Ocular hyperaemia	0	4 (1.0%)	4 (0.9%)
Vision blurred	0	4 (1.0%)	4 (0.9%)
Dry eye	0	3 (0.8%)	3 (0.6%)
Conjunctival hyperaemia	2 (2.6%)	0	2 (0.4%)
Eye pain	0	2 (0.5%)	2 (0.4%)
Lacrimation increased	0	2 (0.5%)	2 (0.4%)
Macular cyst	1 (1.3%)	1 (0.3%)	2 (0.4%)
Asthenopia	0	1 (0.3%)	1 (0.2%)
Blepharitis	0	1 (0.3%)	1 (0.2%)
Conjunctivitis allergic	0	1 (0.3%)	1 (0.2%)
Corneal infiltrates	0	1 (0.3%)	1 (0.2%)
Eczema eyelids	0	1 (0.3%)	1 (0.2%)
Eye allergy	0	1 (0.3%)	1 (0.2%)
Eye discharge	0	1 (0.3%)	1 (0.2%)
Eye pruritus	0	1 (0.3%)	1 (0.2%)
Eyelid disorder	0	1 (0.3%)	1 (0.2%)
Heterophoria	1 (1.3%)	0	1 (0.2%)
Photopsia	0	1 (0.3%)	1 (0.2%)
Retinal exudates	1 (1.3%)	0	1 (0.2%)
Strabismus	1 (1.3%)	0	1 (0.2%)
Visual impairment	0	1 (0.3%)	1 (0.2%)

Results:

All SMA Patients

Overall, 33 AEs in the SOC Eye disorders were reported in 29 patients (6.2%) in the All Patients with SMA population.

Patients with Type 1 SMA

Overall, 6 AEs in the SOC Eye disorders were reported in 5 patients (6.5%). All AEs were mild, reported as unrelated to study medication, and resolved without change to risdiplam treatment, with the exception of 2 AEs in 2 patients: 1 AE of moderate strabismus at Month 20, in FIREFISH, considered as unrelated; 1 AE of moderate heterophoria in both eyes at Month 12, in FIREFISH.

Patients with Type 2 and Type 3 SMA

Overall, 27 AEs in the SOC Eye disorders were reported in 24 patients (6.2%). All AEs were mild, unrelated to study medication and resolved without change of study therapy, with the exception of 7 AEs reported in 6 patients. One patient had an AE of mild visual impairment unresolved at the CCOD (minimal decrease in sight, -0.5 dioptries) with an onset on Study Day 324 and no corresponding findings were reported in other ophthalmological tests. It was assessed as unrelated to risdiplam and had not resolved at CCOD, glasses were recommended. 1 AE of moderate dry eye (onset on Day 266) resolved and considered unrelated without corresponding findings at ophthalmological assessments; 1

AE of moderate lacrimation increased, resolved; 1 AE of moderate eye allergy, resolved; 1 AE of moderate corneal infiltrates with lamp examination showing corneal infiltrates in the left eye, subsequently resolved; 1 macular cyst detected on SD-OCT assessment reported as related to study treatment that was not confirmed at subsequent assessments;

In addition to the AEs in the SOC of Eye disorders, there was another eye-related AE which had not resolved, in the SOC of Neoplasms: one patient had an AE of mild eye naevus (conjunctival naevus in the right eye) with onset Day 15 which remained unresolved and was assessed as unrelated to study therapy.

In the double-blind, placebo-controlled SUNFISH *Part 2*, more patients in the placebo group had AEs in the SOC Eye disorders compared with risdiplam arm (10.0% vs. 6.7%). The AEs that occurred in at least 1 patient of the risdiplam group versus none in the placebo group were: cataract subcapsular, eye pruritus, eyelid disorder, ocular hyperaemia, posterior capsular opacification, vision blurred, visual impairment (1 each vs. 0). All events were reported as unrelated to study treatment and resolved except for 3 AEs in 2 patients: 1 mild AE of visual impairment, already mentioned above, considered unrelated to treatment in a patient that lost 0.5 dioptries and was advised to wear glasses in the absence of findings observed at OCT and with a subsequent BCVA improved compared to baseline; 2 mild events of cataract subcapsular and posterior capsule opacification both reported as related to treatment, but not confirmed at subsequent assessment made after CCOD.

Serious adverse events and deaths

A total of 103 patients (22.2%) in the All Patients with SMA population reported 194 SAEs. The rate of SAEs per 100PY was 37.21 (95% CI: 32.16, 42.83). Serious AEs were most commonly reported in the SOC Infections and infestations; at a rate of 21.10 per 100PY (95% CI: 17.34, 25.43) and in the Respiratory, thoracic and mediastinal disorders with a rate of 6.14 per 100PY (95% CI: 4.20, 8.66). No SAEs were reported in the SOCs Skin and subcutaneous tissue disorders or Eye disorders.

Table 62

Table 20 Serious Adverse Events by System Organ Class

Serious Adverse Events, by SMA Type, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety - EMA Filing 2020

MedDRA System Organ Class MedDRA Preferred Term	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Total number of patients with at least one adverse event	42 (54.5%)	61 (15.7%)	103 (22.2%)
Overall total number of events	86	108	194
Infections and infestations			
Total number of patients with at least one adverse event	33 (42.9%)	40 (10.3%)	73 (15.7%)
Total number of events	49	61	110
Pneumonia	18 (23.4%)	17 (4.4%)	35 (7.5%)
Upper respiratory tract infection	3 (3.9%)	4 (1.0%)	7 (1.5%)
Influenza	2 (2.6%)	4 (1.0%)	6 (1.3%)
Lower respiratory tract infection	3 (3.9%)	2 (0.5%)	5 (1.1%)
Respiratory tract infection	3 (3.9%)	2 (0.5%)	5 (1.1%)
Gastroenteritis	1 (1.3%)	3 (0.8%)	4 (0.9%)
Viral upper respiratory tract infection	2 (2.6%)	2 (0.5%)	4 (0.9%)
Respiratory tract infection viral	3 (3.9%)	0	3 (0.6%)
Bacteraemia	0	2 (0.5%)	2 (0.4%)
Bronchiolitis	2 (2.6%)	0	2 (0.4%)
Bronchitis	1 (1.3%)	1 (0.3%)	2 (0.4%)
Pneumonia bacterial	1 (1.3%)	1 (0.3%)	2 (0.4%)
Pneumonia mycoplasmal	0	2 (0.5%)	2 (0.4%)
Pneumonia viral	1 (1.3%)	1 (0.3%)	2 (0.4%)
Appendicitis	0	1 (0.3%)	1 (0.2%)
Device related infection	0	1 (0.3%)	1 (0.2%)
Encephalitis	0	1 (0.3%)	1 (0.2%)
Escherichia urinary tract infection	1 (1.3%)	0	1 (0.2%)
Gastrointestinal infection	0	1 (0.3%)	1 (0.2%)
Herpes zoster	0	1 (0.3%)	1 (0.2%)
Infective thrombosis	0	1 (0.3%)	1 (0.2%)
Laryngitis	0	1 (0.3%)	1 (0.2%)
Lower respiratory tract infection viral	0	1 (0.3%)	1 (0.2%)
Pharyngitis	1 (1.3%)	0	1 (0.2%)
Pyelonephritis	0	1 (0.3%)	1 (0.2%)
Tracheitis	1 (1.3%)	0	1 (0.2%)
Tracheobronchitis	1 (1.3%)	0	1 (0.2%)

Metabolism and nutrition disorders			
Total number of patients with at least one adverse event	4 (5.2%)	4 (1.0%)	8 (1.7%)
Total number of events	5	4	9
Dehydration	2 (2.6%)	2 (0.5%)	4 (0.9%)
Decreased appetite	1 (1.3%)	1 (0.3%)	2 (0.4%)
Acidosis	0	1 (0.3%)	1 (0.2%)
Failure to thrive	1 (1.3%)	0	1 (0.2%)
Hypoglycaemia	1 (1.3%)	0	1 (0.2%)
Cardiac disorders			
Total number of patients with at least one adverse event	3 (3.9%)	2 (0.5%)	5 (1.1%)
Total number of events	3	2	5
Cardiac arrest	2 (2.6%)	0	2 (0.4%)
Atrial fibrillation	0	1 (0.3%)	1 (0.2%)
Sinus tachycardia	1 (1.3%)	0	1 (0.2%)
Supraventricular tachycardia	0	1 (0.3%)	1 (0.2%)
Nervous system disorders			
Total number of patients with at least one adverse event	3 (3.9%)	2 (0.5%)	5 (1.1%)
Total number of events	3	2	5
Hypotonia	2 (2.6%)	0	2 (0.4%)
Febrile convulsion	0	1 (0.3%)	1 (0.2%)
Hydrocephalus	1 (1.3%)	0	1 (0.2%)
Partial seizures	0	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions			
Total number of patients with at least one adverse event	0	4 (1.0%)	4 (0.9%)
Total number of events	0	4	4
Pyrexia	0	3 (0.8%)	3 (0.6%)
Medical device pain	0	1 (0.3%)	1 (0.2%)
Musculoskeletal and connective tissue disorders			
Total number of patients with at least one adverse event	0	2 (0.5%)	2 (0.4%)
Total number of events	0	2	2
Back pain	0	1 (0.3%)	1 (0.2%)
Kyphoscoliosis	0	1 (0.3%)	1 (0.2%)
Renal and urinary disorders			
Total number of patients with at least one adverse event	0	2 (0.5%)	2 (0.4%)
Total number of events	0	3	3
Haematuria	0	1 (0.3%)	1 (0.2%)
Hydronephrosis	0	1 (0.3%)	1 (0.2%)
Nephrolithiasis	0	1 (0.3%)	1 (0.2%)

Respiratory, thoracic and mediastinal disorders			
Total number of patients with at least one adverse event	13 (16.9%)	7 (1.8%)	20 (4.3%)
Total number of events	22	10	32
Respiratory failure	4 (5.2%)	1 (0.3%)	5 (1.1%)
Atelectasis	2 (2.6%)	2 (0.5%)	4 (0.9%)
Respiratory distress	3 (3.9%)	1 (0.3%)	4 (0.9%)
Acute respiratory failure	3 (3.9%)	0	3 (0.6%)
Pneumonia aspiration	2 (2.6%)	1 (0.3%)	3 (0.6%)
Aspiration	1 (1.3%)	1 (0.3%)	2 (0.4%)
Asthma	0	1 (0.3%)	1 (0.2%)
Bronchial secretion retention	1 (1.3%)	0	1 (0.2%)
Chronic respiratory failure	0	1 (0.3%)	1 (0.2%)
Hypoxia	1 (1.3%)	0	1 (0.2%)
Pneumothorax	1 (1.3%)	0	1 (0.2%)
Respiratory tract inflammation	1 (1.3%)	0	1 (0.2%)
Sleep apnoea syndrome	1 (1.3%)	0	1 (0.2%)
Injury, poisoning and procedural complications			
Total number of patients with at least one adverse event	0	9 (2.3%)	9 (1.9%)
Total number of events	0	10	10
Femur fracture	0	3 (0.8%)	3 (0.6%)
Brain contusion	0	1 (0.3%)	1 (0.2%)
Concussion	0	1 (0.3%)	1 (0.2%)
Contusion	0	1 (0.3%)	1 (0.2%)
Fall	0	1 (0.3%)	1 (0.2%)
Femoral neck fracture	0	1 (0.3%)	1 (0.2%)
Near drowning	0	1 (0.3%)	1 (0.2%)
Tibia fracture	0	1 (0.3%)	1 (0.2%)
Gastrointestinal disorders			
Total number of patients with at least one adverse event	1 (1.3%)	7 (1.8%)	8 (1.7%)
Total number of events	1	9	10
Vomiting	1 (1.3%)	3 (0.8%)	4 (0.9%)
Gastritis	0	2 (0.5%)	2 (0.4%)
Constipation	0	1 (0.3%)	1 (0.2%)
Nausea	0	1 (0.3%)	1 (0.2%)
Oesophagitis	0	1 (0.3%)	1 (0.2%)

Blood and lymphatic system disorders			
Total number of patients with at least one adverse event	1 (1.3%)	0	1 (0.2%)
Total number of events	1	0	1
Neutropenia	1 (1.3%)	0	1 (0.2%)
Congenital, familial and genetic disorders			
Total number of patients with at least one adverse event	1 (1.3%)	0	1 (0.2%)
Total number of events	1	0	1
Cryptorchism	1 (1.3%)	0	1 (0.2%)
Investigations			
Total number of patients with at least one adverse event	1 (1.3%)	0	1 (0.2%)
Total number of events	1	0	1
Weight decreased	1 (1.3%)	0	1 (0.2%)
Surgical and medical procedures			
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.2%)
Total number of events	0	1	1
Lung operation	0	1 (0.3%)	1 (0.2%)

Investigator text for AEs is coded using MedDRA version 22.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of risdiplam up to the clinical cutoff date, excluding AEs reported during the safety follow-up period.

Table 63

Table 21 Serious Adverse Event Rate Adjusted for Patient-Years at Risk

Time on Treatment:	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Overall			
Total patient-years at risk	92.1	429.2	521.4
Number of Adverse Events	86	108	194
Number of Adverse Events per 100 patient-years	93.33	25.16	37.21
95% CI	(74.66, 115.27)	(20.64, 30.38)	(32.16, 42.83)
0 - <= 6 Months			
Total patient-years at risk	33.6	164.2	197.8
Number of Adverse Events	45	39	84
Number of Adverse Events per 100 patient-years	133.74	23.76	42.47
95% CI	(97.55, 178.95)	(16.89, 32.48)	(33.87, 52.58)
>6 - <= 12 Months			
Total patient-years at risk	28.9	100.6	129.5
Number of Adverse Events	25	27	52
Number of Adverse Events per 100 patient-years	86.53	26.83	40.15
95% CI	(56.00, 127.73)	(17.68, 39.04)	(29.99, 52.65)
>12 - <= 18 Months			
Total patient-years at risk	19.1	87.4	106.4
Number of Adverse Events	12	28	40
Number of Adverse Events per 100 patient-years	62.89	32.05	37.58
95% CI	(32.50, 109.86)	(21.30, 46.32)	(26.85, 51.17)
>18 - <= 24 Months			
Total patient-years at risk	7.8	39.4	47.2
Number of Adverse Events	2	8	10
Number of Adverse Events per 100 patient-years	25.70	20.29	21.18
95% CI	(3.11, 92.85)	(8.76, 39.98)	(10.16, 38.96)

Total patient-years at risk is the sum over all patients of the time intervals (in years) from the start of risdiplam treatment to the earliest of the
last treatment date or the clinical cutoff date. 95% CI for rates was constructed using exact method.
Includes AEs with onset from first dose of risdiplam up to the clinical cutoff date, excluding AEs reported during the safety follow-up period.
Modified from: t_ae_rt_SER_SMA_SE

Table 64 - Serious Adverse Events Reported per 100PY (in Any Group) by System Organ Class: SOCs with Imbalance between Type 1 and Type 2/3 SMA

MedDRA System Organ Class	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Nervous system disorders			
Rate per 100PY	3.26	0.47	0.96
95% CI	(0.67, 9.51)	(0.06, 1.68)	(0.31, 2.24)
#Patients with at least 1 SAE (%)	3 (3.9%)	2 (0.5%)	5 (1.1%)
#SAEs	3	2	5
Musculoskeletal and connective tissue disorders			
Rate per 100PY	0.00	0.47	0.38
95% CI	NE	(0.06, 1.68)	(0.05, 1.39)
#Patients with at least 1 SAE (%)	0	2 (0.5%)	2 (0.4%)
#SAEs	0	2	2
Injury, poisoning and procedural complications			
Rate per 100PY	0.00	2.33	1.92
95% CI	NE	(1.12, 4.28)	(0.92, 3.53)
#Patients with at least 1 SAE (%)	0	9 (2.3%)	9 (1.9%)
#SAEs	0	10	10

The rate of SAEs was overall approximately 3.5-fold higher in patients with Type 1 SMA (54.5% of patients, at a rate of 93.33 per 100PY [95% CI: 74.66, 115.27]) compared with patients with Type 2 and 3 SMA (15.7%, at a rate of 25.16 per 100PY [95% CI: 20.64, 30.38]. This difference was mainly driven by the higher rate of SAEs in the Type 1 SMA patients compared with Type 2 and 3 SMA patients in the SOC of Infection and Infestations (42.9% of patients vs. 10.3%, at a rate of 53.18 vs. 14.21 per 100PY) and Respiratory, thoracic and mediastinal disorders (16.9% of patients vs. 1.8%, at a rate of 23.88 vs. 2.33 per 100PY), and in particular by the AE pneumonia (23.4% [18 patients] at a rate of 23.88 per 100PY vs. 4.4% [17 patients] at a rate of 5.82 per 100PY). All SAEs pneumonia resolved except for two fatal cases in patients with Type 1 SMA.

Due to low exposure time in PY beyond 18 months, rates after 18 months should be viewed with caution. Although the rate overall was stable, a clear decline in SAE rates over time was observed in patients with Type 1 SMA. In patients with Type 2 and 3 SMA, a trend towards higher SAE rates was observed in the first 18 months of treatment followed by a decrease thereafter.

SAEs were reported as unrelated to risdiplam with the exception of:

- one patient with an SAE of neutropenia in the type 1 SMA group. The patient had a neutrophil count of $0.23 \cdot 10^9$/L (normal range: 1.5□8.5 $\cdot 10^9$/L) on Study Day 280, which occurred in the context of an SAE of pneumonia on Study Day 282. Both events resolved (neutropenia after 3 days and pneumonia after 7 days), and the dose of risdiplam was not changed as a result of these SAEs.

- and one patient in the Type 2 and 3 SMA group that had an SAE of supraventricular tachycardia, reported on study Day 49 and maximum intensity (Grade 2), occurred in the context of hypoxia secondary to a lower respiratory tract infection. It resolved without change to study medication.

SAEs that resulted in dose interruption were reported in 15 patients, with interruptions ranging from 1□19 days. Risdiplam treatment was permanently discontinued due to an AE in one patient with Type 1 SMA who discontinued risdiplam due to an AE of respiratory tract infection viral to receive palliative care 3 days prior to her death. One patient had an SAE (decreased appetite) with no outcome reported as of the CCOD. All SAEs resolved with the exception of one report of partial seizures in one patient in the Type 2 and 3 SMA group, occurring during the open-label period of the SUNFISH Part 2.

In *Type 1 SMA* pool, a total of 42 patients (54.5%) with Type 1 SMA reported 86 SAEs. Besides the abovementioned infection- and respiratory SAEs, other frequent SAEs occurring in at least 1 patient were: dehydration, cardiac arrest, hypotonia (2.6% [2]), vomiting, decreased appetite, sinus tachycardia, hydrocephalus, neutropenia, cryptorchism, weight decreased (1.3% [1]). It is plausible that most of these SAEs reflect possible complications related to the underlying disease. Two SAEs were associated with congenital abnormalities (cryptorchism and hydrocephalus).

Only one SAE, i.e. neutropenia, was considered treatment-related by the investigator: the patient had a neutrophil count of $0.23x10^9$/L (normal range: $1.5\text{-}8.5x10^9$/L) on Study Day 280, which occurred in the context of a SAE of pneumonia on Study Day 282. Both events resolved (neutropenia after 3 days and pneumonia after 7 days), and the dose of risdiplam was not changed as a result of these SAEs.

All SAEs resolved by CCOD except for the abovementioned SAE, i.e. decreased appetite, for which no outcome was reported as of CCOD. The results on the SAEs from FIREFISH (Study BP39056) were consistent with the integrated safety analysis.

In *Type 2 and 3 SMA* pool, a total of 61 patients (15.7%) reported 108 SAEs. Besides the abovementioned infection- and respiratory SAEs, other frequent SAEs occurring in at least 1 patient were: femur fracture, vomiting, pyrexia, (0.8% [3 patients]), gastritis, dehydration, (0.5% [2]), brain contusion, concussion, contusion, fall, femoral neck fracture, near drowning, tibia fracture, constipation, nausea, oesophagitis, decreased appetite, atrial fibrillation, supraventricular tachycardia, hypotonia, partial seizures, back pain, kyphoscoliosis, haematuria, hydronephrosis, nephrolithiasis (0.3% [1]).

One SAE of supraventricular tachycardia was reported in JEWELFISH study that was considered by the Investigator to be related to study treatment. Patient was previously enrolled in Study WN29836 (Olesoxime). The SAE was reported on study Day 49 and maximum intensity (Grade 2) occurred in the context of hypoxia secondary to a lower respiratory tract infection. Supraventricular tachycardia was well tolerated without hemodynamic impact and resolved with adenosine after failure of vagal manoeuvres. No ECG details were provided.

All SAEs resolved by CCOD except for 1 SAE, i.e., as mentioned above, partial seizures occurring during the open-label period of the SUNFISH Part 2. This was a case of an 11-year-old female (White) non-ambulant patient without medical history besides SMA, that on Study Day 592 presented Grade 3 partial seizures; she was hospitalised and was started on treatment with antiepileptic medications; EEG were reported as normal. The event of partial seizures remained unresolved at the time of clinical cut-off day (i.e.49 days after the event onset). There was no change in risdiplam treatment due to this event. The Investigator considered partial seizures to be unrelated to risdiplam and related to medical history or concurrent illness (suspicion of epilepsy).

The results on the SAEs from SUNFISH (Study BP39055) were consistent with the integrated safety analysis. During the double-blind, placebo-controlled period of Part 2, 20.0% of patients receiving risdiplam (24/120) and 18.3% of those receiving placebo (11/60) experienced a total of 39 and 14 SAEs, respectively (rate 32.72 vs. 23.29 per 100PY). Less patients aged 18 to 25 years had SAEs compared to those aged 2 to 18 years. SAE occurring with a higher rate in risdiplam patients compared with placebo patients or only in patients receiving risdiplam were: pneumonia (7.5% [9] vs. 1.7% [1]),

bacteraemia and influenza, pyrexia (1.7% [2] vs. 0), bronchitis, laryngitis, lower respiratory tract infection viral, pneumonia bacterial, upper respiratory tract infection, viral upper respiratory tract infection, aspiration, asthma, atelectasis, pneumonia aspiration, fall, hydronephrosis, constipation, febrile convulsion (0.8% [1] vs. 0). None of these SAEs were considered related to study treatment. SAEs leading to dose interruption occurred in 3.3% of patients in both the risdiplam and placebo arms. The rate of SAE was higher in the risdiplam arm compared with placebo in the first 6 months, then in the 6 to 12-month period declined in the risdiplam group and increased 2.5-fold in the placebo group.

Overall, in the integrated safety dataset, in All SMA Patient Population, the SAE rate was stable over the first 18 months of treatment (0-6 months: 42.47; 6-12 months: 40.15; 12-18 months: 37.58 per 100PY). Rates after 18 months should be interpreted with caution due to low exposure time in PY beyond 18 months. SAE rates declined more markedly in Type 1 SMA patients while in Type 2 and 3 SMA there was a trend towards an increase of rate in the first 18 months followed by a decrease.

Deaths

At the time of the CCOD for each study, 6 deaths had been reported during the treatment period, all of which were infants with Type 1 SMA in Study BP39056 (FIREFISH) who died of SMA-related respiratory complications (3 deaths in Part 1 and 3 deaths in Part 2; 3 females and 3 males; age range: 136-212 days at first dose [approximately, 4.5-7.0 months]); 2 White and 3 Asian, 1 patient of unknown race). One additional patient (Asian male) died 3.5 months after discontinuation from risdiplam therapy during the safety follow-up period.

The cause of death was classified as "progressive disease" in 6 out of 7 cases and as "adverse event" (pneumonia) for 1 patient. None of the deaths were considered by the investigator to be related to study treatment.

All six patients who died had advanced disease at baseline: they all had disease duration greater than 3 months at baseline and 4 patients were older than 5 months of age at first dose. 4/6 patients died within 3 months (range: 21-79 days) of starting treatment with risdiplam, prior to any efficacy assessment.

In the 2 patients and with available post-baseline efficacy assessments, there was evidence of improved motor function, as indicated by increases from baseline in the CHOP-INTEND total score).

The causes of the 6 deaths were: viral respiratory tract infection (Day 21; 3 days after receiving the last dose), cardiac arrest and respiratory failure (Day 236, approximately 8 months; 1 day after the last dose), respiratory tract infection (Day 387, approximately 1 year; 1 day after the last dose) (this is the only patient who underwent autopsy), acute respiratory failure (Day 68; 1 day after the last dose; of note, this patient was diagnosed with a Grade 1 hepatocellulary injury considered not related to risdiplam by the investigators), pneumonia (Day 51; 1 day after the last dose). All these causes of deaths were classified as "progressive disease". In 1 case of pneumonia (Day 79, 1 day after the last dose) the cause of death was classified as "adverse event".

Patient who died during the safety follow-up was an Asian male, aged 112 days at first dose, who died of cardiac arrest on Day 691 (approximately 2 years), 106 days (approximately 4 months) after receiving the last dose. The patient experienced acute airway obstruction from secretion/mucous plug which caused hypoxia and consequently cardiac arrest. The cause of death was classified as "progressive disease".

Laboratory findings

Haematological parameters

During nonclinical studies with risdiplam, bone marrow depression with decreased cell counts across all 4 blood cell lines (erythroid, granulocytic, monocytic, and megakaryocytic) were observed at exposures at least 4 times higher than the mean exposures observed in the clinical studies. At high doses, this effect occurred with high incidence due to an effect of risdiplam on alternative targets, the *MADD* and *FOXM1* genes involved in cell division and apoptosis.

Regarding haematological findings, isolated shifts in laboratory parameters were observed;

Across timepoints, the mean percentage change from baseline ranged from:

i) -20% to 37% for lymphocytes (Type 1 SMA: -22% to 11%; Type 2 and 3 SMA: -20% to 37%);

ii) -35% to 119% for neutrophils (Type 1 SMA: -4% to 424%; Type 2 and 3 SMA: -35% to 61%);

iii) -6% to 2% for erythrocytes (Type 1 SMA: -6% to 8%; Type 2 and 3 SMA: -11% to -0.5%)

iv) -13% to 50% for platelets (Type 1 SMA: -13% to 88%; Type 2 and 3 SMA: -1% to 54%)

The maximum individual decreases were observed more in the Type 1 patients compared with the Type 2 and 3 SMA patients (-93% vs. -72% for lymphocytes; -89% vs. -79% for neutrophils; -48% vs. -39% for erythrocytes; -100% vs. -95% for platelets).

The highest AE intensity was observed for lymphopenia (Grade 3 in Type 1 SMA and Grade 2 in Type 2 and 3 SMA), neutropenia (Grade 4 and Grade 3, respectively), and thrombocytopenia (Grade 4 each) in few subjects.

In *type 1 SMA* patients, 6 reported AEs suggestive of a clinically significant decline in cell lines. In particular one patient (with already low neutrophil values at screening) experienced an AE of neutropenia (onset on Day 14) reported as related to risdiplam, resolved without change to study medication after 43 days. By Day 363 the patient's neutrophil value was within the normal range. Another AE of neutropenia (Grade 4) was reported in one patient in the context of pneumonia (onset on Day 280) and was resolved after a short period by Day 294. One patient, who had already low haemoglobin values at screening, developed a Grade 2 anaemia (onset on Day 378) which was reported as unrelated to risdiplam and remained unresolved at the CCOD.

In *type 2-3 SMA* pool, 3 patients reported AEs suggestive of significant changes in laboratory parameters. One case of Grade 1 anaemia (onset on Day 611) in a patient with low haemoglobin values at baseline, considered as unrelated to risdiplam and resolved on Day 729. Another case of Grade 1 neutropenia occurred on Day 175 which resolved after 5 days despite ongoing treatment with risdiplam.

In the **double-blind placebo-controlled SUNFISH Part 2**, more patients in the risdiplam arm (10.8%) had shift from normal to low in monocyte count compared to placebo arm (3.3%) at their last assessment; however, this was not observed consistently throughout the study and was not observed for any other cell line.

In conclusion, overall the results not seem to be significant and mostly not related to the treatment, except for the patient with Type 1 SMA that had an SAE of neutropenia

Liver enzymes

No Hy's law cases were reported in patients with SMA, which was also confirmed by the liver enzyme assessments. In the All SMA Patients population, the number of patients with shifts (to low or high values) in AST, ALT or total bilirubin was low, and did not increase over time.

In *Type 1 SMA* patients, 5 patients had AST values >3x ULN at a single post-baseline visit. Their AST values were elevated at baseline and remained elevated at all post-baseline visits. 3 patients with increased AST/ALT >3xULN did not have an associated AE: in 1 patient, the liver enzyme increase along with a concurrent decreased neutrophil count were considered related to risdiplam treatment, both resolved without change to study medication; in 1 patient, a mild hepatocellular injury occurred on Day 58 with AST and ALT <1.5xULN with an unknown outcome, the patient died of respiratory failure probably consequent to a respiratory tract infection; another patient, who had previously received nusinersen, had an increase in ALT levels >3xULN post-baseline, the patient developed a SAE of upper respiratory tract infection.

In *Type 2 and 3 SMA* patients, the highest abnormal high value was Grade 3 (>5xULN) for ALT and below Grade 2 (<3xULN) for AST. 4 patient had increased AST/ALT >2xULN without an associated AE: 1 patient had a significant Grade 3 increase in ALT >5x ULN and AST >2x ULN but below 3xULN on Day 56, both values had returned to baseline levels on Day 118 and treatment with risdiplam was not changed; 1 patient developed ALT above 2 x ULN twice, on Study Day 484 in the context of an AE of hand-foot-and-mouth disease and on Study Day 911 when patient had just recovered from an episode of gastroenteritis; 1 patient, in the previous treatment group olesoxime had an increase in ALT levels >3xULN at baseline and remained >2-3x ULN throughout the study; 1 patient, who in the previous treatment group RO6885247 had an increase in ALT levels >5x ULN post-baseline, had a significant increase in ALT >5x ULN and AST >2x ULN on Day 56, both values returned to baseline levels thereafter through to study day 367.

AEs associated with liver enzymes occurred in 4 patients: 1 patient had mild hepatic enzymes increased on Day 121 which resolved without change to study medication; 1 patient, who in the previous group olesoxime had an increase in ALT levels >3xULN postbaseline, with hepatic enzymes already elevated at baseline, had a further increase on Day 14 and was reported with AEs of ALT/AST increased unrelated to study medication and resolved after 2 weeks without change to study medication; 1 patient, who previously was in the treatment group R06885247, had a mild unrelated AE of hepatic enzyme increased on Day 187 that resolved 3 days later; 1 patient had mild lipase and amylase elevations on Day 186 that resolved.

During the double-blind, placebo-controlled period of SUNFISH *Part 2*, 2 patients in each arm had ALT >3x ULN, one additional patient had ALT >3x ULN during the open-label treatment phase in the risdiplam arm.

Vital signs

Tachypnea and tachycardia were observed throughout the study in some patients, including at baseline in patients with Type 1 SMA. In patients with Type 2 and 3 SMA, isolated shifts in pulse rate were observed at isolated timepoints. Shifts in other vital signs (body temperature, blood pressure [systolic and diastolic]) were observed; however, the percentage of patients with shifts toward higher values and shifts toward lower values was similar and did not increase over time.

ECG

As of the CCODs for this analysis, there were few clinically significant changes from baseline in ECG parameters.

The percentage of patients with average QT, QTcB or QTcF above 450 ms, or change from baseline above 30 ms, was low and did not increase with time. The prolonged QT intervals were mostly associated with isolated outliers in triplicate QT interval measurement on one or two of the three ECGs obtained per timepoint. No relevant differences were reported between risdiplam and placebo arms in the double-blind, controlled period of SUNFISH *Part 2*.

According to the applicant, based on the analysis of time-matched ECG and PK data obtained from studies BP29840, NP39625, BP39054 (JEWELFISH), and BP39056 (FIREFISH) Part 2, there is no evidence for an effect of risdiplam on the QTc interval.

Patients with Type 1 SMA

Four patients with Type 1 SMA had AEs during the treatment period reported in the SOC of Cardiac disorders and suggestive of clinically significant changes in ECG parameters:

- One patient was reported with mild, unrelated bradyarrhythmia on Day 244, which resolved after 64 days without change to study medication. ECG parameters are indicative of sinus tachycardia until Day 490.

- One patient was reported with a serious unrelated event of sinus tachycardia on Day 179 in the context of viral infection with fever; sinus tachycardia resolved after 4 days without change to study medication. ECG showed mild tachycardia throughout including Day -1.

- One patient was reported with a serious unrelated event of Grade 4 cardiac arrest.

- One patient, a White female infant, aged 211 days at enrolment died on Study Day 236, 1 day after receiving her last dose of study drug, due to fatal cardiac arrest and respiratory failure, both with onset on Study Day 236 and maximum intensity Grade 5. The cause of death was classified as progressive disease. The investigator assessed the cardiac arrest and respiratory failure as not related to risdiplam.

Patients with Type 2 and 3 SMA

A total of 13 AEs in 10 patients with Type 2 and 3 SMA that were suggestive of clinically significant changes in ECG parameters were reported in the SOC of Cardiac disorders.

- One patient was reported with a non-serious acrocyanosis (MedDRA PT cyanosis) not suspected to be of cardiac origin, as reported in the context of livedo reticularis.

- One patient was reported with the serious AE of moderate atrial fibrillation on Study Day 326/Day 177 on risdiplam therapy, which was confirmed by ECG and occurred in the context of alcohol consumption and a history of anxiety.

- Three patients were reported with AEs of non-serious mild tachycardia that resolved without treatment and without change to risdiplam therapy. ECG and heart rate at screening were normal, or abnormal not clinically significant, and no values were provided at the time of the tachycardia events. One of the patients had two occurrences of tachycardia after approximately 12 and 14 months on risdiplam treatment.

- One patient in the risdiplam arm, had a clinically significant abnormal ECG result at Week 17 during the double-blind treatment period. The patient had average QRS prolongation at 93 msec (NR 40-90 msec) (individual measures: 96, 93, 89) and was reported with a Grade 1 non-serious AE of bundle branch block which resolved after 70 days. The patient's QRS interval measures at baseline were 89 msec on average with individual measures at 93, 88 and 87 msec.

- One patient in the risdiplam arm had a clinically significant abnormal ECG result at Week 70 during the open-label active treatment period, which was the patient's last ECG assessment prior

to the CCOD. The patient's ECG showed a T wave inversion which was also reported as a Grade 1 non-serious AE, unrelated to risdiplam, and unresolved at the CCOD.

- One patient in the risdiplam arm had a clinically significant abnormal ECG result at Week 26. The patient was reported with a non-serious Grade 1 AE of atrioventricular block with onset on Day 187 which resolved after 58 days. The ECG performed at Week 26 did not show prolonged PR interval.

- One patient in the placebo arm had a clinically significant abnormal ECG result at Week 70 during the open-label active treatment period, at the last ECG prior to the CCOD. The patient was reported with a Grade 1 non-serious AE of T wave inversion reported as unrelated to study medication, and unresolved at the CCOD.

- One patient in the risdiplam arm had a clinically significant abnormal ECG result at Week 17. The ECG showed average PR interval at 162 msec (NR 80-160) with individual triplicate measurements of 156, 182 and 147 msec). No corresponding AE was reported in this patient.

Tanner Stage

There was one male patient with delayed puberty at baseline (Tanner stage II at age 15) (n=174 patients assessed); however, this patient moved into puberty at the Month 24 assessment. Three female patients were reported as having delayed puberty at baseline (Tanner stage I).

No patient with delayed puberty was observed post-baseline (n=45 assessed).

One 4-year-old obese female patient had a non-serious AE of hypertrichosis (reported as pubic hair growth) on Study Day 594 with a Tanner staging of II. On Study Day 594, this patient was noted with pubic hair growth and was diagnosed with non-serious Grade 1 hypertrichosis. Tanner stage II was reported and the patient had no endocrinopathy. These early changes were assessed secondary to overweight. No treatment was given for the event. The event of hypertrichosis remained unresolved at the CCOD. There was no change in study drug due to this event. The Investigator considered hypertrichosis to be unrelated to risdiplam.

One female patient (3-year old white female) in the risdiplam arm had precocious puberty during the double-blind period (onset Day 161 [partial date]), which did not result in dose interruption and was not related to the study drug. The AE was considered not serious, did not require treatment, and was unresolved at the time of the CCOD for this report.

Overall, it seems that there is no evidence of an effect of risdiplam on sexual maturation as measured by the Tanner stage.

Male germ cells

Non-clinical studies showed an effect of risdiplam on male germ cells. 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).

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 micronucleus 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 haematology investigation.

Risdiplam is not tumorigenic in animals when tested in a transgenic model suitable to address non-genotoxic and genotoxic mechanisms to tumorigenesis. As risdiplam is used to treat a severe, life threatening disease, a standard 2-year carcinogenicity study in the rat is planned to be conducted post-approval.

Suicidality

Suicidal ideation or behaviour, measured with the Columbia-suicide severity rating scale (adults, adolescents, and children aged 6-11 years) was infrequently reported at baseline or at any postbaseline assessment. There was no evidence for increased incidence of suicidal ideation or behaviours with time.

In the double-blind, placebo-controlled SUNFISH Part 2, no substantial difference for suicidal ideation or behaviour was found between the risdiplam and placebo arms.

Safety in special populations

Age

For the analysis of age as intrinsic factor patients are presented in the following categories based on age at start of risdiplam treatment:

Patients aged 0–<2 years (n=67). The overall exposure in this subgroup was 88.8 PY.

Patients aged 2–<12 years (n=189). The overall exposure in this subgroup was 230.3 PY.

Patients aged 12–<18 years (n=119). The overall exposure in this subgroup was 123.9 PY.

Patients aged ≥18 years (n=90). The overall exposure in this subgroup was 78.4 PY.

Table 65 - Overview of Adverse Events, by Age Group, Safety-Evaluable Patients

	0 to <2 Years	2 to <12 Years	12 to <18 Years	18 Years or Older	All Patients
	(N=67)	(N=189)	(N=119)	(N=90)	(N=465)
Total number of patients with at least one AE	65 (97.0%)	169 (89.4%)	89 (74.8%)	70 (77.8%)	393 (84.5%)
Total number of AEs	516	1399	613	483	3011
Total number of deaths	7 (10.4%)	0	0	0	7 (1.5%)
Total number of patients withdrawn from study due to an AE	0	0	0	0	0
Total number of patients with at least one					
AE with fatal outcome	6 (9.0%)	0	0	0	6 (1.3%)
Serious AE	39 (58.2%)	43 (22.8%)	19 (16.0%)	2 (2.2%)	103 (22.2%)
Serious AE leading to withdrawal from treatment	1 (1.5%)	0	0	0	1 (0.2%)
Serious AE leading to dose modification/interruption	2 (3.0%)	4 (2.1%)	7 (5.9%)	2 (2.2%)	15 (3.2%)
Related Serious AE	1 (1.5%)	0	1 (0.8%)	0	2 (0.4%)
AE leading to withdrawal from treatment	1 (1.5%)	0	0	0	1 (0.2%)
AE leading to dose modification/interruption	3 (4.5%)	14 (7.4%)	11 (9.2%)	5 (5.6%)	33 (7.1%)
Related AE	9 (13.4%)	29 (15.3%)	14 (11.8%)	13 (14.4%)	65 (14.0%)
Related AE leading to withdrawal from treatment	0	0	0	0	0
Related AE leading to dose modification/interruption	0	1 (0.5%)	0	0	1 (0.2%)
Grade 3-5 AE	33 (49.3%)	36 (19.0%)	16 (13.4%)	3 (3.3%)	88 (18.9%)

Adverse Event Rate Adjusted for Patient-Years at Risk - All Occurrences, by Age Group, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety - EMA Filing 2020

Time on Treatment:	0 to <2 Years (N=67)	2 to <12 Years (N=189)	12 to <18 Years (N=119)	18 Years or Older (N=90)	All Patients (N=465)
Overall					
Total patient-years at risk	88.8	230.3	123.9	78.4	521.4
Number of Adverse Events	516	1399	613	483	3011
Number of Adverse Events per 100 patient-years	580.98	607.53	494.92	615.80	577.50
95% CI	(531.92, 633.34)	(576.11, 640.22)	(456.51, 535.70)	(562.10, 673.25)	(557.06, 598.51)
0 - <= 6 Months					
Total patient-years at risk	30.7	83.1	48.4	35.7	197.8
Number of Adverse Events	208	660	330	279	1477
Number of Adverse Events per 100 patient-years	677.72	794.49	682.25	782.20	746.71
95% CI	(588.74, 776.34)	(735.03, 857.49)	(610.61, 759.97)	(693.10, 879.57)	(709.11, 785.78)
>6 - <= 12 Months					
Total patient-years at risk	28.5	57.4	27.0	16.6	129.5
Number of Adverse Events	157	300	122	101	680
Number of Adverse Events per 100 patient-years	550.43	522.71	451.98	608.45	525.06
95% CI	(467.70, 643.59)	(465.23, 585.33)	(375.34, 539.66)	(495.59, 739.32)	(486.33, 566.05)
>12 - <= 18 Months					
Total patient-years at risk	19.1	50.2	23.7	13.5	106.4
Number of Adverse Events	112	251	89	77	529
Number of Adverse Events per 100 patient-years	587.00	499.63	376.20	571.86	497.00
95% CI	(483.33, 706.31)	(439.73, 565.42)	(302.12, 462.94)	(451.31, 714.73)	(455.54, 541.21)
>18 - <= 24 Months					
Total patient-years at risk	7.8	20.6	10.6	8.2	47.2
Number of Adverse Events	30	130	39	19	218
Number of Adverse Events per 100 patient-years	385.56	631.16	367.42	231.25	461.78
95% CI	(260.13, 550.41)	(527.34, 749.46)	(261.27, 502.27)	(139.23, 361.12)	(402.51, 527.32)

Total patient-years at risk is the sum over all patients of the time intervals (in years) from the start of risdiplam treatment to the earliest of the last treatment date or the clinical cutoff date. 95% CI for rates was constructed using exact method.
Includes AEs with onset from first dose of risdiplam up to the clinical cutoff date, excluding AEs reported during the safety follow-up period.

When summarised by age, the rate of AEs per 100 PY for the overall treatment period was similar in age groups below 12 and above 18 years of age: 0–<2 years age group (580.98, 95% CI: 531.92, 633.34) and the 2–<12 years age group (607.53, 95% CI: 576.11, 640.22), and patients aged ≥18 years (615.80, 95% CI: 562.10, 673.25). Rates were lower in patients in the 12-<18 years age group (494.92, 95% CI: 456.51, 535.70).

As per the overall patient population, and analysis by SMA type, the highest rates of AE by SOC were Infections and infestations followed by Gastrointestinal disorders for all age groups, except for the ≥18 years age group, where rates were highest in the SOCs Nervous system disorders followed by Infections and infestations and the 0–<2 years age group, where rates were highest in the Infections and infestations SOC followed by General administration and site conditions. The high rate in the SOC Nervous system disorders in the ≥18 years age group (173.39 per 100PY [95% CI: 145.48, 205.11]) was driven by episodes of headache reported (101 events in 17 patients [18.9%]).

Grade 3–5 AEs were reported at higher rates in patients below 2 years of age (Grade 3: 48.41 events per 100 PY [95% CI: 35.04, 65.21], Grade 4: 22.52 per 100 PY [95% CI: 13.75, 34.78], Grade 5: 7.88 per 100 PY [95%CI: [3.17, 16.24]) compared with patients in the 2-12 years (Grade 3: 30.83 per 100 PY [95% CI: 24.08, 38.89], Grade 4: 0.43 per 100 PY [95% CI: 0.01, 2.42]), 12-18 years (Grade 3: 16.15 per 100 PY [95% CI: 9.86, 24.94], Grade 4: 2.42 per 100 PY [95% CI: 0.50, 7.08]), and 18 years and older groups (Grade 3: 5.10 per 100 PY [95% CI: 1.39, 13.06], Grade 4: 1.27 per 100 PY [95% CI: 0.03, 7.10]).

The rates of AEs in the SOC Skin and subcutaneous tissue disorders appeared to decline with age with rates of 41.66 per 100PY (95% CI: 29.33, 57.42) in patients aged 0–<2 years, 35.18 per 100PY (95% CI: 27.93, 43.72) in patients aged 2–<12 years, 23.41 per 100PY (95% CI: 15.68, 33.63) in patients aged 12–<18 and 30.60 per 100PY (95% CI: 19.61, 45.53) in patients aged ≥18 years. AEs were further assessed by the AEGT for rash, with the majority of the reported events captured under the SOC Skin and subcutaneous tissue disorders. Rates of AEs in the SOCs General disorders and administration site conditions, and Infections and infestations also appeared to decline with age.

The percentages of treatment-related AEs were comparable between the different age groups with a trend towards higher rates in the 2-<12 and ≥18 years age groups (15.3% and 14.4%, respectively, vs. 13.4% and 11.8% in the 0-<2 and 12-<18 years age groups, respectively). The rate per 100PY of related AEs was comparable across the younger age groups with a trend towards higher rates only in patients ≥18 years.

AEs had resolved for the majority (82.8%) of patients across all age groups despite ongoing treatment with risdiplam, i.e., in 63 patients (94.0%) aged 0-<2 years, 168 patients (88.9%) aged 2–<12 years, 88 patients (73.9%) aged 12–<18 years, and 66 patients (73.3%) aged ≥18 years.

Seven fatal AEs occurred in 6 patients (9.0%), only in patients with Type 1 SMA (aged 0–<2 years) in line with the severity of the underlying type of SMA.

Serious AEs were observed more frequently in the younger patient age group of 0–<2 years; a total of 39 patients (58.2%) reported 81 SAEs. Of these, SAEs were most commonly reported in the SOC Infections and infestations; 46 SAEs were reported in 30 patients (44.8%). Pneumonia was reported in 18 patients (26.9%) aged 0–<2 years and 17 patients in the older age groups. SAEs were reported in 43 patients (22.8%; 80 SAEs) in the 2–<12 years age group, 19 patients (16.0%; 30 SAEs) in the 12–<18 years age group, and 2 patients (2.2%; 3 SAEs) aged ≥18 years.

When summarised by age, the rate of SAEs per 100PY for the overall treatment period was at least 2.5-fold higher in the 0–<2 years age group (91.20, 95% CI: 72.43, 113.35) compared with the rates in the 2–<12 years group (34.74, 95% CI: 27.55, 43.24) and the 12-<18 years group (24.22, 95% CI: 16.34, 34.58). The rate of SAEs was lowest in patients ≥18 years (3.82; 95% CI: 0.79, 11.18). The rate of SAEs decreased approximately 1.5-fold in the 0–<2 age group between the 0-6 month treatment period and the >6–12 months period.

Race

Of the patients with SMA included in this analysis, 343 patients were White, 63 patients were Asian, 3 were Black or African American, 2 were identified as Multiple, and race was unknown for 54 patients, mostly due to country specific data protection requirements.

The majority of patients were included in the Type 2 and 3 pool (Asian: 45, Black or African American: 2, White: 297, Multiple: 2, Unknown: 42). In patients with Type 1 SMA, the race distribution was as follows: Asian: 18, Black or African American: 1, White: 46, Multiple: 0, Unknown: 12.

The analysis was focused on White and Asian race due to the small number of patients in other race categories. Patients of unknown race were not considered as this will not contribute meaningful information on any potential impact of race on the safety profile of risdiplam.

Table 66 - Overview of Adverse Events, by Race Group, Safety-Evaluable Patients

Patients	Asian	Black or African American	White	Multiple	Unknown	All
	(N=63)	(N=3)	(N=343)	(N=2)	(N=54)	(N=465)
Total number of patients with at least one AE (84.5%)	57 (90.5%)	3 (100%)	284 (82.8%)	2 (100%)	47 (87.0%)	393
Total number of AEs	337	23	1898	10	743	3011
Total number of deaths (1.5%)	4 (6.3%)	0	2 (0.6%)	0	1 (1.9%)	7
Total number of patients withdrawn from study due to an AE	0	0	0	0	0	0
Total number of patients with at least one						
AE with fatal outcome (1.3%)	3 (4.8%)	0	2 (0.6%)	0	1 (1.9%)	6
Serious AE (22.2%)	18 (28.6%)	1 (33.3%)	69 (20.1%)	1 (50.0%)	14 (25.9%)	103
Serious AE leading to withdrawal from treatment (0.2%)	0	0	1 (0.3%)	0	0	1
Serious AE leading to dose modification/interruption (3.2%)	3 (4.8%)	0	10 (2.9%)	0	2 (3.7%)	15
Related Serious AE (0.4%)	0	0	1 (0.3%)	0	1 (1.9%)	2
AE leading to withdrawal from treatment (0.2%)	0	0	1 (0.3%)	0	0	1
AE leading to dose modification/interruption (7.1%)	6 (9.5%)	0	25 (7.3%)	0	2 (3.7%)	33
Related AE (14.0%)	17 (27.0%)	0	41 (12.0%)	0	7 (13.0%)	65
Related AE leading to withdrawal from treatment	0	0	0	0	0	0
Related AE leading to dose modification/interruption (0.2%)	0	0	1 (0.3%)	0	0	1
Grade 3-5 AE	16 (25.4%)	1 (33.3%)	59 (17.2%)	0	12 (22.2%)	88 (18.9%)

To highlight:

- The proportion of patients with Type 1 SMA was higher among Asian patients (18 of 63 patients, 28.6%) than among White patients (46 of 343 patients, 15.5%).
- Among the 77 patients with Type 1 SMA, all 15 non-treatment-naïve patients from Study BP39054 (JEWELFISH) are non-Asian and the majority are ≥2 years of age (10 out of 15 [range: 2–19 years]), and thus likely to have milder manifestations of SMA and fewer AEs overall due to older age compared to the Asian Type 1 population who are exclusively treatment-naïve and ≤7 months of age.

The rate of AEs per 100PY for the overall treatment period was similar among Asian patients (483.50, 95% CI: 433.25, 537.98) and White patients (489.07, 95% CI: 467.31, 511.58). The rate of AEs per 100 PY was, however, different between Asian and White patients in the two SMA by Type pools. In patients with Type 1 SMA, the rate was higher among Asian compared to White patients (686.18 AEs per 100 PY [95% CI: 578.69, 807.86] and 411.44 per 100 PY [95% CI: 360.31, 467.81], respectively). Conversely, in the Type 2 and 3 population the rate of AEs was higher in White patients compared with Asian patients (502.33 per 100 PY [95% CI: 478.49, 527.05] and 396.19 per 100 PY [95% CI: 342.26, 456.20], respectively). The higher rate of AEs in Asian patients with Type 1 SMA should be viewed with caution given the imbalanced distribution of treatment-non-naive vs. treatment-naïve patients between White and Asian patients.

In White and Asian patients, the most frequently reported AE by SOC was Infections and infestations, with rates of 197.99 per 100 PY (95% CI: 166.34, 233.92) and 160.53 per 100 PY (95% CI: 148.17, 173.65), respectively.

Most AEs resolved in White and Asian patients. Unresolved events were reported in 55 White patients (16.0%) and 14 Asian patients (22.2%).

Given the low number of AEs leading to discontinuation of study treatment (fatal AEs only), or those that led to interruption of study treatment, no trend by race can be observed.

In the All Patients with SMA pool, the overall rate per 100PY of AEs and Grade 1–3 AEs was similar between White and Asian patients. The rates of Grade 4 and 5 AEs were approximately 3.3- and 5.6-fold higher in Asian patients compared with White patients, respectively. In patients with Type 2 and 3 SMA, the rate of AEs per 100PY by Grade was similar or lower in Asian patients, Grade 4 events occurred only in White patients, and no Grade 5 event was reported. In patients with Type 1 SMA, the differences in AE rates per 100PY between White and Asian patients were observed at all intensity Grades and were more pronounced at higher Grades, (1.4-, 2-, 1.8-, 2.4-, and 2.7-fold higher in Asian patients for Grades 1, 2, 3, 4 and 5, respectively). The higher rate of Grade 4 and 5 events in Asian patients in the All patients with SMA population is driven by patients with Type 1 SMA. The difference is more pronounced in the All patients with SMA pool compared to the Type 1 SMA pool due to a higher proportion of Type 1 SMA among Asian patients. The difference in Grade 4 and 5 AEs in patients with Type 1 SMA seems to be driven by the over-representation of older, treatment-non-naive Type 1 SMA patients among White patients compared to Asians.

In the All Patients with SMA pool, the rate of AEs reported as related to risdiplam was approximately 2.5-fold higher in Asian patients (38.74 per 100PY [95% CI: 25.53, 56.36]) compared with White patients (16.75 per 100PY [95% CI: 12.93, 21.35]). This difference was driven mainly by patients in the Type 1 SMA pool. In patients with Type 1 SMA, the rate of AEs reported as related to risdiplam was approximately 17.5-fold higher in Asian patients (61.95 per 100PY [95% CI: 32.98, 105.93) compared with White patients (3.53 per 100PY [95% CI: 0.43, 12.76]). In the patients with Type 2 and 3 SMA, the rate of AEs reported as related to risdiplam was approximately 1.5-fold higher in Asian patients (28.74 per 100PY [95% CI: 15.71, 48.22) compared with White patients (19.01 per 100PY [95% CI: 14.61, 24.32]).

In the All Patients with SMA pool, the rate of SAEs per 100PY for the overall treatment period was approximately 1.5-fold higher among Asian patients (53.08, 95% CI: 37.38, 73.17) than among White patients (32.21, 95% CI: 26.81, 38.38), driven by patients with Type 1 SMA, where the rate of SAEs per 100 PY was approximately 1.5-fold higher in Asian patients (104.83, 95% CI: 65.70, 158.72) as compared to White patients (74.17, 95% CI: 53.45, 100.25). In patients with Type 2 and 3 SMA, rates were comparable between Asian patients (30.79, 95% CI: 17.23, 50.79) and White patients (25.04, 95% CI: 19.95, 31.04). SAEs generally resolved and did not lead to dose modifications.

Overall, there are differences in age and imbalance in treatment-naïve vs. treatment non-naive patients in the different race groups (over-representation of older, treatment-non-naive Type 1 SMA patients among White patients compared to Asians).

Safety in Treatment-Naïve vs. Treatment Non-Naïve Patients

An analysis of the effect of prior treatment with nusinersen or Zolgensma (AVXS-101) on the safety profile of risdiplam was conducted.

A total of 90 patients are included in the treatment-non-naive group (76 patients previously treated with nusinersen and 14 patients previously treated with Zolgensma (AVXS-101)). The rate of AEs per 100 PY was comparable between treatment-non-naïve patients in JEWELFISH and treatment-naïve patients with SMA who were treated with risdiplam in SUNFISH (Part 1 and Part 2) and FIREFISH (Part 1 and Part 2). Due to shorter median duration of treatment in treatment non-naïve patients compared with treatment-naïve patients (FIREFISH Part 1: 23.33 months [range: 0.6–34.6]; FIREFISH Part 2: 15.24 months [range 1.6–20.1]; JEWELFISH: 3.02 months [range: 0.0–32.8]; SUNFISH Part 1: 996.0 days [range: 287.0–1183.0 days]; SUNFISH Part 2: 540.0 days [range: 100.0–807.0]) the analysis focused on the 0–≤6 month treatment period, where exposure times are most comparable (Naïve: Type 1: 29.8 PY, Type 2/3: 114.6 PY; Non-naïve: Type 1: 3.1 PY, Type 2/3: 22.1 PY).

In All SMA Patient Population, the rate of AEs per 100 PY was comparable between treatment-non-naïve patients in JEWELFISH and treatment-naïve patients with SMA who were treated with risdiplam in SUNFISH (Part 1 and Part 2) and FIREFISH (Part 1 and Part 2). The impact of previous treatment was noticeable in the Type 1 population where patients who had been on previous approved SMA therapies did not experience any Grade 4 or Grade 5 (fatal) events; however, due to the limited data in the non-naïve Type 1 population, these results should be interpreted with caution.

Patients with Type 1 SMA

During the 0–≤6 month treatment period, a total of 13 patients with Type 1 SMA who were previously treated with nusinersen (n=9) or AVXS-101 (n=4) had a total of 3.1 patient-years at risk (nusinersen: 2.8 PY, AVXS-101: 0.3 PY). The rate of AEs in all patients with Type 1 SMA was comparable between the treatment non-naive and the treatment-naïve populations (treatment non-naive: 580.27 per 100 PY [95% CI: 343.91, 917.08] vs. treatment-naïve: 681.17 per 100 PY [95% CI: 590.69, 781.60]).

In both populations, the highest rates of AEs were in the Infections and infestations SOC. At least 2 AEs were reported in treatment non-naïve patients in the SOC Infections and Infestations and Respiratory, thoracic and mediastinal disorders. While the rates in the respiratory SOC were comparable, a numerically higher rate of infections was reported in the treatment non-naive patients (treatment non-naive: 354.61 per 100 PY [95% CI: 177.02, 634.50] vs. treatment-naïve: 187.91 per 100 PY [95% CI: 141.95, 244.02]). In both populations, infections were mostly affecting the respiratory tract and generally resolved with ongoing treatment with risdiplam.

The rate of SAEs in all treatment non-naïve patients with Type 1 SMA during the 0–≤6 month treatment period was comparable between the treatment non-naive and the treatment-naïve populations (treatment non-naive: 193.42 per 100 PY [95% CI: 70.98, 421.00] vs. treatment-naïve: 130.87 per 100 PY [95% CI: 93.06, 178.90]). SAEs were reported in more than one treatment non-naïve patient

only in the SOC Infections and infestations. In both populations the most common SAEs were in the Infections and infestations SOC driven by respiratory tract infections.

The intensity of AEs reported in both populations was reflective of the previous SMA treatment, with Grade 4 and 5 AEs reported only in treatment-naïve patients.

Patients with Type 2 and 3 SMA

During the 0–≤6 month treatment period, a total of 77 patients with Type 2 and 3 SMA who were previously treated with nusinersen (n=67) or AVXS-101 (n=10) had a total of 22.1 patient-years at risk (nusinersen: 20.4 PY, AVXS-101: 1.6 PY). The rate of AEs overall was comparable in both populations (non-naïve: 932.82 per 100 PY [95% CI: 809.78, 1069.28] vs. treatment-naïve: 773.82 per 100 PY [95% CI: 723.73, 826.47]).

AEs which occurred at the highest rates were in the SOC Infections and infestations (treatment non-naïve: 271.70 per 100 PY [95% CI: 207.33, 349.73] vs. treatment-naïve: 215.48 per 100PY [95% CI: 189.45, 244.10]), with upper respiratory tract infection being the most common preferred term in both groups, followed by Gastrointestinal disorders (172.07 per 100 PY [95% CI: 121.77, 236.19] vs. 131.73 per 100 PY [95% CI: 111.56, 154.50]), and General disorders and administrative site conditions (104.15 per 100 PY [95% CI: 66.02, 156.28] vs. 61.94 per 100PY [95% CI: 48.38, 78.13]), with the most common AE being pyrexia in both groups.

A higher rate of SAE was observed in non-naïve patients during the first 6 months of treatment (40.75 vs. 22.68 per 100PY in naïve patients). However, this did not correspond to higher rates of specific AEs. The most common SAEs were in the SOC Infections and infestations where the rate of SAEs was similar between the two groups (non-naïve 13.58 vs. naïve 14.83 per 100 PY). Other SOCs with 2 or more AEs in either population were: Respiratory, thoracic and mediastinal disorders (non-naïve: 9.0 vs. naïve: 0.87 per 100 PY); General disorders and administration site conditions and Renal and urinary disorder (0 vs. 1.74 per 100 PY for both).

The rate of Grade 3 events was approximately 3-fold higher in treatment-non-naive patients. No Grade 5 events were reported in either population in the entire treatment period and few patients had Grade 4 events in both populations.

Use in Pregnancy and Lactation

There are no clinical data from the use of risdiplam in pregnant women. Risdiplam has been shown to be embryo-fetotoxic and teratogenic in animals. Based on the findings from animal studies, risdiplam crosses the placental barrier and may cause foetal harm.

Risdiplam should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated with risdiplam she should be clearly advised on the potential risk to the foetus.

The safe use of risdiplam during labour and delivery has not been established.

It is not known whether risdiplam is excreted in human breast milk. Studies in rats show that risdiplam is excreted into milk. It is recommended not to breastfeed during treatment with risdiplam.

Immunological events

N/A.

Safety related to drug-drug interactions and other interactions

Risdiplam is primarily metabolised by flavin monooxygenase 1 and 3 (FMO1 and 3), and also by CYPs 1A1, 2J2, 3A4, and 3A7. Risdiplam is not a substrate of human multidrug resistance protein 1 (MDR1).

Effects of Other Medicinal Products on Risdiplam

Coadministration of 200 mg itraconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 6 mg risdiplam did not exhibit a clinically relevant effect on the PK of risdiplam (11% increase in AUC,9% decrease in C_{max}). No dose adjustments are required when risdiplam is co-administered with a CYP3A inhibitor.

No drug-drug interactions are expected via the FMO1 and FMO3 pathway.

Effects of Risdiplam on Other Medicinal Products

In vitro risdiplam and its major circulating metabolite M1 did not induce CYP1A2, 2B6, 2C8, 2C9, 2C19, or 3A4. *In vitro* studies showed that risdiplam and M1 did not inhibit (reversible or time-dependent inhibition) any of the CYP enzymes tested (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6) with the exception of CYP3A.

In healthy adult subjects, administration of risdiplam 8 mg once daily for 2 weeks slightly increased the exposure of the sensitive CYP3A substrate midazolam (AUC 11%; C_{max} 16%). The extent of the interaction is not considered clinically relevant, and therefore no dose adjustment is required for CYP3A substrates. Based on physiologically based pharmacokinetic (PBPK) modelling a similar magnitude of the effect is expected in children and infants as young as 2 months old.

In vitro studies have shown that risdiplam and its major metabolite are not a significant inhibitor of human MDR1, organic anion-transporting polypeptide (OATP)1B1, OATP1B3, organic anion transporter 1 and 3 (OAT 1 and 3) transporters. Risdiplam and its metabolite are however *in vitro* inhibitors of the human organic cation transporter 2 (OCT2) and the multidrug and toxin extrusion (MATE)1 and MATE2-K transporters. At therapeutic drug concentrations, no interaction is expected with OCT2 substrates. The clinical relevance of the coadministration with MATE1/2-K substrates is unknown.

Overdose

There is limited clinical trial experience in SMA with doses higher than the proposed dose of risdiplam.

In the Patients with Type 1 SMA pool, 9 patients received doses more than 10% above the pivotal dose. Doses above the pivotal dose were administered for up to 79 consecutive days and were up to 33% higher than the pivotal dose. AEs were reported in temporal association with overdoses in 4 patients; these events were all reported as unrelated to study medication and were reflective of the underlying disease (atelectasis in one patient, kyphosis and scoliosis in one patient, pyrexia in one patient, and upper respiratory tract infection [SAE] and upper respiratory tract inflammation in one patient). All events resolved with the exception of kyphosis and scoliosis.

In the Patients with Type 2 and 3 SMA pool, 9 patients received doses more than 10% above the pivotal dose. Four patients with a dose above the pivotal dose for more than 1 day received a dose up to 30% higher than planned, for up to 65 consecutive days. Four patients received double the planned dose for a single day. No AEs were associated with these higher doses.

Very low safety margins were seen for most toxicities observed in animal studies. Risdiplam likely has a narrow therapeutic window. Clinical trial experience in SMA with doses higher than the proposed dose of risdiplam is very limited. There is no antidote.

Drug abuse potential

AEs that may potentially be indicative of the abuse potential of risdiplam were defined using an Adverse Event Group Term (AEGT) MedDRA basket defined in accordance with the FDA guidance document "Assessment of Abuse Potential of Drugs (CDER)" January 2017 (CDER 2017). An evaluation of risdiplam's abuse potential was performed using the predefined basket of AE MedDRA preferred terms applied to the SMA pool and to the non-integrated datasets - 12 Feb 2019", MedDRA Version 22.1.

Adverse Events Indicative of Abuse Potential

Table 67

Adverse Events Indicative of Abuse Potential, by SMA Type, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety - EMA Filing 2020

MedDRA System Organ Class MedDRA Preferred Term	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Total number of patients with at least one adverse event	2 (2.6%)	8 (2.1%)	10 (2.2%)
Overall total number of events	6	8	14
Nervous system disorders			
Total number of patients with at least one adverse event	0	6 (1.5%)	6 (1.3%)
Total number of events	0	6	6
Dizziness	0	4 (1.0%)	4 (0.9%)
Lethargy	0	1 (0.3%)	1 (0.2%)
Seizure	0	1 (0.3%)	1 (0.2%)
Psychiatric disorders			
Total number of patients with at least one adverse event	2 (2.6%)	1 (0.3%)	3 (0.6%)
Total number of events	2	1	3
Irritability	2 (2.6%)	0	2 (0.4%)
Apathy	0	1 (0.3%)	1 (0.2%)
General disorders and administration site conditions			
Total number of patients with at least one adverse event	1 (1.3%)	1 (0.3%)	2 (0.4%)
Total number of events	4	1	5
Crying	1 (1.3%)	0	1 (0.2%)
Feeling abnormal	0	1 (0.3%)	1 (0.2%)

Investigator text for AEs is coded using MedDRA version 22.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of risdiplam up to the clinical cutoff date, excluding AEs reported during the safety follow-up period.

Program: root/clinical_studies/RO7034067/CDFT7916/share/pool_safety_202004_MAAFiling/prod/program/t_ae.sas
Output: root/clinical_studies/RO7034067/CDFT7916/share/pool_safety_202004_MAAFiling/prod/output/t_ae_AB_SMA_SE.out
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Two patients with Type 1 SMA (2.6%) experienced a total of 6 AEs, and 8 patients (2.1%) with Type 2 and 3 SMA experienced a total of 8 AEs. The AEs were all unique occurrences in these patients despite ongoing treatment with risdiplam and were assessed as unrelated to study treatment, with the exception of 7 events in 4 patients:

- One patient had 4 AEs of crying which were all mild, unrelated and resolved without change to risdiplam therapy, most within 1-2 days and treatment with paracetamol. The same patient also had an AE of irritability (mild, unrelated and resolved).

- One patient had an AE of mild apathy which was reported as related to risdiplam; the AE had an onset on Study Day 1 and resolved within 14 days without change of risdiplam therapy and without treatment for the AE.

- Two AEs of mild dizziness in two patients which were reported as related to risdiplam; in both patients the AE resolved without change of study therapy and without treatment for the AE.

One additional patient in the non-integrated dataset for the completed Phase 1 studies had a mild AE of dizziness after a single dose of risdiplam, which resolved the same day without therapy; a second patient in the non-integrated dataset (drug-drug interaction study BP41361) had a non-serious AE of euphoric mood on Study Day 3, 2 days after midazolam (2 mg, PO Days 1 and 15, QD) and on the first day of risdiplam treatment (risdiplam (8 mg, PO) Days 3 to 16, QD) which resolved the same day without therapy and did not recur despite continuation of the study medication.

Overall, these events do not suggest a signal of an abuse potential of risdiplam.

Withdrawal and rebound

No information is available regarding withdrawal or rebound effects of risdiplam.

Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effects on the ability to drive and to use machines have been performed. The pharmacological activity and AEs reported to date in clinical studies of healthy volunteers and SMA patients do not indicate such an effect is likely.

Overall, 22 AEs potentially suggestive of effects on ability to drive or operate machinery or impairment of mental ability were reported in 20 patients with SMA in the pooled dataset (t_ae_IMP_SMA) and 4 AEs in 4 healthy volunteers from the non-integrated datasets for the completed healthy volunteer studies.

Table 68

Adverse Events Indicative of Impaired Ability to Drive or Operate Machines or Impaired Mental Ability, by SMA Type, Safety-Evaluable Patients
Protocol: Risdiplam Pooled Safety - EMA Filing 2020

MedDRA System Organ Class MedDRA Preferred Term	Type 1 (N=77)	Type 2/3 (N=388)	All Patients (N=465)
Total number of patients with at least one adverse event	2 (2.6%)	18 (4.6%)	20 (4.3%)
Overall total number of events	3	19	22
Nervous system disorders			
Total number of patients with at least one adverse event	0	7 (1.8%)	7 (1.5%)
Total number of events	0	7	7
Dizziness	0	4 (1.0%)	4 (0.9%)
Tremor	0	2 (0.5%)	2 (0.4%)
Febrile convulsion	0	1 (0.3%)	1 (0.2%)
Eye disorders			
Total number of patients with at least one adverse event	0	6 (1.5%)	6 (1.3%)
Total number of events	0	6	6
Vision blurred	0	4 (1.0%)	4 (0.9%)
Photopsia	0	1 (0.3%)	1 (0.2%)
Visual impairment	0	1 (0.3%)	1 (0.2%)
Ear and labyrinth disorders			
Total number of patients with at least one adverse event	0	3 (0.8%)	3 (0.6%)
Total number of events	0	3	3
Vertigo	0	3 (0.8%)	3 (0.6%)
Psychiatric disorders			
Total number of patients with at least one adverse event	2 (2.6%)	1 (0.3%)	3 (0.6%)
Total number of events	3	1	4
Irritability	2 (2.6%)	0	2 (0.4%)
Abnormal behaviour	0	1 (0.3%)	1 (0.2%)
Sleep disorder	1 (1.3%)	0	1 (0.2%)
General disorders and administration site conditions			
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.2%)
Total number of events	0	1	1
Feeling abnormal	0	1 (0.3%)	1 (0.2%)
Musculoskeletal and connective tissue disorders			
Total number of patients with at least one adverse event	0	1 (0.3%)	1 (0.2%)
Total number of events	0	1	1
Muscular weakness	0	1 (0.3%)	1 (0.2%)

Investigator text for AEs is coded using MedDRA version 22.1. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately. Includes AEs with onset from first dose of risdiplam up to the clinical cutoff date, excluding AEs reported during the safety follow-up period.

Program: root/clinical_studies/RO7034067/CDPT7916/share/pool_safety_202004_MAAFiling/prod/program/t_ae.sas
Output: root/clinical_studies/RO7034067/CDPT7916/share/pool_safety_202004_MAAFiling/prod/output/t_ae_IMP_SMA_SE.out
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All events were mild to moderate in intensity. Events resolved and were reported as unrelated to study medication with the exception of:

- One patient with pre-existing obesity (BMI: 34.39 Kg/m2) was reported with non-serious mild vertigo on Study Day 54 (partial day) which had not resolved 48 days after onset. The event was reported as

related to risdiplam. The patient also had a concurrent mild AE of unrelated weight increase, which was also unresolved at CCOD. Risdiplam was not changed as a result of these events.

- One patient was reported with a non-serious mild event of visual impairment with a small reduction in visual acuity 0.5 diopters which remained unresolved 411 days after onset at the time of CCOD and was reported as unrelated to risdiplam. Risdiplam treatment was not changed as a result of this event.

- One patient had a non-serious mild event of dizziness reported as related to risdiplam with onset on Study Day 15 and which was reported as resolved on Study Day 101. Treatment with risdiplam was not changed as a result of this event.

- One patient had a non-serious mild event of dizziness reported as related to risdiplam with onset on Study Day 11 and which was reported as resolved on the same day. Treatment with risdiplam was not changed as a result of this event and the event did not recur.

- Four AEs in 4 healthy volunteers of Phase 1 studies (non-integrated data) after a single dose of risdiplam: 2 AEs of sleep disorder and 1 AE of dizziness, all mild and resolved; 1 mild AE of bilateral vision blurred, due to worsening of pre-existing cataract in a 58-year-old Asian participant after a single dose of risdiplam, the event resolved after laser surgery and the events were unlikely related to risdiplam (see Study NP39625).

Discontinuation due to AES

Adverse Events Leading to Discontinuation of Study Treatment

One patient with Type 1 SMA had an AE that led to discontinuation of study treatment. This was a case of Grade 5 (fatal) respiratory tract infection viral, which was considered not related to risdiplam.

Adverse Events Leading to Dose Modification or Interruption of Study Treatment

Thirty-three patients had AEs that led to interruption of study treatment (3 SMA 1 and 30 SMA 2-3 type).

3 *Type 1 SMA* patients had AEs leading to treatment interruption: 2 of these events were SAEs (Grade 4 hypoxia and Grade 4 pneumonia, in Part 1 and in Part 2 of FIREFISH, respectively), 1 was a Grade 1 pyrexia (in Part 2 of FIREFISH) which occurred after gastrostomy. All events resolved and were considered not related to study treatment.

In the *Type 2 and 3 SMA* pool, there were 30 patients who experienced 46 AEs leading to interruption of study treatment; all events resolved and were considered unrelated to risdiplam except for 1 AE of diarrhoea.

In particular, in SUNFISH Part 1 and Part 2, at the time of CCOD, no patients had withdrawn from study treatment due to an AE. In *Part 1*, there were 4 patients (2 aged 2-11 years and 2 aged 12-25 years) reporting 8 AEs that led to modification (interruption) of study treatment and resolved: gastroenteritis, gastrointestinal infection, pneumonia, pain, pyrexia, abdominal pain upper, vomiting, chronic respiratory failure (1 patient each). In the double-blind, placebo-controlled *Part 2*, more patients in the risdiplam arm had AEs leading to dose interruption compared with placebo (6.7% vs. 3.3%) with the rate of SAE leading to dose modification being similar between the two arms (3.3% each). The AEs were: gastroenteritis, pharyngitis, upper respiratory tract infection, varicella, constipation, vomiting, physical deconditioning, pyrexia, traumatic shock, aspiration (for all, 1 in risdiplam group vs. none in placebo group). All AEs resolved and did not recur following risdiplam treatment re-initiation except for one case of pharyngitis recurrence which in any case resolved.

All patients resumed study treatment , with the exception of two patients who had not restarted risdiplam by the time of CCOD.

Post marketing experience

At the time of the MAA submission, risdiplam was not commercially available in any part of the world so no post-marketing data exist. In United States, FDA has recently approved risdiplam for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

2.6.1. Discussion on clinical safety

The Safety data on risdiplam are based on: i) safety data available from the ongoing pivotal clinical studies FIREFISH (Study BP39056), a two-part, multicentre, single arm, open study (Part 1 and Part 2; n=62 patients with infantile-onset SMA (Type 1)), and SUNFISH (Study BP39055), a two-part, multicentre, randomised, placebo-controlled, double-blind study (Part 1 and Part 2; n=231 patients with later-onset SMA (Type 2 and 3)), as well as ii) from the ongoing supportive study JEWELFISH (Study BP39054) an open-label, non-comparative study on treatment-non-naïve SMA patients (n=174 including 159 patients with later-onset SMA (Type 2 and 3) and 15 patients with infantile-onset SMA (Type 1)). The clinical cut-off date (CCOD) was November 2019 for FIREFISH and January 2020 for SUNFISH and JEWELFISH. As requested, an update of safety data has been provided. Data cut-off varied; apart from compassionate use and ongoing RAINBOWFISH, safety databases were updated. Overall, the requested updated review of the safety data at the most recent clinical cutoff dates did not indicate relevant differences compared with the safety data presented with the MAA at the previous clinical cutoff dates.

All data were integrated and analysed in 3 pools: i) All patients with SMA; ii) Patients with Type 1 SMA (infantile-onset); iii) Patients with Type 2 and Type 3 SMA (later-onset). Overall, 465 patients (77 with Type 1 SMA and 388 with Type 2 and 3 SMA) received at least one dose of risdiplam and are included in the safety population for the pooled analysis.

Non-integrated safety data from 5 completed studies in healthy volunteers and from the double-blind placebo-controlled period of SUNFISH (Part 2) were also considered.

An analysis on safety data in treatment-non-naïve versus treatment-naïve patients was presented, with a discussion on whether the inclusion of data of patients previously treated with other specific SMA therapies could be confounding for a reliable assessment of integrated safety data on risdiplam were provided. While the data is scarce, the safety of non-naïve patients does not seem to be different from naïve patients regarding TEAEs. Insufficient data precludes providing information about the interval between stopping a previous SMA treatment and starting on risdiplam.

Overall, the sample size of the safety dataset is considered adequate given the prevalence of the disease.

Advanced disease in both Type 1 (infantile onset) and Type 2 and 3 (later onset) SMA as well as adult type (Type 4) SMA have not been specifically studied in clinical trials. This discussion has previously been held on efficacy. Only limited safety data is available for patients below 2 months of age. SMA type 4 patients do not have safety data available.

Exposure

The median duration of exposure to risdiplam was 12.68 months (range: 0.0–38.9), with an overall exposure of 521.4 PY. Type 1 SMA patients tended to have a longer median exposure compared with Type 2 and 3 SMA patients: 15.24 months (range 0.1-34.6) vs. 9.30 months (range 0.0-38.9) (overall exposure of 92.1 PY vs. 429.2 PY). In All patients with SMA, 34% of patients were treated for up to 6 months, 14.8% received the treatment from 6 to 12 months, 18.3% from 12 to 18 months and 18 to 24 months, and 14.6% for more than 24 months. The majority of Type 1 SMA patients (71.4%) had been treated for >12 months while most Type 2 and 3 SMA patients (63.4%) had been treated for >6 months. Most cumulative safety data comes from the first 6 mths of exposure. The applicant provided

an analysis of AE over time in SUNFISH, FIREFISH and JEWELFISH studies. The overall rate of AEs was highest in the first 6-12 months period after exposure to risdiplam. There were no observed patterns of AEs that had not resolved by the respective study clinical CCODs (possible chronic AEs) and no new AEs that occurred following 24 months of treatment with risdiplam (possible delayed onset AEs). Given the above, the long-term safety profile of risdiplam is still uncertain. Long-term safety of risdiplam, including comprehensive ophthalmological monitoring, will be further characterised in open label extension phases of four ongoing clinical studies (BP39055, BP39056, BP39054, and BN40703) including over 460 patients (infants, children, teenagers, adults, early and late onset disease) for a period of up to 5 years of treatment with risdiplam. In addition, the applicant is currently negotiating to participate in existing registries in North America and Europe to further assess long-term efficacy and safety profile of risdiplam.

The integrated analysis of AEs has been presented mainly in rates per 100PY in order to adjust for differences in exposure time between the SMA pools.

In All SMA patients, the median duration of exposure to the pivotal dose (0.2 mg/kg for patients from 2 months to <2 years old and 0.25 mg/kg for patients with body weight <20 kg or 5 mg for patients with body weight ≥20 kg for patients ≥2 years old) was approximately 12 months (11.98, range 0.0-34.5; 480.9 PY).

The demographic characteristics of the All SMA Patients population were overall consistent with those expected for a broad population of patients with Type 1-3 SMA. The median age was 10.8 years (range from 2 months to 60.9 years). Patients were predominantly White (73.8%; Type 1 SMA: 59.7%; Type 2 and 3 SMA: 76.5%); 13.5% were Asian (Type 1 SMA: 23.4%; Type 2 and 3 SMA: 11.6%). Overall, 77.2% of patients were enrolled at sites in European countries.

Adverse events

Overall, 393/465 (84.5%) patients treated with risdiplam had at least one AE. In the All SMA Patient Population pool, the AE rate was 577.50 per 100 PY (95% CI 557.06, 598.51) with comparable rates between the two Type 1 SMA and Type 2 and 3 SMA pools (577.37 and 577.53 per 100 PY; 93.5% vs. 82.7%).

The majority of AE were of Grade 1 or 2 (418.21 and 124.48 per 100 PY, respectively). Grade 3, 4, and 5 AEs were reported with rates of 26.47, 4.79, and 1.34 per 100 PY, respectively, with 2.5-fold to 18.5-fold higher rates in the Type 1 SMA compared with the Type 2 and 3 SMA for Grade 3 and Grade 4 AEs respectively (Grade 3: 49.92 vs. 21.43; Grade 4: 21.71 vs. 1.16); and in Grade 5 AEs a rate of 7.60 vs. 0 per 100PY in Type 1 SMA compared to Type 2 and 3 SMA respectively. This could be expected given the more severe SMA phenotype.

Overall, in All patients with SMA, the three SOCs with the highest rate of AEs by 100PY were Infections and Infestations (65.6%, at a rate of 178.37 AEs per 100PY), Gastrointestinal disorders (39.1%, 88.99 per 100PY), and Nervous system disorders (17.4%, 67.13 per 100PY). A trend towards a higher rate of AEs was observed in Type 1 SMA patients compared with Type 2 and 3 SMA patients in the SOC Infections and Infestations (particularly driven by upper respiratory tract infection related AEs), General disorders and administration site conditions (particularly driven by pyrexia), Respiratory, thoracic and mediastinal disorders, and Skin and subcutaneous disorders. In Type 2 and 3 SMA patients, rates of AEs were higher in the SOCs Nervous system disorders and Musculoskeletal and connective tissue disorders (driven by pain in extremity, arthralgia, back pain, and headache) followed by the SOCs Injury, poisoning and procedural complications and Reproductive system and breast disorders.

The most common AEs reported at the highest rates per 100PY in the All patients with SMA were: headache (55.81), pyrexia (43.15), upper respiratory tract infection (41.62), and nasopharyngitis (27.81), vomiting (22.82), and cough (18.41).

In patients with Type 1 SMA, among most commonly AEs reported at rates ≥10 per 100PY, there were pyrexia (40.3%), upper respiratory tract infection (41.6%), pneumonia (27.3%), vomiting (11.7%), nasopharyngitis (14.3%), constipation (15.6%), respiratory tract infection (10.4%), diarrhoea (13.0%), rhinitis (10.4%). Other frequently reported AEs (rate <10 per 100PY) were cough (7.8%) and gastroenteritis (3.9%). Among the AEs with a frequency of 2 patients or more there were: urinary tract infection, ear infection, lower respiratory tract infection, viral infection (5.2% each), respiratory failure (6.5%, 5 patients), rash (6.5%), eczema (5.2%), erythema (3.9%), rash maculo-papular (5.2%), dermatitis atopic (1.3%). Neutropenia occurred in 2 patients (2.6%). Rash and diarrhoea are already reported in the proposed Table of ADRs for Type 1 SMA in the SmPC section 4.8.

The higher rate of pneumonia and upper respiratory tract infections, in general, in Type 1 SMA patients compared to Type 2 and 3 SMA patients may be related to the higher severity of the disease observed with the Type 1 SMA phenotype.

Overall, the results of FIREFISH (Study BP39056) (Part 1 and Part 2) in terms of common AEs showed consistent results with the integrated analysis. Given the lack of a control group in this study, it is not possible to draw definite conclusions on the actual drug relationship for most AEs occurring in Type 1 SMA.

In patients with Type 2 and 3 SMA, the most commonly reported AEs (>5% of frequency) were headache (16.5%), pyrexia (19.1%), upper respiratory tract infection (22.2%), nasopharyngitis (18.3%), vomiting (13.9%), cough (11.9%), diarrhoea (12.4%), nausea (7.7%), gastroenteritis (9.0%), pneumonia (6.7%), rash (6.4%), constipation (4.9%), respiratory tract infection (5.2%), and rhinitis (3.4%).

Of note, headache and nausea were reported only in Type 2 and 3 SMA patients; this, although possibly related to the fact that infants (Type 1 SMA) do not easily detail AEs should be reflected in the SmPC.

Urinary tract infections occurred with a <5% frequency (3.6%), pain in extremity (4.4%), arthralgia (3.9%), back pain (3.6%), dysmenorrhoea (2.8%).

Overall, the results of SUNFISH in terms of common AEs showed consistent results with the integrated analysis. In the double-blind, placebo-controlled Part 2, AEs that occurred with a higher frequency in the risdiplam group compared with the placebo group were pyrexia (20.8% vs 16.7%), headache (20.0% vs. 16.7%), diarrhoea (16.7% vs. 8.3%). AE diarrhoea is already included in the proposed ADR Table for Type 2 and 3 SMA of the SmPC section 4.8. Pyrexia could be confounded by concurrent infections. However, pyrexia and headache were reported with a 4.1% and 3.3% higher frequency in patients treated with risdiplam compared with placebo and should be included in the list of ADRs reported in the SmPC section 4.8. Following a review of all events of headache in patients treated with risdiplam, the applicant initially considered that the events were mild and did not deserve mentioning in SmPC. Although headaches are common in both the general population, as well as in patients with SMA, they do occur with treatment with risdiplam. As such, the applicant agreed to report frequency in section 4.8 of SmPC for later onset SMA (toddlers did not report headaches in early SMA).

The applicant discussed as requested not only AEs per 100PtY but also the rate of AEs between risdiplam and placebo for SUNFISH and risdiplam and comparable databases for FIREFISH. Differences beyond 2% in frequency should be added to SmPC. Following a comprehensive review and thorough causality assessments of events selected as described below, the applicant has not identified any new

risks requiring a warning under Section 4.4 of the SmPC or any new adverse drug reaction. However, the applicant proposes to include "diarrhoea" into the ADR table in Section 4.8 for both patient populations, in light of the magnitude of difference between treatment arms in the double-blind, placebo-controlled period of BP39055 (SUNFISH) Part 2 as well as the clinical relevance of diarrhoea in patients with limited mobility. The applicant also proposes to include "rash" into the ADR table in Section 4.8 for both patient populations in light of the magnitude of difference between treatment arms in the double-blind, placebo-controlled period of Study BP39055 (SUNFISH) Part 2.

Other AEs occurring with a higher frequency in risdiplam group compared with placebo were: pneumonia (8.3% vs. 6.7%), viral upper respiratory tract infection (4.2% vs. 1.7%), gastroenteritis viral (3.3% vs. 1.7%), urinary tract infection (4.2% vs. 0), cystitis (2.5% vs. 0), mouth ulceration (4.2% vs. 0), aphthous ulcer (2.5% vs. 0), rash (7.5% vs. 1.7%), eczema (4.2% vs. 1.7%), erythema and rash maculo-papular, (2.5% vs. 0), acne, dermatitis allergic, dry skin, rash erythematous (1.7% vs. 0), migraine (2.5% vs. 1.7%), contusion (3.3% vs. 0), fall and joint dislocation (2.5% vs. 0), head injury, and ligament sprain (1.7% vs. 0), arthralgia (5.0% vs. 0), pain in extremity and scoliosis (3.3% vs. 1.7%), myalgia (2.5% vs. 0), activated partial thromboplastin time prolonged (1.7% vs. 0), C-reactive protein increased (1.7% vs. 0), decreased appetite, dysmenorrhea (1.7% vs. 0), seasonal allergy (3.3% vs. 1.7%).

Some of the AEs in the SOC Skin and subcutaneous tissue disorders, such as rash maculo-papular, erythema, dermatitis, dermatitis allergic, rash erythematous are already included in the ADR Table for Type 2 and 3 SMA of the SmPC section 4.8 under the PT rash.

In the double-blind placebo-controlled Part 2 of the SUNFISH study there was an imbalance in the frequency of pyrexia between risdiplam and placebo groups (20.8% [25 patients] versus 16.7% [10 patients]), with a difference of 4.1%. In the open-label extension phase when placebo patients switched to risdiplam, this difference persisted (risdiplam 13.3% vs. placebo 10.0%). In most cases pyrexia was associated with infections, however not in all cases. .

Arthralgia occurred with a relatively high frequency, in 5.0% of risdiplam patients versus none in the placebo group. Furthermore, during the open-label extension phase all patients originally assigned to placebo switched to risdiplam and more patients in the placebo arm compared with the risdiplam patients reported arthralgia (5.0% [n=3] vs. 1.7% [2]) at the clinical cutoff date of 30 September 2020.

Urinary tract infection, cystitis, mouth ulceration, aphthous ulcer, occurred only in the risdiplam arm versus none in the placebo group of SUNFISH Part 2 and the last two AEs were considered related to study treatment by the investigators. These four events should be included for later-onset SMA in the ADR table of section 4.8 of the SmPC with the corresponding frequency category. .

Given all the above, the applicant agreed to add mouth ulcerations and aphthous ulcers, urinary tract infection (including cystitis), arthralgia and pyrexia (including hyperpyrexia) for both infantile- and later-onset SMA, in the ADR table in Section 4.8 with the corresponding frequency category.

The applicant also stated that alignment with FDA label has also been implemented whenever possible.

The AE rate decreased over time despite the ongoing treatment with risdiplam in the 3 pools.

Overall, the rate of discontinuation was low. Only 1 patient in the Type 1 SMA pool (Part 1 of FIREFISH) (versus none in the Type 2 and 3 pool) had an AE leading to study treatment discontinuation i.e, a Grade 5 (fatal) respiratory tract infection viral, which was considered not related to risdiplam. Regarding the AEs leading to treatment interruption, 3 Type 1 SMA patients (3.9%) had 2 SAEs (Grade 4 hypoxia and Grade 4 pneumonia) and 1 Grade 1 pyrexia (which occurred after gastrostomy). All events resolved and were considered not related to study treatment. In the Type 2

and 3 SMA pool, there were 30 patients (7.7%) who experienced 46 AEs leading to interruption of study treatment; all events resolved and were considered unrelated to risdiplam except for 1 AE of diarrhoea. In the double-blind, placebo-controlled SUNFISH Part 2, more patients in the risdiplam arm had AEs leading to dose interruption compared with placebo (6.7% vs. 3.3%). The AEs were: gastroenteritis, pharyngitis, upper respiratory tract infection, varicella, constipation, vomiting, physical deconditioning, pyrexia, traumatic shock, aspiration (for all, 1 in risdiplam group vs. none in placebo group). All AEs resolved and did not recur following risdiplam treatment re-initiation except for one case of pharyngitis recurrence which in any case resolved.

Treatment-related AEs

The majority of AEs were reported as unrelated to study treatment. In the All SMA Patient Population, 14% of patients had at least 1 treatment-related AE (11.7% in Type 1 SMA pool; 14.4% in Type 2 and 3 SMA pool) with 3.3% of all AEs reported as related to study treatment with a rate of 19.18 per 100PY (95% CI 15.61. 23.33). These data were comparable between the two SMA patient populations. Overall, the most frequently reported related AE was diarrhoea (9 patients, 1.9%), followed by nausea (7, 1.5%), rash (5, 1.1%), and headache (5, 1.1%). The majority of AEs resolved despite ongoing treatment with risdiplam.

The applicant included nausea upon request for revision, in the Table of ADRs of the SmPC section 4.8 with the corresponding frequency category. Similar to headaches, nausea has not been reported in patients with infantile-onset SMA..

In Type 1 SMA patients, the most frequently reported treatment-related AEs were rash maculo-papular, skin discoloration, constipation, and neutropenia (2 patients, 2.6% each). One SAE was considered related to treatment (neutropenia).

Half of the reported AEs of neutropenia were considered as related to risdiplam treatment and one of them was serious; neutropenia could be clinically relevant in terms of risk of infection, particularly in a population of patients like those with SMA. After a review of these cases, the applicant pointed out that all AEs of neutropenia resolved despite the ongoing treatment with risdiplam and hence are not suggestive of risdiplam-induced bone marrow toxicity. Furthermore, neutropenia was already present at screening in some of these cases or occurred concomitantly with conditions like infections which may have led to temporary decrease in the neutrophil count. The applicant reassured that haematological parameters and related AEs will be collected until patients complete the 5 years of treatment with risdiplam in the long-term open-label phase of all ongoing clinical studies. As a further reassurance, as requested, the applicant committed to monitor for and to provide detailed data on the occurrence of AEs of neutropenia and other haematological-related AEs also in the post-marketing setting. Therefore, the applicant committed to provide a thorough analysis of these data in the upcoming PSURs.

In Type 2 and 3 SMA patients, the most frequently reported related AEs were diarrhoea (8 patients, 2.1%), nausea (7 patients, 1.8%), rash (5 patients, 1.3%), and headache (5 patients, 1.3%). Other AEs considered as treatment-related were: aphthous ulcer and dry skin (3, 0.8% each), mouth ulceration, skin exfoliation, weight increased, dizziness, upper respiratory tract infection (2, 0.5% each).

As regard to the AEs of skin discoloration, investigators considered these events related to study treatment. Indeed, skin discoloration could develop in a certain part of the body due to difference in melanin levels, this could be plausibly related to the physicochemical properties and mechanism of action of risdiplam. The applicant has been requested to provide more detailed information on these events and elaborate on underlying potential causes. According to the applicant, since these AEs of

skin discoloration resolved under risdiplam treatment and were reported from the same study site, a causal association is unlikely. However, the applicant has proposed to include "Effects on epithelial tissue" as important potential risk in the RMP. This was considered acceptable. As requested, the applicant committed to monitor for the occurrence of skin lesions such as exfoliation, dry skin, pruritus, photosensitivity reaction, Erythema, palmar erythema, hyperkeratosis, skin induration, skin lesion, eczema, dandruff, skin erosion, urticaria, dermatitis acneiform, skin discoloration, macule in the long-term open-label phase of all ongoing clinical studies (follow-up duration of 5 years) and in the post-marketing setting, and thorough analyses and detailed data will be provided in incoming PSURs.

A late communication by the applicant on a quality defect on leakage from commercial product and the potential efficacy / safety consequences have been discussed particularly for the quality and related safety issues. The complaints were not associated with adverse events. The applicant stated that in clinical studies, there was no reports of accidental exposure and no indication in any report of adverse events coding to the System Organ Class Skin and Subcutaneous tissue disorders and Eye disorders. The applicant pointed out that since Evrysdi is administered orally oral mucosal contact is expected; oral mucosal events were generally single episodes and resolved despite continued oral dosing. The systemic exposure by transdermal absorption of small amounts of Evrysdi solution or powder during handling of leaking bottles has been estimated by the applicant to be low and thus negligible. It is substantially below the no observed adverse effect level established clearly and consistently in various toxicology studies, even if caregivers are in direct, repeated, and prolonged skin contact. Therefore, there should be no relevant risk associated with handling of leaking bottles. A microbiological risk has been deemed low by the applicant as the solution contains sodium benzoate, is stable for at least 64 days of multi-dose usage and is administered orally.

It could not be neglected that in some, although few cases, mild non-serious dizziness occurred with apparent causal relationship with the risdiplam treatment based on the investigator's judgement. After a review of these cases, the applicant pointed out that none of these events was reported in the risdiplam arm during the double-blind placebo-controlled phase of the SUNFISH study while 2 AEs were reported in 2 (3.3%) patients in the placebo arm. Of note, the AE of mild dizziness associated with nausea was reported in a healthy volunteer who received risdiplam and the event resolved the same day. As a further reassurance, as requested, the applicant committed to monitor for and to provide detailed data on the occurrence of AEs of dizziness/vertigo in the long-term open-label phase of all ongoing clinical studies (follow-up duration of 5 years) and in the post-marketing setting. Therefore, the applicant committed to provide a thorough analysis of these data in the incoming PSURs also to evaluate whether dizziness/vertigo should be mentioned in section 4.7 of the SmPC for driving or using machines.

The results on the type of AEs considered related to treatment from SUNFISH (Study BP39055) were consistent with the results of the integrated safety analysis. In Part 2, during the double-blind, placebo-controlled period, the overall percentage of patients with at least one related AE was slightly higher in the risdiplam arm compared with the placebo arm (13.3% [16] vs. 10.0% [6]): mouth ulceration, nausea, upper respiratory tract infection, headache (2 patients each, 1.7%), abdominal pain upper, dermatitis acneiform, eczema, rash, rash maculo-papular, skin discoloration, gastroenteritis viral, palpitations, cataract subcapsular, posterior capsule opacification, hypercholesterolemia (1 patient each). All AEs reported as related to study medication resolved without change to study medication with the exception of dry skin in 1 patient and 2 AEs of cataract in 1 patient.

Adverse Events of Special Interest (AESI)

AESIs occurred only in Type 2 and 3 SMA patients. There were 2 events: 1 event of dyspnoea and tongue oedema on Day 480 that resolved and diagnosed as allergic reaction in a 23-year-old patient included in SUNFISH Part 1; 1 event of cyanosis (acrocyanosis) (described as blue discoloration of the distal limbs in the absence of pain, swelling or fever) and livedo reticularis, preceding days before by rash and pruritus generalised, occurred in a 46-year-old patient included in the JEWELFISH Study, previously enrolled in MOONFISH study (on the splicing modifier RO6885247). According to the applicant, this AE of livedo reticularis associated to acrocyanosis is secondary to vascular manifestations of SMA. It is acknowledged that literature data are supportive of this hypothesis. Indeed, the primary source of vascular perfusion abnormalities in SMA patients could be related to autonomic dysfunction. Vasculature defects and capillary bed depletion have been reported in patients with SMA and animal models; furthermore, microvascular injury has been reported in Type 2 and 3 SMA patients; it has been reported that patients with SMA are more likely to develop vascular defects, such as such as peripheral vascular disease, chronic venous insufficiency, and chronic vascular insufficiency of the intestines, before any sign of neuromuscular disease. Therefore, the explanations for this event provided by the applicant have been considered biologically plausible.

Effects on epithelial tissues

The occurrence of AEs in the SOC Skin and subcutaneous tissue disorders are of particular interest given the mechanism of action of risdiplam in terms of induction of alternative splicing of other off target genes and the nonclinical findings.

In the All SMA Patient Population, 171 AEs in the SOC Skin and subcutaneous tissue disorders were reported in 110 patients (23.7%) at a rate of 32.80 per 100PY (95% CI: 28.07, 38.10) (Type 1 SMA: 35.1% at a rate of 41.24 per 100PY; Type 2 and 3 SMA: 21.4% at a rate of 30.98 per 100PY). Of these, 3.9% were reported as treatment-related; all, except for 4 AEs in 2 patients (livedo reticularis, palmar erythema, erythema, and skin exfoliation, all occurring in Type 2 and 3 SMA patients) resolved despite the ongoing treatment with risdiplam. Treatment-related AEs occurred in 5.2% of patients with Type 1 SMA and 3.6% of patients with Type 2 and 3 SMA.

14 patients (3.0%) (1 [1.3%] patient with Type 1 SMA and 13 [3.4%] patients with Type 2 and 3 SMA) had at least 1 AE that had not resolved by the CCODs for this analysis; these were: 5 cases of acne and one case each of: dermatitis, dermatitis atopic, dry skin, dyshidrotic eczema, erythema, hair growth abnormal, hypertrichosis, livedo reticularis, palmar erythema, seborrhoeic dermatitis, skin disorder, skin exfoliation, skin odour abnormal. Unresolved skin events did not lead to a change in study medication and did not worsen despite ongoing treatment, with the exception of livedo reticularis. Overall, the rate of the AEs in the SOC Skin and subcutaneous tissue disorders declined during the first 12 months and then stabilised.

Although it is acknowledged that in a young population such as that affected by Type 1 and Type 2 and 3 SMA, skin-related disorders can be frequent compared with older subjects, it should be considered that in the double-blind, placebo-controlled SUNFISH Part 2 there is a clear higher frequency (approximately 3-fold higher) of epithelial tissue-related AEs in patients receiving risdiplam compared with those receiving placebo (30.8% vs. 11.7%). AEs reported in more than 1 patient from this SOC in the risdiplam arm were rash (9 patients), eczema (5 patients), erythema (3 patients), rash maculo-papular (3 patients) and (in 2 patients each) acne, dermatitis allergic, dry skin, and rash erythematous. In the placebo arm, all AEs were single occurrences. All events were mild to moderate in intensity and none of the events were reported as a SAE or led to a change in study medication. Events were mostly reported as unrelated to study medication with the exception of 6 events in 6 patients in the risdiplam arm (dermatitis acneiform, dry skin, eczema, rash, rash maculo-papular and

skin discoloration) and 1 event in one patient in the placebo arm (dermatitis herpetiformis). Events resolved in most patients with the exception of 7 patients in the risdiplam arm and 1 patient in the placebo arm. AEs which were unresolved at the CCOD are events expected to have a prolonged course: acne, dry skin, seborrheic dermatitis, dermatitis contact, dyshidrotic eczema, hair growth abnormal, pityriasis rosea, intertrigo (this last in the placebo arm), all reported as unrelated to study treatment.

Some of these AEs are already included in the ADRs Table of the SmPC section 4.8 under the PT "rash". However, other AEs, although occurring in only 1 or 2 patients in the risdiplam arm versus none in the placebo arm (particularly skin discoloration but also eczema, skin erosion, dry skin, dermatitis atopic, hair growth abnormal, pruritus, pityriasis rosea, etc.) can be suggestive of an effect of risdiplam on skin and epithelial tissues in general. As mentioned above, the applicant was asked to commit to monitor for the occurrence of these events and to provide detailed data in the upcoming PSURs. As mentioned above, the applicant agreed to comply with the requested commitments.

Ophthalmology AEs

The occurrence of AEs in the SOC Eye disorders and, in general, in the SOCs of Investigations or General disorders and administration site conditions, are of particular interest given the mechanism of action of risdiplam, its physicochemical properties, and the nonclinical ophthalmological findings of retinal toxicity. For these reasons, a comprehensive panel of ophthalmological assessments was followed in the clinical development programme of risdiplam in SMA patients, including imaging to detect structural changes of the retina and visual function testing to detect potential functional impairment in central or peripheral vision.

Overall, 90% of the 465 patients included in the integrated safety dataset completed the SD-OCT assessment.

In the All SMA Patient Population, 33 AEs in the SOC Eye disorders were reported in 29 (6.2%) patients.

In Type 1 SMA patients, 6 AEs in 5 (6.5%) patients; all these events were mild, considered unrelated to study treatment, and resolved without change in risdiplam treatment, except for 2 AEs in 2 patients: 1 AE of moderate strabismus; 1 AE of moderate heterophoria in both eyes.

In Type 2 and 3 SMA, 27 AEs were reported in 24 (6.2%) patients; all events were mild, considered unrelated to study treatment and resolved without treatment changes except for 7 AEs reported in 6 patients: moderate dry eye; moderate lacrimation increased; moderate eye allergy; moderate corneal infiltrates; macular cyst detected on SD-OCT assessment reported as related to study treatment but it was not confirmed at subsequent assessments; mild visual impairment unresolved at the CCOD with minimal decrease in sight (onset on Day 324) with no corresponding findings in other ophthalmologic tests, considered unrelated to risdiplam. Of note, 1 AE in the SOC Neoplasms (mild eye naevus with onset on Day 15) did not resolve either and was considered as non-related to study treatment that was not changed.

In the double-blind, placebo-controlled SUNFISH Part 2, more patients in the placebo group had AEs in the SOC Eye disorders compared with risdiplam arm (10.0% vs. 6.7%). The AEs that occurred in at least 1 patient of the risdiplam group versus none in the placebo group were: cataract subcapsular, eye pruritus, eyelid disorder, ocular hyperaemia, posterior capsular opacification, vision blurred, visual impairment (1 each vs. 0). All events were reported as unrelated to study treatment and resolved except for 3 AEs in 2 patients: 1 mild AE of visual impairment considered unrelated to treatment in a patient that lost 0.5 dioptries in the absence of findings observed at OCT and with a subsequent BCVA improved compared to baseline; 2 mild events of cataract subcapsular and posterior capsule opacification both reported as related to treatment, but not confirmed at subsequent assessment made after CCOD.

Overall, these findings suggest that that there is no evident signal of retinal toxicity associated with risdiplam treatment from clinical data, in the absence of structural changes to the retina or relevant visual acuity or visual field impairment detected on neuroimaging assessment or visual function testing. However, it should be considered that the majority of patients (approximately half of patients, n=243) had an ophthalmological follow-up of at least 1 year, 72 completed a follow-up of at least 2 years and only 12 of at least 3 years. In the setting of a chronic treatment like the treatment with risdiplam is, there is the possibility that events related to delayed retinal toxicity could be observed in a longer term and with a very low frequency that would need a longer exposure. Therefore, in the absence of long-term safety data, at the moment it is not completely and definitely known whether the non-clinical findings translate into an actual risk in humans. The applicant considered retinal toxicity observed in monkey as an important potential risk and put in place risk minimisation measures (SmPC section 5.3, preclinical safety data; effect on retinal structure) in the RMP as well as routine pharmacovigilance activities beyond adverse reaction reporting and signal detection (routine PSUR/PBRER reporting until completion of the open-label extension phases of the risdiplam studies where patients will continue to be monitored for ophthalmological findings). However, given the non-completely known clinical relevance of nonclinical retinal toxicity findings in the long-term, in order to provide the prescriber with a complete information on risdiplam safety aspects, a specific warning in section 4.4 is being added:

"Retinal toxicity

"The effects of Evrysdi on retinal structure observed in the non-clinical safety studies have not been observed in clinical studies with SMA patients. However, long-term data are still limited. The clinical relevance of these nonclinical findings in the long-term has therefore not been established (see section 5.3).".

The applicant pointed out that in order to exclude any risk of retinal toxicity in the long-term, ophthalmological monitoring in clinical studies with risdiplam will continue until patients have completed 5 years of risdiplam treatment and that such data will be available before patients initiating treatment in the early post-marketing phase will be treated for longer durations. These data which are continuously reviewed will lead the applicant to submit any confirmed finding of risdiplam-induced retinal toxicity to the Health Authorities as an Emerging Safety Issue. These data will guide any future regulatory decision making for any subsequent labelling. If these data continue to show no evidence of retinal toxicity, the applicant proposes to remove the statements relative to retinal toxicity in Section 4.4 of the SmPC. However, this will be evaluated only when these data will be available. As a further reassurance, the applicant was requested to commit to monitor for and to provide detailed data on the occurrence of AEs related to retinal toxicity also in the post-marketing setting. The applicant committed to provide a thorough analysis of the data from post-marketing evidence together with the 5-year follow-up data from the studies, upon incoming PSURs.

SAEs

In All SMA Patient Population, a total of 103 patients (22.2%) reported 194 SAEs with a rate of 37.21 SAEs per 100PY (95% CI 32.16, 42.83), most commonly observed in the SOC Infections and Infestations (21.10 per 100PY) and in the Respiratory, thoracic and mediastinal disorders (6.14 per 100PY).

Of note, no SAEs were reported in the SOCs Skin and subcutaneous tissue disorders or Eye disorders.

The rate of SAEs was approximately 3.5-fold higher in patients with Type 1 SMA compared with patients with Type 2 and 3 SMA (54.5% vs. 15.7% at a rate of 93.33 vs. 25.16 SAEs per 100PY). This difference was mainly driven by the higher rate of SAEs in the Type 1 SMA patients compared with Type 2 and 3 SMA patients in the SOC of Infection and Infestations (42.9% vs. 10.3%) and Respiratory, thoracic and mediastinal disorders (16.9% vs. 1.8%), and in particular by the AE

pneumonia (23.4% vs. 4.4%). All SAEs pneumonia resolved except for two fatal cases in patients with Type 1 SMA. These observed differences between the two SMA patient populations are plausible considering the more severe disease phenotype in patients with Type 1 SMA who are more prone to develop respiratory complications and infections.

All SAEs were considered unrelated to treatment, except for 1 SAE of neutropenia and 1 SAE of supraventricular tachycardia (in JEWELFISH study previously enrolled in Study WN29836 (Olesoxime)) that resolved without change to study treatment.

SAEs resulting in dose interruption occurred in 15 patients; SAEs leading to a permanent treatment discontinuation were reported in 1 patient with Type 1 SMA (fatal SAE respiratory tract infection viral) and 1 patient had a SAE (decreased appetite) with no outcome reported as of the CCOD.

All SAEs resolved with the exception of 1 SAE partial seizures in 1 patient in the Type 2 and 3 SMA group. Overall, in the integrated safety dataset, in All SMA Patient Population, the SAE rate was stable over the first 18 months of treatment (0-6 months: 42.47; 6-12 months: 40.15; 12-18 months: 37.58 per 100PY).

In Type 1 SMA besides the abovementioned infection- and respiratory SAEs, other frequent SAEs occurring in at least 1 patient were: dehydration, cardiac arrest, hypotonia (2.6% [2]), vomiting, decreased appetite, sinus tachycardia, hydrocephalus, neutropenia, cryptorchism, weight decreased (1.3% [1]). It is plausible that most of these SAEs reflect possible complications related to the underlying disease.

In Type 2 and 3 SMA pool, a total of 61 patients (15.7%) reported 108 SAEs. Besides the abovementioned infection- and respiratory SAEs, other frequent SAEs occurring in at least 1 patient were: femur fracture, vomiting, pyrexia, (0.8% [3 patients]), gastritis, dehydration, (0.5% [2]), brain contusion, concussion, contusion, fall, femoral neck fracture, near drowning, tibia fracture, constipation, nausea, oesophagitis, decreased appetite, atrial fibrillation, supraventricular tachycardia, febrile convulsion, partial seizures, back pain, kyphoscoliosis, haematuria, hydronephrosis, nephrolithiasis (0.3% [1]).

All SAEs resolved by CCOD except for 1 SAE i.e., partial seizures occurring during the open-label period of the SUNFISH Part 2. Updated information allowed the definite diagnosis of epilepsy confirmed by the investigator and as still ongoing, the patient is medicated with carbamazepine. The SAE is not related to risdiplam.

The results on the SAEs from SUNFISH (Study BP39055) were consistent with the integrated safety analysis. During the double-blind, placebo-controlled period of Part 2, 20.0% of patients receiving risdiplam (24/120) and 19.3% of those receiving placebo (11/60) experienced a total of 39 and 14 SAEs, respectively (rate 32.72 vs. 23.29 per 100PY).

Deaths

At the time of CCOD for each study included in the integrated safety dataset, 6 deaths were reported during the treatment period, all occurred in Type 1 SMA patients due to SMA-related respiratory complications (viral respiratory tract infection, cardiac arrest and respiratory failure, respiratory tract infection, acute respiratory failure, pneumonia in 2 patients). One additional patient died 3.5 months after discontinuation from risdiplam therapy during the safety follow-up period due to acute airway obstruction from secretion/mucous plug which caused hypoxia and consequently cardiac arrest. None of these deaths were considered by the investigator as related to study treatment: the cause of death was classified as "progressive disease" in 6 out of 7 cases and as "adverse event" not related to the treatment (pneumonia) for 1 patient. All 6 patients had advanced disease at baseline.

Laboratory findings

Haematology. In non-clinical studies, an effect of risdiplam in determining bone marrow depression with decreased cell counts across all 4 blood cell lines was found at exposure at least 4 times higher than the mean exposures observed in the clinical studies. This is due to the mechanism of action of risdiplam on alternative targets, the MADD and FOXM1 genes involved in cell division and apoptosis.

In Type 1 SMA pool, a clinically relevant decline in cell lines was reported in 6 patients (the most relevant were 2 AEs of neutropenia and 1 of anaemia). In Type 2 and 3 SMA pool, a clinically relevant decline in cell lines was reported in 3 patients (the most relevant were 1 case of neutropenia and 1 case of anaemia).

Overall, these findings suggest that that there is not an evident signal of relevant bone marrow toxicity from clinical data associated with risdiplam treatment.

Liver enzymes. No Hy's law cases were reported in patients with SMA. In the All SMA Patients population, the number of patients with shifts (to low or high values) in AST, ALT or total bilirubin was low, and did not increase over time. In Type 1 SMA patients, 5 patients had AST values >3x ULN at a single post-baseline visit. In Type 2 and 3 SMA patients, the highest abnormal high value was Grade 3 (>5xULN) for ALT and below Grade 2 (<3xULN) for AST. AEs associated with liver enzymes occurred in 4 patients. During the double-blind, placebo-controlled period of SUNFISH Part 2, 2 patients in each arm had ALT >3x ULN, one additional patient had ALT >3x ULN during the open-label treatment phase in the risdiplam arm.

SMA patients may be more at risk of having transaminase elevations because deletion of SMN exon 7 directed to liver leads to severe defect of liver development in mouse models. The applicant discussed the safety data from 474 patients treated for up to 43.1 months showed that risdiplam does not increase the risk of hepatocellular injury in SMA patients. It was highlighted that patients with SMA may be at increased risk for transaminase elevations based on the evidence of deleterious effects of SMN protein depletion on liver development in mouse models and evidence for abnormal fatty acid metabolism and liver steatosis in patients with SMA Type 1-3. For this reason, according to the applicant, the treatment with risdiplam may contribute to stabilizing liver function in SMA patients by increasing SMN protein levels also outside of the CNS. As a further reassurance, the applicant was asked to commit to monitor for and to provide detailed data on the occurrence of AEs related to hepatic injury in the open-label extension phase of all ongoing clinical studies (follow-up duration of 5-year) and in the post-marketing setting. Therefore, the applicant was requested to provide a thorough analysis of these data in the upcoming PSURs. The applicant agreed to comply with the requested commitments.

ECG parameters

In the All SMA Patient Population, there were changes from baseline in ECG parameters, although in few patients. The percentage of patients with average QT, QTcB or QTcF above 450 ms, or change from baseline above 30 ms, was low and did not increase with time. No relevant differences were reported between risdiplam and placebo arms in the double-blind, controlled period of SUNFISH Part 2.

Overall, 4 patients with Type 1 SMA had AEs during the treatment period reported in the SOC of Cardiac disorders and associated with clinically significant changes in ECG parameters (1 bradyarrhythmia, 1 SAE of sinus tachycardia, 1 SAE of cardiac arrest, 1 fatal cardiac arrest).

In patients with Type 2 and 3 SMA, a total of 13 AEs in the SOC Cardiac disorders associated with clinically significant changes in ECG parameters occurred in 10 patients. In particular, 1 patient had a SAE of moderate atrial fibrillation; 3 patients had a non-serious mild tachycardia; 1 patient in the risdiplam arm of the double-blind, placebo-controlled period, had average QRS prolongation at 93 msec (NR 40-90 msec) (individual measures: 96, 93, 89) and was reported with a Grade 1 non-serious

AE of bundle branch block which resolved. 1 patient in the risdiplam arm of the double-blind, placebo-controlled period, had a T wave inversion on ECG; 1 patient in the risdiplam arm had a non-serious Grade 1 AE of atrio-ventricular block which resolved. Finally, 1 patient in the risdiplam arm had an ECG showing average PR interval at 162 msec (NR 80-160) with individual triplicate measurements of 156, 182 and 147 msec).

According to the applicant, based on the analysis of time-matched ECG and PK data obtained from studies BP29840, NP39625, BP39054 (JEWELFISH), and BP39056 (FIREFISH) Part 2, there is no evidence for an effect of risdiplam on the QTc interval. However, clarification on QTc analysis has been requested and concerns have been raised regarding the potential effect of the chronic treatment with risdiplam on QTc also after excluding in some patients (JEWELFISH) the confounding effect of previously administered anti-SMA treatment, in particular the one-shot gene therapy with Onasemnogene abeparvovec (Zolgensma)

Analysis on QT exposure was performed with no evidence for a prolongation in QTc. Analysis on adverse event data was performed with description of all cardiac AEs in type 1 and type 2-3 SMA and significant ECG abnormalities reported, with new data regarding the new CCODs. No evidence that risdiplam has any effect on cardiac rhythm itself nor that it worsens any pre-existing, SMA related, cardiac rhythm abnormality was found.

It is agreed, based on the current evidence, that there is no need to cardiac monitoring during treatment with risdiplam and no need to reflect cardiac AEs/QT prolongation in a separate paragraph of section 4.8 of the SmPC or as a warning in section 4.4.

The applicant has added a planned tQT Study BP42817, a Phase I, double-blind, placebo- and positive-controlled crossover study to investigate the effects of risdiplam on QTc interval in healthy subjects, as an additional pharmacovigilance activity. The study is included in Section III.3 "Additional Pharmacovigilance Activities", as well as in Table 25 - Ongoing and Planned Additional Pharmacovigilance Activities.

Tanner stage

No patient with delayed puberty post baseline was observed, therefore, there is no evidence of an effect of risdiplam on sexual maturation as measured by the Tanner stage.

Male germ cells

Consistent observation of the effect of risdiplam on male germ cells in monkeys and rats, although, reversible, 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. The potential risk of adverse effects of risdiplam on human sperm as a consequence of its mechanism of action on secondary splice targets has not been characterised in clinical studies. Patients may reach reproductive age or some patients with Type 2 or 3 SMA may have already reached this age at the time of starting treatment with risdiplam. The applicant clarified that no data had been collected in humans and that it is not planned to collect these data in the future. After further discussion on male fertility impact of risdiplam, the applicant proposes to add information in sections 4.4 and 4.6 of the SmPC, providing a recommendation to avoid sperm cell donation and consider preservation strategies prior to treatment initiation or after a drug free period of at least 4 months. Furthermore, upon request, the applicant also added the following to section 4.4 Potential effects on male fertility: "The effects of Evrysdi on male fertility have not been investigated in humans".

Genotoxicity and carcinogenicity

A study using rasH2 transgenic mice with 6 months duration of treatment did not generate evidence for a tumorigenic potential. There is no evidence of genotoxicity and carcinogenicity from the available

clinical data at the CCOD. However, long-term non-clinical and clinical data on the carcinogenicity risk of risdiplam safety are still missing and this represents a concern since risdiplam is used to treat a severe, life threatening disease. In clinical studies patients with history of malignancy if not considered cured were excluded. Therefore, definite conclusions on the carcinogenicity potential of risdiplam in humans cannot be still drawn. However, and open-label extension studies will be followed patients up to 5 years. Furthermore, a 2-year carcinogenicity study in rats has been started in September 2020 and the final study report is expected by Q3 2023; this is reflected in the SmPC section 5.3 "Preclinical safety data". In clinical studies patients with history of malignancy if not considered cured were excluded. Therefore, definite conclusions on the carcinogenicity and genotoxicity potential of risdiplam in humans cannot be still drawn. For these reasons, information in the SmPC will be updated as soon as an adequate evidence is produced.

Suicidality

There was no evidence for increased incidence of suicidal ideation or behaviours with time.

Special population

Age. The rate of AEs per 100PY was overall similar in the age groups <12 and >18 years (0-<2: 580.90; 2-<12: 607.53; >18: 615.80) and lower in the 12-<18 age group (494.92). The highest rates of AE were in the SOC Infection and Infestations followed by Gastrointestinal disorders for all age groups, except for the ≥18 years age group where rates were higher in the SOC Nervous system disorders, mainly driven by AE headache, and the 0-<2 years age group where rates were highest in the Infections and infestations SOC. Grade 3-4 AEs and SAEs were reported more frequently in patients <2 years of age compared with patients of the other age groups as well as deaths, which occurred only in this age group reflecting the severity of the underlying SMA phenotype. The percentages of treatment-related AEs were comparable between the different age groups with a trend towards higher rates in the 2-<12 and ≥18 years age groups (15.3% and 14.4%, respectively, vs. 13.4% and 11.8% in the 0-<2 and 12-<18 years age groups, respectively). The rate per 100PY of related AEs was comparable across the younger age groups with a trend towards higher rates only in patients ≥18 years.

Race. The differences in the distribution of AEs observed in White and Asian subgroups with an apparent worse safety profile in Asian patients (higher rates of Grade 4-5 AEs, treatment-related AEs and SAEs), should be interpreted with caution because they are likely due to differences in the proportion of Type 1 SMA patients that was higher in the Asian group (28.6% vs. 15.5% in the White patients) and in the proportion of Type 1 SMA non-treatment-naïve patients from JEWELFISH that were all non-Asian and the majority were ≥2 years of age, and thus likely to have a milder manifestation of the disease and fewer AEs overall due to older age compared to the Asian Type 1 population who are exclusively treatment-naïve and ≤7 months of age. In fact, overall, the rate of AEs was similar between Asian and White group, however there were differences based on the SMA Type: in patients with Type 1 SMA, the rate of AEs was higher in the Asian compared to the White group while in Type 2 and 3 SMA patients the rate of AEs was higher in the White group.

Safety in Treatment-Naïve vs. Treatment Non-Naïve Patients. An analysis on the effect of prior treatment, like nusinersen (Spinraza) (n=76 patients) or AVXS-101 (Zolgensma) (n=14) on the safety profile of risdiplam was conducted and focused on the first 6-month treatment period when the exposure between naïve and non-naïve patients was overall comparable (Naïve: Type 1: 29.8 PY, Type 2/3: 114.6 PY; Non naïve: Type 1: 3.1 PY, Type 2/3: 22.1 PY). In All SMA Patient Population, the rate of AEs per 100PY was comparable between treatment-non-naïve patients in JEWELFISH and treatment-naïve patients with SMA who were treated with risdiplam in SUNFISH (Part 1 and Part 2) and FIREFISH (Part 1 and Part 2). The impact of previous treatment was noticeable in the Type 1 SMA population where patients who had been on previous approved SMA therapies did not experience any Grade 4 or

Grade 5 (fatal) events, although a numerically higher rate of infections was reported in non-naïve patients compared with naïve patients. However, due to the limited data in the non-naïve Type 1 population, these results should be interpreted with caution. In Type 2 and 3 SMA patients, the rate of Grade 3 events was approximately 3-fold higher in treatment-non-naive patients; a higher rate of SAE was observed in non-naïve patients during the first 6 months of treatment however, this did not correspond to higher rates of specific AEs. An analysis of the effect of race on AEs regarding treatment-naïve patients included in Study BP39055 (SUNFISH) in Type 2 and 3 SMA patients, and Study BP39056 (FIREFISH) in Type 1 SMA patients. Overall, the safety profile was similar in both Asian and Non-Asian groups.

Use in pregnancy. Risdiplam has been shown to be embryo-fetotoxic and teratogenic in animals. Risdiplam should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated with risdiplam she should be clearly advised on the potential risk to the foetus.

Drug to drug interactions

Based on *in vitro* investigations, co-administration with risdiplam may increase plasma concentrations of drugs that are substrates of the MATE1/2-K transporters. In all clinical studies with risdiplam, medications that are MATE1/2-K substrates were explicitly prohibited per protocol. Among prohibited medications in SMA clinical studies there were also medications with known phototoxicity and retinal toxicity liabilities. Upon request, the applicant agreed to add specific wording into Section 4.5 of the SmPC: "The potential for synergistic effects of concomitant administration of risdiplam with retinotoxic drugs has not been studied. Therefore, caution in using concomitant medications with known or suspected retinal toxicity is recommended". The applicant requested not to include the term "phototoxicity" in this context, as this term generally refers to light-induced skin reactions. As such, it was considered acceptable to maintain only the overarching term "retinotoxicity". Furthermore, the applicant pointed out that during the open-label extension phase of the ongoing clinical studies in SMA, retinotoxic medications are no longer prohibited and therefore, after the completion of this study, they will want to reassess the appropriateness of this wording in section 4.5 of the SmPC.

Overdose

Very low safety margins were seen for most toxicities observed in animal studies. Risdiplam likely has a narrow therapeutic window. Clinical trial experience in SMA with doses higher than the proposed dose of risdiplam is very limited. There is no antidote.

Drug abuse potential

Overall, available safety data do not suggest a signal of an abuse potential of risdiplam.

Post-marketing data

At the time of the MAA submission, the applicant stated that risdiplam was not presently commercially available in any part of the world so no post-marketing data exist. In United States, FDA has recently approved risdiplam for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older.

2.6.2. Conclusions on the clinical safety

Overall, no major issues were found in the clinical assessment of the safety profile of risdiplam. However, taken together with efficacy assessment, there are some concerns raised by the safety profile of risdiplam remain, especially the long-term adverse events, but their relevance is being clarified in the open-label extension phase (with a 5-years follow-up) of all ongoing clinical studies and in the post-marketing setting and will be dealt with the appropriate risk minimisation measures. Regarding the communication on leakage from commercial product, further clarifications on the safety impact of this quality defect and further implementations of the PI were made as well as clarifications on the measures put in place to actively search for leaking bottles events and to actively monitor potential safety issues related to leaking bottles in the open-label extension phase of all ongoing clinical studies and in the post-marketing setting.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns

Important identified risks	None
Important potential risks	Retinal toxicity Embryofetal toxicity Effect on epithelial tissues
Missing information	Long-term safety

Pharmacovigilance plan

On-going and planned additional pharmacovigilance activities

Table 69

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 minimisation activities			
BP39056 (FIREFISH) OLE Ongoing	Target population: infants (aged 1 to 7 months at enrolment) with Type 1 SMA OLE: Continued general safety as well as ophthalmological monitoring.	Retinal toxicity 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.	Retinal toxicity 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
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.	Retinal toxicity Long-term safety Effect on epithelial tissues	Initial protocol: 02 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.	Retinal toxicity Long-term safety Effect on epithelial tissues	Initial protocol date: 13 July 2018 Current protocol date: Version 3, 18 September 2020 Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the OLE phase Final CSR Estimated: Q3 2026

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 foetal/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	Final protocol: 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 Planned	To estimate the effects of single oral doses of risdiplam on QT interval of the electrocardiogram (QT)/QT corrected for heart rate (QTc) interval in healthy subjects.	Missing information: long-term safety	Final protocol available: Q4 2021 Final report: Estimated Q2 2023

Risk minimisation measures

Summary of pharmacovigilance activities and risk minimisation activities by safety concern

Table 70

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk: Retinal toxicity	**Routine risk minimisation measures:** • Section 4.4 of the SmPC (Special warnings and precautions for use) • Section 5.3 of the SmPC (Preclinical safety data; Effect on retinal structure) **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** • Section 4.5 of the SmPC (Interaction with other medicinal products and other forms of interaction) **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimisation 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: Effect on Epithelial tissues	**Routine risk minimisation measures:** • SmPC Section 5.3 (Preclinical safety data; Effect on Epithelial tissues) **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimisation 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 minimisation 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, breast-feeding and male fertility) **Routine risk-minimisation activities recommending specific clinical measures to address the risk:** • SmPC Section 4.6 (Fertility, pregnancy and lactation) *Pregnancy testing* The pregnancy status of female patients of reproductive potential should be verified prior to initiating risdiplam therapy. Pregnant women should be clearly advised of the potential risk to the foetus. *Contraception in male and female patients* Female patients of childbearing potential should use highly effective contraception during treatment and for at least 1 month after the last dose. Male patients, with female partners of childbearing potential, should both use highly effective contraception during treatment and for at least 4 months after his last dose. • Section 2 of the Package Leaflet (What you need to know before you or your child take Evrysdi; Pregnancy, contraception, breast-feeding and male fertility) *Pregnancy* Do not take Evrysdi if you are pregnant. This is because taking this medicine while you are pregnant could harm your unborn baby. Before you start treatment with Evrysdi, your doctor should do a pregnancy test. This is because Evrysdi may harm your unborn baby. If you do become pregnant during your treatment with Evrysdi, tell your doctor straight away. You and your doctor will decide what is best for you and your unborn baby. *Contraception*	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Study BN42833 (Risdiplam Pregnancy Surveillance Study)

	For women: Do not become pregnant: • during your treatment with Evrysdi and • for one month after you stop taking Evrysdi. Talk to your doctor about reliable methods of birth control that you and your partner should use during treatment and for one month after you stop treatment. For men: If your female partner is of childbearing potential, you need to avoid pregnancy. Use condoms during your treatment with Evrysdi and continue to use condoms 4 months after treatment has finished. **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimisation measures:** • None	
Missing Information: Long-term safety	**Routine risk minimisation measures:** • None **Other risk minimisation measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimisation 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)

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 07.08.2020. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Evrysdi (risdiplam) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed therapeutic indication was:

"Treatment of spinal muscular atrophy (SMA)"

The severity of spinal muscular atrophy is highly variable and SMA subtypes are defined by age at onset and the most advanced motor milestone achieved during development.

SMA is an 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*. 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 functional SMN protein produced by the *SMN2* gene. Children born with multiple copies of the *SMN2* gene have milder phenotypes, further demonstrating that the pathophysiology of the disease is due to insufficient production of functional SMN protein.

To date, 4 *SMN2* copies have been reported causing disease across the whole SMA spectrum, including in patients with a more severe phenotype, the Type 1 albeit very rarely. According to the largest worldwide series of genetically confirmed SMA patients ever published to date (n=2834), the great majority of the 459 patients with 4 *SMN2* copies had Types 2 or 3 SMA (11% and 82%%, respectively).

Clinical studies have involved patients with SMA types 1, 2 and 3. Furthermore, studied patients with known *SMN2* copy number status, only patients with two to four copies have been studied. As such, the finally adopted indication is:

"Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies.".

3.1.2. Available therapies and unmet medical need

There are currently two authorised disease specific agents for the treatment of SMA: Spinraza (nusinersen) and Zolgensma (onasemnogene abeparvovec).

The intrathecally administered *SMN2*-targeting antisense oligonucleotide nusinersen (Spinraza) is approved for the treatment of SMA in paediatric and adult patients. Onasemnogene abeparvovec (Zolgensma) is a one-time intravenously administered, gene replacement therapy that uses a non-replicating adeno-associated virus 9 (AAV9) capsid to deliver a functional copy of the *SMN* gene by intravenous infusion; it is approved in the United States and Japan for paediatric patients with SMA <2 years of age. In the European Union (EU), onasemnogene abeparvovec is approved conditionally for the treatment of patients up to 21 kg in weight with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the *SMN2* gene.

There remains a significant unmet clinical need for effective treatments for SMA patients because not all SMA patients respond, tolerate and have access to approved medications.

A group of expert clinicians and scientists convened in 2020 to develop a treatment algorithm for SMA. The working group recommended immediate treatment for infants with 4 copies of *SMN2* diagnosed with SMA via newborn screening (Glascock et al. 2020). The expert group recognised that early treatment could prevent possible long-term disease complications, reduce the costs related to morbidity management, and reduce parents' anxiety and stress of waiting for the imminent onset of SMA disease.

3.1.3. Main clinical studies

Study BP39056 (FIREFISH)

Study BP39056 (FIREFISH) is an ongoing open-label single-arm study in infants with genetically confirmed Type 1 SMA. The study inclusion criteria allowed the characterisation of the effects of risdiplam treatment in infantile-onset SMA type 1. The enrolment criteria selected infants with two SMN2 copies and early onset of SMA symptoms, ensuring only patients with symptoms and diagnosis of Type 1 SMA disease at baseline were recruited, warranting the most representative patient population for the assessment of risdiplam benefits in infants living with SMA.

A comparator placebo group was not included in Study BP39056 (FIREFISH), given the rapid decline of the disease. At the time of study start there were no approved disease modifying therapies, which precluded an active comparator arm. Instead, the MAA has used a natural history source, with similar population, to define thresholds of achievement.

The primary endpoint for Part 2 (sitting unassisted) can be objectively measured. Sitting without support is never achieved in untreated patients with Type 1 SMA, thus developing this motor milestone would clearly diverge from the natural disease course of infantile-onset SMA.

Other relevant outcomes have been assessed, namely overall survival, for young infants diagnosed with infantile-onset SMA. In addition, the effect of risdiplam therapy was assessed in a combined

endpoint: the survival rates of affected infants and survival without permanent ventilation (event-free survival), two severe complications of Type 1 SMA. Risdiplam efficacy was supported by assessments of further clinical outcomes, such as the maintenance of the swallowing function and the ability to feed orally, and further gains in motor milestones and motor function.

The scales used in this trial to assess further motor milestone development (Hammersmith Infant Neurological Examination Module 2 [HINE-2]) and motor function development (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders [CHOP-INTEND]) are the most widely used and well-known scales for the assessment of changes in Type 1 SMA in both clinical practice and clinical research, including clinical trials.

Study BP39055 (SUNFISH)

Study BP39055 (SUNFISH) was designed to include a broad sample of patients with Type 2 and 3 SMA, representative both in age and disability status of patients seen in clinical practice. Consequently, recruited patients had a wide range of disease duration at the time of enrolment, and experienced different degrees of SMA-related complications such as severe scoliosis, muscle weakness and joint contractures. A narrower study population focusing, for example, on young patients only would have allowed a more homogeneous and easier assessment of efficacy (as size and type of treatment effects may vary by age) and could lead to a higher chance for the study to be successful. On the other hand, however, the heterogeneity of patients enrolled in Study BP39055 (SUNFISH) allowed characterisation of the effects of treatment with risdiplam on the most prevalent SMA patient population: children, teenagers and adults living with Type 2 and non-ambulant type 3 SMA.

Study BP39055 (SUNFISH) enrolled adults up to 25 years of age. Patients with disease onset at adulthood (such as Type 4) were not included in this study. Type 4 SMA is a very rare type of the disease and enrollment of a sufficient number of patients would have been challenging to achieve in a timely manner. In addition, the majority of Type 4 patients are stronger and their disease progresses much more slowly as compared to other SMA types. Ambulant type 3 SMA patients were also excluded from the pivotal trial.

Study BP39055 (SUNFISH) Part 2 was designed based on two sets of data: a longitudinal, retrospective, natural history study of Type 2 and 3 SMA patients where the MFM was used to monitor disease progression (Vuillerot et al. 2013) and the data from the placebo control arm of Study WN29836 (a Phase II SMA study for a discontinued development compound, olesoxime), including Type 2 and non-ambulant Type 3 patients. Both sources of data helped to determine the treatment effect of Study BP39055 (SUNFISH) as they assessed a population of similar SMA type and age range. After consideration of all options, including the rare nature of the disease and limited patient pool available, Roche decided to power the trial for a 3-point difference leading to a trial size still feasible in the SMA population.

3.2. Favourable effects

Reaching sitting status in SMA 1 or walking in SMA 2 and non-ambulant 3 are self-explanatory as benefits, as these describe developmental milestones that will be unachievable in these patients otherwise. However, sitting status is valid beyond 5 secs without help, which reduces external validity.

The observed results in developing a milestone, improving motor function and event free survival in the treated patients with different SMA types are presented below:

SMA 1: Proportion of patients sitting without support for at least 5 seconds (BSID-III) (90% CI): 29.3% (17.8%, 43.1%)

SMA 2&3: Change from baseline in MFM32 total score, LS means (SE) difference from placebo (95% CI): 1.55 (0.64) (0.30, 2.81), p-value 0.0156

Proportion of patients reaching a milestone or improving a minimally significant endpoint may have different impact on QOL.

SMA1: Proportion of motor milestone responders as assessed by the HINE-2 (90% CI): 78.0% (64.8%, 88.0%)

SMA 2&3: Motor Function Measure 32 (MFM32) (Proportion of patients with a change from baseline in MFM32 ≥3 at 12 months): Odds ratio for overall response (95% CI): 2.35 (1.01, 5.44); p-value: unadjusted p=0.0469; adjusted p=0.0469

SMA 1: Percentage alive without permanent ventilation (90% CI) :85.4% (73.4%, 92.2%) (performance criterion from natural history expected to be 42%)

There is consistency between effects in SMA 1 and SMA 2&3.

In risdiplam studies enrolling later-onset SMA (Type 2 and 3), 44/405 (11%) of patients had 4 *SMN2* copies. This number represents 22/231 (10%) of patients seen in Study BP39055 (SUNFISH) (both Parts 1 and 2) and 22/174 (13%) in Study BP39054 (JEWELFISH). These patients' age ranged from 2□24 years in Study BP39055 (SUNFISH) and 13□60 years in Study BP39054 (JEWELFISH).

3.3. Uncertainties and limitations about favourable effects

SMA 1 trial was not placebo controlled. SMA 2&3 patients were mostly non-ambulant most of the time; therefore, effect on ambulant children is not available.

Only mild to moderately severe patients were included. Severely diseased patients were not included, and response in these patients (efficacy and safety) is not known.

SMA type 4 patients were also excluded, thus not providing enough data to reliably assess the B/R ratio in this population.

The relevance of sitting for ≥5 seconds without support is of less relevance than sitting without support for ≥30 seconds at 12 months (7/41, 17.1%).

The results with risdiplam have been contextualised with the results in other SMA directed treatments. The need to include or exclude from the indication patients that previously received treatment with Zolgensma, also in light of updated data from the JEWELFISH study, needs further discussion.

Benefit of treatment on respiratory status of Type 2 or 3 SMA patients has not been demonstrated.

In later-onset SMA, even though the difference from PBO on the primary endpoint (MFM-32) in SUNFISH trial Part 2 was statistically significant, the absolute difference from PBO was relatively modest (1.6-point difference on a 100-point scale) and no statistically significant difference from PBO was observed in the secondary endpoints HFMSE. The modest effects observed may be due to the short study duration (12 months) and to the heterogeneity of the patient population enrolled in the trial.

The absence of significant differences from PBO observed on the secondary endpoint Hammersmith Functional Motor Scale Expanded (HFMSE) are likely a consequence of the low motor function scores at baseline. Subgroup analyses according to disease severity defined as HFMSE total score ≥ 10 or < 10 at baseline, for the HFMSE, MFM-32 and RULM endpoints (mean change from baseline and responders analysis) at 12 months and at 24 months have been provided, which support robustness of data.

The applicant argues that for the patient population enrolled in SUNFISH Study Part 2, that includes older patients with progressed disease, functional stabilisation (≥0 change from baseline in MFM-32) is an important treatment benefit. However, in Part 2 of the SUNFISH trial, according to clinician's impression of a patient's change in global health from baseline (CGI-C), a similar proportion of patients global health either improved or did not change from baseline in the risdiplam arm (85.8%) compared to the placebo arm (83.3%) at Month 12 .

Given the limitations of the available data described above, more comprehensive long term data are needed to assess whether treatment with risdiplam significantly changes the natural history of the disease in later onset SMA (Type 2 and Type 3), and characterise the effect in pre-symptomatic patients and pts with 4 SMN2 copies. A PAES study is being implemented to respond to these pending questions.

The proposed PAES objectives (outcomes in treated pre-symptomatic stage pts, pts with 4 SMN2 copies and long-term maintenance of efficacy and safety in SMA pts) will respond to the impending issues. The outcomes, however, should be compared to similar condition patients who have not been treated with risdiplam (natural history patients). The population (including both risdiplam treated and non-treated patients) should ideally come from the same registries, to decrease the risk of biases resulting from different study populations and different epochs. This aspect is especially relevant for the assessment of B/R in patients with 4 SMN2 copies: longitudinal data for both treated and non-treated patients must be available at the end of the study in this population. Status reports are expected annually, independently from the planned interim analysis. These status reports will allow assessment of ongoing recruitment and follow-up attrition, to confirm feasibility within the proposed timeframe, and to implement recruitment strategies if needed.

3.4. Unfavourable effects

Overall, 84.5% of patients treated with risdiplam had at least one AE with comparable rates between the two SMA patient populations (Type 1 SMA 93.5% vs. 82.7%). Grade 3 and 4 AEs were reported with 2.5-fold and 18.5-fold higher rates in the Type 1 SMA group compared with the Type 2 and 3 SMA group respectively. Consistently, Grade 3-4 AEs and SAEs were reported more frequently in patients <2 years of age compared with patients of the other age groups as well as deaths, which occurred only in this age group, as it could be generally expected given the more severe SMA phenotype. Overall, the requested updated review of the safety data at the most recent clinical cutoff dates did not indicate relevant differences compared with the safety data presented with the MAA at the previous clinical cutoff dates.

A trend towards a higher rate of AEs was observed in Type 1 SMA patients compared with Type 2 and 3 SMA patients in the SOC Infections and Infestations (particularly driven by upper respiratory tract infection related AEs), General disorders and administration site conditions (particularly driven by pyrexia), Respiratory, thoracic and mediastinal disorders, and Skin and subcutaneous disorders. In Type 2 and 3 SMA patients, rates of AEs were higher in the SOCs Nervous system disorders and Musculoskeletal and connective tissue disorders (driven by pain in extremity, arthralgia, back pain, and headache) followed by the SOCs Injury, poisoning and procedural complications and Reproductive system and breast disorders.

In the whole SMA Patient Population, the rate of AEs per 100PY was comparable between treatment-non-naïve patients in JEWELFISH and treatment-naïve patients with SMA who were treated with risdiplam in SUNFISH (Part 1 and Part 2) and FIREFISH (Part 1 and Part 2). The impact of previous treatment was noticeable in the Type 1 SMA population where patients who had been on previous approved SMA therapies did not experience any Grade 4 or Grade 5 (fatal) events, although a

numerically higher rate of infections was reported in non-naïve patients compared with naïve patients. However, due to the limited data in the non-naïve Type 1 population, these results should be interpreted with caution, and no recommendations can be made. In Type 2 and 3 SMA patients, the rate of Grade 3 events was approximately 3-fold higher in treatment-non-naive patients; a higher rate of SAE was observed in non-naïve patients during the first 6 months of treatment however, this did not correspond to higher rates of specific AEs.

The most common AEs reported at the highest rates per 100PY in the All patients with SMA were: headache (55.81), pyrexia (43.15), upper respiratory tract infection (41.62), and nasopharyngitis (27.81), vomiting (22.82), and cough (18.41). The higher rate of pneumonia and upper respiratory tract infections, in general, in Type 1 SMA patients compared to Type 2 and 3 SMA patients may be related to the higher severity of the disease observed with the Type 1 SMA phenotype.

In patients with Type 1 SMA, the most commonly reported AEs were pyrexia (40.3%), upper respiratory tract infection (41.6%), pneumonia (27.3%), vomiting (11.7%), nasopharyngitis (14.3%), constipation (15.6%), respiratory tract infection (10.4%), diarrhoea (13.0%), rhinitis (10.4%).

In patients with Type 2 and 3 SMA, the most commonly reported AEs (>5% of frequency) were headache (16.5%), pyrexia (19.1%), upper respiratory tract infection (22.2%), nasopharyngitis (18.3%), vomiting (13.9%), cough (11.9%), diarrhoea (12.4%), nausea (7.7%), gastroenteritis (9.0%), pneumonia (6.7%), rash (6.4%), constipation (4.9%), respiratory tract infection (5.2%), and rhinitis (3.4%). In the double-blind, placebo-controlled Part 2, AEs that occurred with a higher frequency in the risdiplam group compared with the placebo group were pyrexia (20.8% vs 16.7%), headache (20.0% vs. 16.7%), diarrhoea (16.7% vs. 8.3%).

Rash and all AEs included in the proposed SmPC section 4.8 under the PT rash (rash maculo-papular, erythema, dermatitis, dermatitis allergic, rash popular, folliculitis) occurred in both SMA patient populations with a frequency >10%.

The most frequently reported treatment-related AE in All SMA patients was diarrhoea (9 patients, 1.9%), followed by nausea (7, 1.5%), rash (5, 1.1%), and headache (5, 1.1%). In Type 1 SMA patients: rash maculo-papular, skin discoloration, constipation, and neutropenia (2 patients, 2.6% each); One SAE was considered related to treatment (neutropenia). In Type 2 and 3 patients: diarrhoea (8 patients, 2.1%), nausea (7 patients, 1.8%), rash (5 patients, 1.3%), and headache (5 patients, 1.3%). Other AEs considered as treatment-related were: aphthous ulcer and dry skin (3, 0.8% each), mouth ulceration, skin exfoliation, weight increased, dizziness, upper respiratory tract infection (2, 0.5% each).

It could not be neglected that in some, although few cases, mild non-serious dizziness occurred with apparent causal relationship with the risdiplam treatment based on the investigator's judgement. After a review of these cases, the applicant pointed out that none of these events was reported in the risdiplam arm during the double-blind placebo-controlled phase of the SUNFISH study while 2 AEs were reported in 2 (3.3%) patients in the placebo arm. Of note, the AE of mild dizziness associated with nausea was reported in a healthy volunteer who received risdiplam and the event resolved the same day. As a further reassurance, as requested, the applicant committed to monitor for and to provide detailed data on the occurrence of AEs of dizziness/vertigo in the long-term open-label phase of all ongoing clinical studies (follow-up duration of 5 years) and in the post-marketing setting. Therefore, the applicant committed to provide a thorough analysis of these data in the incoming PSURs also to evaluate whether dizziness/vertigo should be mentioned in section 4.7 of the SmPC for driving or using machines.

In the SUNFISH Part 2, during the double-blind, placebo-controlled period, the overall percentage of patients with at least one related AE was slightly higher in the risdiplam arm compared with the placebo arm (13.3% [16] vs. 10.0% [6]): mouth ulceration, nausea, upper respiratory tract infection, headache (2 patients each, 1.7%), abdominal pain upper, dermatitis acneiform, eczema, rash, rash maculo-papular, skin discoloration, gastroenteritis viral, palpitations, cataract subcapsular, posterior capsule opacification, hypercholesterolemia (1 patient each).

In order to provide the prescriber with a complete information on the risdiplam safety, the following AEs reported with a relative higher frequency, considered related to the treatment by investigators, or related to the mechanism of action of risdiplam, have been included in section 4.8 of the SmPC: headaches, mouth ulcerations and aphthous ulcers, urinary tract infections including cystitis, arthralgia, pyrexia (including hyperpyrexia), and nausea.

The occurrence of AEs in the SOC Skin and subcutaneous tissue disorders, Eye disorders, the effects on bone marrow, male germ cells, and on heart are of particular interest given i) the physicochemical properties of risdiplam and its mechanism of action of risdiplam in terms of induction of alternative splicing of other off target genes and the nonclinical findings; ii) the relationship between some of these AEs and risdiplam treatment; iii) the fact that some of these AEs did not resolve with the ongoing risdiplam treatment; iv) the very low safety margin and, hence the likely narrow therapeutic window, of risdiplam, iv) the chronic treatment with risdiplam, and v) the potential low frequency of these AEs probably non-adequately detected due to the relatively low exposure to risdiplam in the current safety dataset.

In the All SMA Patient Population, AEs in the SOC Skin and subcutaneous tissue disorders were reported in 23.7% of patients (Type 1 SMA: 35.1%; Type 2 and 3 SMA: 21.4%). Of these, 3.9% were reported as treatment related. In the double-blind, placebo-controlled SUNFISH Part 2 there is a clear higher frequency (approximately 3-fold higher) of epithelial tissue-related AEs in patients receiving risdiplam compared with those receiving placebo (30.8% vs. 11.7%). Besides rash and correlated terms, other AEs were observed, although in only 1 or 2 patients in the risdiplam arm versus none in the placebo arm (particularly skin discoloration but also skin exfoliation, dry skin, pruritus, photosensitivity reaction, erythema, palmar erythema, hyperkeratosis [which is a skin/epithelial tissue-related event similar to those reported in non-clinical studies], skin induration, skin lesion, eczema, dandruff, skin erosion, urticaria, dermatitis acneiform, skin discoloration, macule), which can be suggestive of an effect of risdiplam on skin and epithelial tissues in general. The applicant has proposed to include "Effects on epithelial tissue" as important potential risk in the RMP which has been accepted. The applicant agreed to comply with the requested commitment to monitor of to provide detailed data on the occurrence of skin/epithelial tissue-related AEs other than those under the PT "rash" (already reported in the ADR Table of the SmPC section 4.8) in the long-term open-label phase of all ongoing clinical studies (follow-up duration of 5 years) and in the post-marketing setting. Therefore, a thorough analysis of these data in the upcoming PSURs will be provided.

Retinal degeneration has been observed in non-human primates. Concerning ophthalmology AEs, in the All SMA Patient Population, events in the SOC Eye disorders were reported in 29 (6.2%) patients (Type 1 SMA: 6.5%; Type 2 and 3 SMA: 6.2%). All events were mild, considered unrelated to study treatment. In the double-blind, placebo-controlled SUNFISH Part 2, more patients in the placebo group had AEs in the SOC Eye disorders compared with risdiplam arm (10.0% vs. 6.7%). There is no evident signal of retinal toxicity associated with risdiplam treatment from clinical data, in the absence of structural changes to the retina or relevant visual acuity or visual field impairment detected on neuroimaging assessment or visual function testing. However, still, OCT and ophthalmological examination at very low ages may be problematic. Furthermore, it should be considered that the

majority of patients (approximately half of patients, n=243) had an ophthalmological follow-up of at least 1 year. 72 completed a follow-up of at least 2 years and only 12 of at least 3 years. In the setting of a chronic treatment like the treatment with risdiplam is, there is the possibility that events related to delayed retinal toxicity could be observed in a longer term and with a very low frequency that would need a longer exposure. Therefore, in the absence of long-term safety data, at the moment it is not completely and definitely known whether the non-clinical findings translate into an actual risk in humans. The applicant considered retinal toxicity observed in monkey as an important potential risk and put in place risk minimisation measures (SmPC section 5.3, preclinical safety data in the RMP as well as routine pharmacovigilance activities beyond adverse reaction reporting and signal detection (routine PSUR/PBRER reporting until completion of the open-label extension phases of the risdiplam studies where patients will continue to be monitored for ophthalmological findings). A warning has been added to section 4.4 of the SmPC that long-term data are still limited and the clinical relevance of these nonclinical findings in the long-term has therefore not been established. The applicant agreed to comply with the requested commitments to monitor for and to provide detailed data on the occurrence of AEs related to retinal toxicity in the post-marketing setting.

Consistent observation of the effect of risdiplam on male germ cells in monkeys and rats, although, reversible, 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. The potential risk of adverse effects of risdiplam on human sperm as a consequence of its mechanism of action on secondary splice targets has not been characterised in clinical studies. This represents a concern since patients may reach reproductive age or some patients with Type 2 or 3 SMA may have already reached this age at the time of starting treatment with risdiplam. The applicant clarified that no data had been collected in humans and that it is not planned to collect these data in the future. After further discussion on male fertility impact of risdiplam, the applicant has added information in sections 4.4 and 4.6 of the SmPC, providing a recommendation to avoid sperm cell donation and consider preservation strategies prior to treatment initiation or after a drug free period of at least 4 months.

Overall, the number of patients with shifts in blood cell lines was low and did not increase over time. In Type 1 SMA pool, a clinically relevant decline in blood cell lines was reported in 6 patients (the most relevant were 2 AEs of neutropenia and 1 of anaemia). In Type 2 and 3 SMA pool, a clinically relevant decline in cell lines was reported in 3 patients (the most relevant were 1 case of neutropenia and 1 case of anaemia). Overall, clinical findings suggest that there is not an evident signal of relevant bone marrow toxicity associated with risdiplam treatment. However, 2 AEs of neutropenia were reported to be related to risdiplam treatment, one of them as SAE. Furthermore, neutropenia was already present at screening in some of these cases or occurred concomitantly with conditions like infections which may have led to temporary decrease in the neutrophil count. However, in the setting of a chronic treatment like the treatment with risdiplam is, with very low safety margins, and hence a likely narrow therapeutic window, there could be the possibility that events related to bone marrow toxicity could be observed in a longer term and with a very low frequency that would just need a longer exposure. Furthermore, neutropenia could be clinically relevant in terms of risk of infection, particularly in a population of patients like those with SMA. Therefore, in the absence of long-term safety data, at the moment it is not completely and definitely known whether the non-clinical findings translate into an actual risk in humans. Haematological parameters and related AEs will be collected until patients complete the 5 years of treatment with risdiplam in the long-term open-label phase of all ongoing clinical studies. The applicant agreed to comply with the requested commitments to monitor for and to provide detailed data on the occurrence of AEs of neutropenia and other haematological-related AEs

also in the post-marketing setting. Therefore, a thorough analysis of these data in the upcoming PSURs will be provided.

Cardiac and rhythm AEs have also been identified. Indeed, in the All SMA Patient Population, there were changes from baseline in ECG parameters, although in few patients. The percentage of patients with average QT, QTcB or QTcF above 450 ms, or change from baseline above 30 ms, was low and did not increase with time. No relevant differences were reported between risdiplam and placebo arms in the double-blind, controlled period of SUNFISH Part 2. The applicant has added a planned tQT Study BP42817, a Phase I, double-blind, placebo- and positive-controlled crossover study to investigate the effects of risdiplam on QTc interval in healthy subjects, as an additional pharmacovigilance activity. The study is included in Section III.3 "Additional Pharmacovigilance Activities", as well as in Table 25 - Ongoing and Planned Additional Pharmacovigilance Activities.

SAEs occurred in 22.2% of the All SMA Patient Population. The rate of SAEs was approximately 3.5-fold higher in patients with Type 1 SMA compared with patients with Type 2 and 3 SMA (54.5% vs. 15.7%). This difference was mainly driven by the higher rate of SAEs in the Type 1 SMA patients compared with Type 2 and 3 SMA patients in the SOC of Infection and Infestations (42.9% vs. 10.3%) and Respiratory, thoracic and mediastinal disorders (16.9% vs. 1.8%), and in particular by the AE pneumonia (23.4% vs. 4.4%). All SAEs pneumonia resolved except for two fatal cases in patients with Type 1 SMA. These observed differences between the two SMA patient populations are plausible considering the more severe disease phenotype in patients with Type 1 SMA who are more prone to develop respiratory complications and infections. All SAEs were considered unrelated to treatment, except for 1 SAE of neutropenia e 1 SAE of supraventricular tachycardia.

Six deaths were reported, all occurred in Type 1 SMA patients due to SMA-related respiratory complications. One additional patient died 3.5 months after discontinuation from risdiplam therapy during the safety follow-up period due to acute airway obstruction from secretion/mucous plug which caused hypoxia and consequently cardiac arrest. None of these deaths were considered by the investigator as related to study treatment: the cause of death was classified as "progressive disease" in 6 out of 7 cases and as "adverse event" in the remaining case. Overall data do not show a higher risk of death associated to risdiplam treatment.

3.5. Uncertainties and limitations about unfavourable effects

Patients with advanced disease in both Type 1 (infantile onset) and Type 2 and 3 (later onset) SMA, and hence the very severe population, as well as adult type (Type 4) SMA have not been specifically studied in clinical trials. This discussion has previously been held on efficacy. Only limited safety data is available for patients below 2 months of age. SMA type 4 patients have not been included in clinical studies.

The median duration of exposure to risdiplam was 12.68 months (range: 0.0–38.9), with an overall exposure of 521.4 PY. Type 1 SMA patients tended to have a longer median exposure compared with Type 2 and 3 SMA patients: 15.24 months (range 0.1-34.6) vs. 9.30 months (range 0.0-38.9) (overall exposure of 92.1 PY vs. 429.2 PY). Given the above, the long-term safety profile of risdiplam is still uncertain because data are scarce in both SMA 1 and 2 and 3. Strategies to collect long-term safety data on risdiplam have been discussed and will be added to the PAES. A study using rasH2 transgenic mice with 6 months duration of treatment did not generate evidence for a tumorigenic potential. There is no evidence of genotoxicity and carcinogenicity from the available clinical data at the CCOD. However, long-term non-clinical and clinical data on the carcinogenicity risk of risdiplam are still missing and this represents a concern since risdiplam is used to treat a severe, life threatening disease. In clinical studies patients with a history of malignancy if not considered cured were excluded. Therefore, definite conclusions on the carcinogenicity potential of risdiplam in humans cannot be still

drawn. However, open-label extension studies will be followed patients up to 5 years. Furthermore, a 2-year carcinogenicity study in rats has been started in September 2020 and the final study report is expected by Q3 2023; this needs to be reflected in the SmPC section 5.3 "Preclinical safety data". Information in the SmPC will be updated as soon as adequate evidence is produced.

SMA patients may be more at risk of having transaminase elevations because deletion of SMN exon 7 directed to liver leads to severe defect of liver development in mouse models. As requested, the applicant discussed the safety data from 474 patients treated for up to 43.1 months showing that risdiplam does not increase the risk of hepatocellular injury in SMA patients. It was highlighted that patients with SMA may be at increased risk for transaminase elevations based on the evidence of deleterious effects of SMN protein depletion on liver development in mouse models and evidence for abnormal fatty acid metabolism and liver steatosis in patients with SMA Type 1-3. For this reason, according to the applicant, the treatment with risdiplam may contribute to stabilizing liver function in SMA patients by increasing SMN protein levels also outside of the CNS. The applicant agreed to comply with the requested commitments. to monitor for and to provide detailed data on the occurrence of AEs related to hepatic injury in the open-label extension phase of all ongoing clinical studies (follow-up duration of 5-year) and in the post-marketing setting. Therefore, a thorough analysis of these data in the upcoming PSURs will be provided.

Concerning drug-to-drug interaction, as requested, a recommendation on the concomitant on caution in using medications with known or suspected retinal toxicity has been added to the SmPC.

As regards to quality, the MAA should commit to conduct a new PET study according to Ph. Eur. 5.1.3.

3.6. Effects Table

Table 71: Effects Table for Evrysdi (risdiplam)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
SMA 1 Proportion of patients sitting without support for at least 5 seconds	Sitting frequency	%	29.3	5*	*-Performance criterion as expected from natural history	Study BP39056 (FIREFISH) Part 2
SMA 1 Proportion of motor milestone responders as assessed by the HINE-2	Responders reaching new milestone	%	78	12*	*-Performance criterion as expected from natural history	Study BP39056 (FIREFISH) Part 2
SMA 1 Proportion of patients alive without permanent ventilation	% PT alive w/o ventilation	%	85.4	42*	*-Performance criterion as expected from natural history	Study BP39056 (FIREFISH) Part 2
SMA 1 Proportion of patients alive	% PT alive	%	92.7	60*	*-Performance criterion as expected from natural history	Study BP39056 (FIREFISH) Part 2
SMA 2&3 Change from baseline in MFM32 total score, LS means	MFM32 value (positive = improvement)	Change from baseline	1.36	-0.19	Absolute difference from PBO relatively modest (1.6-point difference on a 100-point scale), although sustained / improved in	Study BP39055 (SUNFISH) Part 2

					patients that reached 2 years of treatment	
SMA 2&3 Proportion with a change from baseline MFM32 total score ≥3	MFM32 responder	%	38.3	23.7		Study BP39055 (SUNFISH) Part 2
SMA 2&3 Change from baseline in RULM total score, LS means	RULM value (positive = improvement)	Change from baseline	1.61	0.02	Translation into benefit mostly in non-ambulant children	Study BP39055 (SUNFISH) Part 2
SMA 2&3 Change from baseline in HFMSE total score, LS means	HFMSE value (positive = improvement)	Change from baseline	0.95	0.37	no statistically significant difference from PBO	Study BP39055 (SUNFISH) Part 2
Unfavourable Effects						
Diarrhoea in SMA 1	incidence	%	13.0% (13.02 Number of events/ 100 patient years)	NA	Impact on patient wellbeing / risk of dehydration	Study BP39056 (FIREFISH) Part 1 and 2 and BP39854 (JEWELFISH)
Rash in SMA 1	incidence	%	6.5%	NA	Relevance of ageing skin	
Diarrhoea in SMA 2&3	incidence	%	12.4% (16.77 per 100PY)	8.3%	Impact on patient wellbeing / risk of dehydration	Study BP39055 (SUNFISH) Part2
Rash in SMA 2&3	incidence	%	6.4%	1.7%	Relevance of ageing skin	Study BP39055 (SUNFISH) Part2
Headache in SMA 2&3	Frequency per 100 PT years	%	16.5% (67.79 per 100PY)	?	Impact on patient wellbeing	Study BP39055 (SUNFISH) Part2

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The patient population enrolled in FIREFISH and SUNFISH trial is not representative of the broad indication initially sought by the applicant as patients with Type 4 SMA were not included in the clinical trials. As the result of the assessment, it was agreed to include in the approved indication only SMA types 1, 2 and 3, thus reflecting the population has been studied in clinical trials.

SMA type 1: The results of FIREFISH Part 2 show favourable effects of risdiplam on motor milestones and survival at 12 months, compared to natural history data of Type 1 SMA patients. The effect is apparently maintained.

Later onset SMA (Type 2 and non-ambulant Type 3): Considering the slow progression of Type 2 and Type 3 SMA, and although the modest effects observed on motor function may be sustained within 24 mths of treatment, the relevance of the efficacy, particularly in older and later onset SMA patients, is still not clear.

Some concerns raised by the safety profile of risdiplam remain, especially the long-term adverse events, but its relevance is being clarified in the ongoing 5 years follow-up study and can be dealt with the appropriate risk minimisation measures.

As regards to quality aspects, the applicant commits to reduce the amount of preservative after the marketing authorisation is granted as recommended in the EMA guidelines. Concerning the communication on leakage from commercial product, besides the commitment requested to the applicant whereby the container closure system and packaging material will be thoroughly reviewed, further requested clarifications on the safety impact of this quality defect and further implementations of the PI were made as well as clarifications on the measures that have been put in place to actively search for leaking bottles events and to actively monitor potential safety issues related to leaking bottles in the open-label extension phase of all ongoing clinical studies and in the post-marketing setting.

3.7.2. Balance of benefits and risks

A clinically relevant effect, of sufficient magnitude and duration, on development milestones in mild to moderate SMA 1, and on motor function in SMA type 2 and non-ambulant type 3 patients, has been identified.

The risks associated with risdiplam treatment are considered manageable in the clinical setting.

Enrolled patients in the risdiplam clinical development programme were symptomatic patients with SMA type 1, type 2 and type 3. For these patients a positive B/R ratio can be established and further information to be gathered in the agreed post authorisation PAES. Patients with type 4 SMA were not included, hence it was not possible to conclude on the B/R ratio in this population.

It may be acknowledged that the overall findings of the risdiplam studies and the literature support the early initiation of treatment with risdiplam. The benefit/risk balance is therefore considered favourable also in patients with up to 4 SMN2 copies that have received a genetic diagnosis, considering the unmet need and extrapolating the observed beneficial effects from the symptomatic patients. The uncertainties of such extrapolation of the data from symptomatic patients to pre- or pauci-symptomatic patients that have not yet reached the criteria for clinical diagnosis are also expected to be clarified by the data, generated in the agreed post-authorisation measures.

The clinical course of SMA in patients with 4 copies of SMN2 that have received a genetic diagnosis is not considered to be straightforward. In the significant majority of cases patients with four copies of the SMN2 gene will develop clinically a milder form of the disease i.e. SMA type 2 or SMA type 3. Even though these are considered "milder" in comparison to SMA type 1, it has to be recognised that SMA type 3 is still a seriously debilitating disease, significantly affecting the life of the patients. In a minority of cases a patient with 4 copies of SMN2 will develop the disorder once adulthood has been reached i.e. SMA type 4. If this is the case, it is reasonable to assume that such patients likely possess protective factors that prevent an earlier expression of the disease. In these patients, together with patients with more than 4 copies of SMN2, the positive benefit cannot yet be extrapolated from the results of the clinical trials in the development programme for risdiplam. As such, the approved indication for risdiplam does not currently include patients with SMA type 4.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

3.8. Conclusions

The overall B/R ratio of Evrysdi is positive in the approved indication.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that risdiplam is not similar to Spinraza (nusinersen) and Zolgensma (onasemnogene abeparvovec) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Evrysdi is favourable in the following indication:

"Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies."

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation Efficacy Study (PAES): 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.	Final study report: 2030

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that risdiplam is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

Risdiplam is not used in any medicinal product previously authorised in the European Union (EU), and is not a salt, complex, or isomer or mixture of isomers, or a derivative of an authorised active substance the administration of risdiplam would not expose the patient to the same therapeutic moiety as an active substance already authorised in the EU.