25 July 2024
EMA/412864/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Evrysdi

International non-proprietary name: Risdiplam

Procedure No. EMEA/H/C/005145/II/0022

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	15 Apr 2024	15 Apr 2024	☐
☐	CHMP Rapporteur Assessment Report	21 May 2024	20 May 2024	☐
☐	CHMP members comments	03 June 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	06 June 2024	n/a	☐
☐	Start of written procedure	11 June 2024	11 June 2024	☐
☐	Request for supplementary information (RfSI)	13 June 2024	13 June 2024	☐
☐	MAH re-submission deadline	25 June 2024	25 June 2024	☐
☐	Re-start of procedure	26 June 2024	26 June 2024	☐
☐	CHMP Rapporteur Assessment Report	10 July 2024	10 July 2024	☐
☐	CHMP members comments	15 July 2024	15 July 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	18 July 2024	18 July 2024	☐
☐	Start of written procedure	23 July 2024	n/a	☐
☒	Opinion	25 July 2024	25 July 2024	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 27 March 2024 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	None

Submission of the final report from study 'BP39055 (SUNFISH)' listed as a category 3 study in the RMP. Study BP39055 is a Two-Part Seamless, Multi-Center Randomized, Placebo-Controlled, Double-blind Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of RO7034067 in Type 2 and 3 Spinal Muscular Atrophy Patients.

The requested variation proposed no amendments to the Product Information.

2. Overall conclusion and impact on the benefit/risk balance

Risdiplam (Evrysdi®) is the first orally administered small molecule *SMN2* (survival of motor neuron 2) splicing modifier developed for the treatment of spinal muscular atrophy (SMA).

Risdiplam was first granted marketing approval in the European Union on 26 March 2021. The approved indication in the European Union is the following:

Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.

In this Type II variation, the final clinical study report for Study BP39055 (SUNFISH) is being submitted to fulfil a Category 3 required pharmacovigilance activity for risdiplam listed in the E.U. Risk Management Plan (RMP). Specifically, submission of this Final CSR addresses the obligation to evaluate the long-term safety of risdiplam and its effect on epithelial tissues.

Study BP39055 was a two-part, operationally seamless, multicenter, randomized, placebo-controlled, double-blind study designed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in patients with later-onset (Type 2 and Type 3) SMA.

The study consisted of an exploratory dose-finding part (Part 1) and a confirmatory part (Part 2) that started after the dose had been selected in Part 1. In Part 1 the initial risdiplam doses were 0.02, 0.05, 0.25 mg/kg (for 2-11 year old patients), and 3 and 5 mg (for 12-25 year old patients). Patients in Part 1 switched to the pivotal risdiplam dose after the dose selection decision: 5 mg (body weight [BW] ≥20 kg) and 0.25 mg/kg (BW < 20 kg). In Part 2, a 5 mg once daily risdiplam regimen was administered to patients with a BW ≥ 20 kg. For patients with a BW < 20 kg, a 0.25 mg/kg once daily regimen was administered.

For Part 1, 51 patients were enrolled, and all entered the open label extension (OLE). From these, 30 patients age 2-11 years and 18 patients age 12-25 years completed OLE period. For Part 2, out of the 180 patients who were enrolled, 175 patients (97.2%) entered the OLE phase after 2 years in the study and 156 patients (86.7%) completed the study.

The previously developed population pharmacokinetic model (dated June 2020), based on observations from 551 subjects (61 healthy subjects and 490 SMA patients) of either of the six clinical studies BP29840, BP39054, BP39055, BP39056, BN40703 or BP41361, was fitted to a final updated dataset which additionally included 1742 samples from Study BP39055 (as available since 2nd of October 2023). The model showed to adequately predict central tendency and inter-individual variability for all populations, as well as for Study BP39055 patients.

The median AUC_{0-24h} of all SMA patients in Study BP39055 at Year 5 Visits was 1830 ng▪h/mL and the median C_{av} was 81.2 ng/mL. These values are consistent with the Month 12 Visit of Part 2 where AUC_{0-24h} and C_{av} of 2050 ng▪h/mL and 83.7 ng▪h/mL were reported, respectively. A sustainable risdiplam exposure along with growth and maturation of the SMA patients by the approved body weight and age based dosing algorithm was observed.

Given the final results derived from Study BP39055, the Applicant has updated section 5.2 (pharmacokinetic properties) of the approved SmPC.

An exploratory pharmacokinetic-pharmacodynamic (PK-PD) analysis was also performed using SMN protein and SMN2 mRNA as PD biomarkers. The PKPD relationship of Study BP39055 patients was compared with the SMA patients of Studies BP39054 and BP39056.

Regarding SMN protein, the analysis showed no obvious difference in risdiplam AUC and SMN protein relationships between SMA patients of Study BP39055 and the two other studies. Regarding SMN2 mRNA, the analysis showed an observed increase in full-length SMN2 mRNA, and the corresponding decrease in Δ7mRNA, which were both well correlated with the time-matched plasma concentration of risdiplam. Moreover, no obvious difference in the relationship was seen between BP39055 vs. BP39054 and BP39056 SMA patients.

The benefit-risk balance of Evrysdi remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.13	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	Type II	I

Submission of the final report from study 'BP39055 (SUNFISH)' listed as a category 3 study in the RMP. Study BP39055 is a Two-Part Seamless, Multi-Center Randomized, Placebo-Controlled, Double-blind Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of RO7034067 in Type 2 and 3 Spinal Muscular Atrophy Patients.

☒is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Update of the SmPC section 5.2 with results from SUNFISH study, with the mean exposure and Cmax following 5 years of treatment.

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Risdiplam (Evrysdi®), also known as RO7034067, is the first orally administered small molecule *SMN2* (survival of motor neuron 2) splicing modifier developed for the treatment of spinal muscular atrophy (SMA). It directly targets the underlying molecular deficiency of the disease, promoting the inclusion of exon 7 to generate full length *SMN2* pre-messenger ribonucleic acid (mRNA) and thereby increasing the production of functional SMN protein. Risdiplam was first granted marketing approval in the United States on 7 August 2020 and in the European Union on 26 March 2021. The approved indication in the European Union is the following:

Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies.

As of the date of this report, risdiplam has received approval for marketing in over 100 countries.

In this Type II variation, the final clinical study report for Study BP39055 (SUNFISH) is being submitted to fulfil a Category 3 required pharmacovigilance activity for risdiplam listed in the E.U. Risk Management Plan (RMP). Specifically, submission of this Final CSR addresses the obligation to evaluate the long-term safety of risdiplam and its effect on epithelial tissues.

6. Clinical Pharmacology aspects

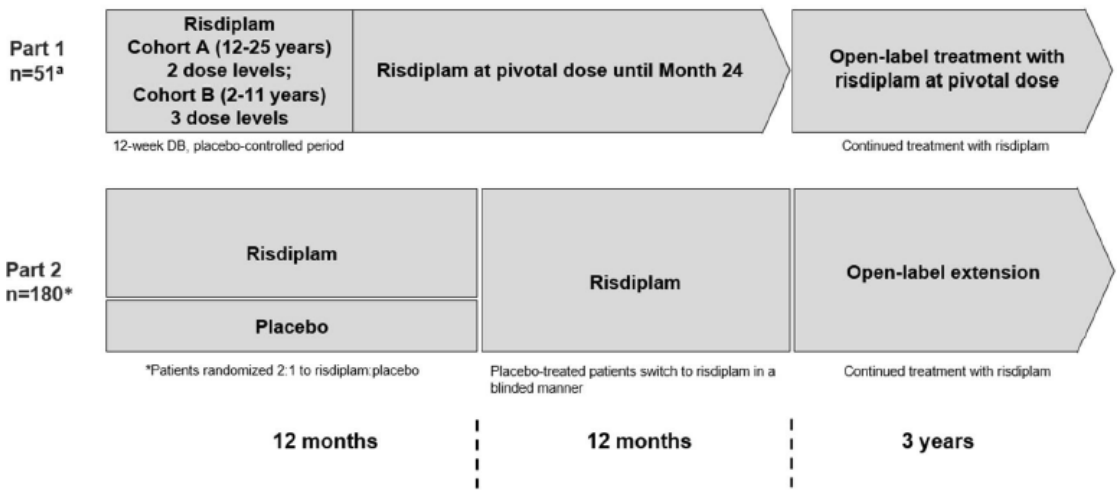
6.1. Methods – analysis of data submitted

Study BP39055 (SUNFISH)

Study BP39055 was a two-part, operationally seamless, multicenter, randomized, placebo-controlled, double-blind study designed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in patients with later-onset (Type 2 and Type 3) SMA.

The study consisted of an exploratory dose-finding part (Part 1) and a confirmatory part (Part 2) that started after the dose had been selected in Part 1. The two parts of the study were independent, had their own objectives and eligibility criteria, and were analyzed separately. Part 1 patients did not roll over into Part 2. The study design is shown in the figure below.

Figure 1. Study Design



[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 (or at a lower dose decided by the review committee) 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 DB placebo-controlled period

Part 1 primary objectives were the evaluation of the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of risdiplam in patients with Type 2 and Type 3 (ambulant or non-ambulant) SMA, and to select the dose for Part 2 of the study. As exploratory objectives for Part 1 it was intended to investigate the PK/PD relationship of risdiplam by PK/PD modelling (PD to include SMN2 mRNA and SMN protein).

Part 2 primary objectives were the evaluation of efficacy of risdiplam compared to placebo in terms of motor function in Type 2 and non-ambulant Type 3 SMA patients, as assessed by the change from baseline in the total score of the 32-item Motor Function Measure (MFM32) at 12 months.

This variation presents final data at the clinical cutoff date (CCOD) of 02 October 2023, which corresponds to the last patient last visit. Results are presented for patients in Part 1, who had received up to 5 years of risdiplam treatment, and patients in Part 2, including those originally randomized to risdiplam who continued to receive risdiplam for 5 years and those originally randomized to placebo who switched to risdiplam at Month 12 and received risdiplam for 4 years.

Dosing Rationale

An oral dose of 3 mg once daily was selected for Dose Level 1 to be administered to Group A (patients aged 12-25 years at age of randomization). Selection of 3 mg dose was based on physiologically based PK (PBPK) modelling using available data in healthy subjects and taking into account the tissue distribution and different body weight and body composition in SMA patients compared to healthy subjects. According to study protocol, the dose of 3 mg was predicted to result in an $AUC_{0\text{-}24h,ss}$ of 700 ng.h/mL in SMA patients aged 12-25 years, which is approximately 3-fold (2.8) below the specified exposure cap and is anticipated to result in the targeted 2-fold SMN protein increase.

The PK data obtained from Group A was then used to update the PBPK model to select a dose for the younger children in Group B (children aged 2-11 years at age of randomization). This dose for the Group B was planned 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.

The dose for Part 2 was selected by the Internal Monitoring Committee (IMC) based on the results obtained from Part 1.

Dosing

Part 1 initial doses: 0.02, 0.05, 0.25 mg/kg (for 2-11 year old patients), and 3 and 5 mg (for 12-25 year old patients). Patients in Part 1 switched to the pivotal dose after the dose selection decision: 5 mg (body weight [BW] ≥20 kg) and 0.25 mg/kg (BW < 20 kg). Risdiplam was administered orally, once daily.

Part 2: 5 mg once daily for patients with a BW ≥ 20 kg, or 0.25 mg/kg for patients with a BW < 20 kg) or placebo. Study medications were given orally, once daily.

Disposition of Patients

For Part 1, all the 51 patients enrolled entered the open label extension (OLE) phase of the study and 48 patients (94.1%) completed this phase. Three patients withdrew consent and discontinued from the study during the OLE phase. Overall, 47 patients (92.2%) completed the follow-up call after Part 1 study

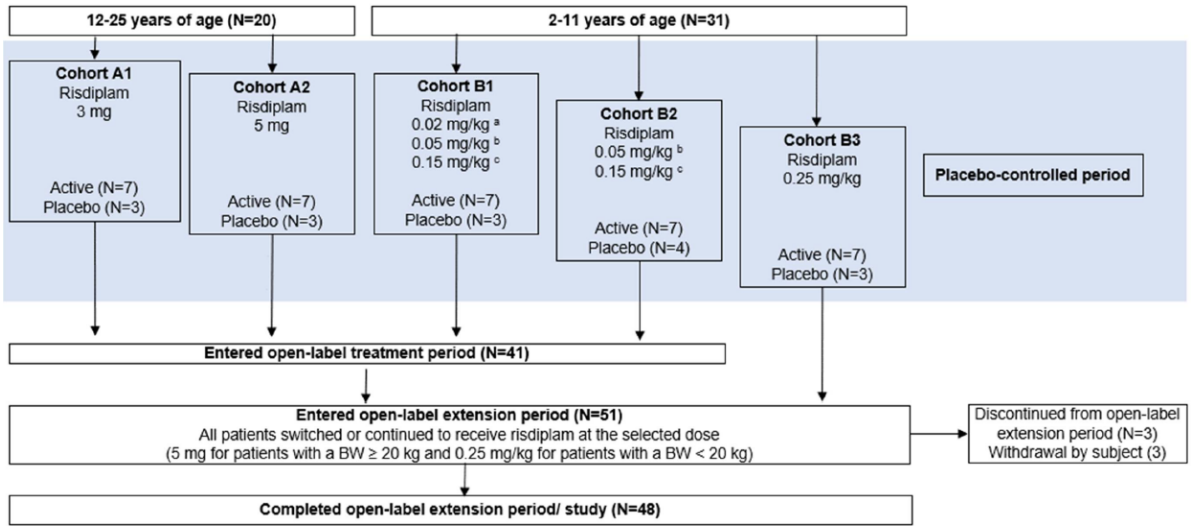
completion and 41 patients opted for continued access to risdiplam. The table and figure below summarizes patient disposition in Part 1.

Table 1. Patient Disposition (Open Label Extension Period), Intent-to-Treat Patients, Part 1 Patients

	Risdiplam (Age 2-11 yrs) (N=31)	Risdiplam (Age 12-25 yrs) (N=20)	All Risdiplam (Age 2-25 yrs) (N=51)
Entered Open Label Extension Period	31 (100%)	20 (100%)	51 (100%)
Completed Open Label Extension Period / Completed Study	30 (96.8%)	18 (90.0%)	48 (94.1%)
Withdrawal from Open Label Extension Period	1 (3.2%)	2 (10.0%)	3 (5.9%)
WITHDRAWAL BY SUBJECT	1 (3.2%)	2 (10.0%)	3 (5.9%)
Completed Follow Up Call After Study Completion	29 (93.5%)	18 (90.0%)	47 (92.2%)
Continued Access to Risdiplam #	25	16	41

Percentages are based on all randomized subjects.
Continued Access to risdiplam is a program for patients with no access to commercial risdiplam at the time patients complete the study
Clinical Cutoff Date: 02OCT2023

Figure 2. Patient Disposition Flowchart for Part 1



Notes: 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 treatment. Cohort B3 patients were switched to the Part 2 risdiplam dose at their next scheduled visit (Week 17 at the earliest); hence, these patients 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.
[c] The IMC recommended increasing the dose for patients in Cohorts B1 and B2 to 0.15 mg/kg.

For Part 2, out of the 180 patients who were enrolled, 175 patients (97.2%) entered the OLE phase after 2 years in the study and 156 patients (86.7%) completed the study. Nineteen patients (10.6%) discontinued from the study during the OLE phase due to the following reasons: 15 patients withdrew consent, one patient died and three patients discontinued due to other reasons. The table below summarizes patient disposition in Part 2. Overall, 76 patients (42.2%) completed the follow-up call after Part 2 study completion and 79 patients (43.9%) opted for continued access to risdiplam.

Table 2. Patient Disposition for Study (Open Label Extension Period), Intent-to-Treat Patients, Part 2 Patients

	Risdiplam (N=120)	Placebo (N=60)	Total (N=180)
Entered Open Label Extension Period	116 (96.7%)	59 (98.3%)	175 (97.2%)
Completed Open Label Extension Period / Completed Study	103 (85.8%)	53 (88.3%)	156 (86.7%)
Withdrawal from Open Label Extension Period	13 (10.8%)	6 (10.0%)	19 (10.6%)
DEATH	1 (0.8%)	0	1 (0.6%)
OTHER	2 (1.7%)	1 (1.7%)	3 (1.7%)
WITHDRAWAL BY SUBJECT	10 (8.3%)	5 (8.3%)	15 (8.3%)
Completed Follow Up Period After Study Completion	53 (44.2%)	23 (38.3%)	76 (42.2%)
Continued Access to Risdiplam *	49	30	79

Percentages are based on all randomized subjects.
* Continued Access to Risdiplam is a program for patients with no access to commercial risdiplam at the time patients complete the study
Clinical Cutoff Date: 02OCT2023

Population Pharmacokinetics-Pharmacodynamics Modelling

The objective of Population Pharmacokinetics (PPK) modelling was to describe risdiplam PK of the 230 SMA patients of Study BP39055 at Year 5 Visit.

The analysis was performed to:

- ✓ Evaluate the previously developed population PK model against the updated data collected from Study BP39055 up to Year 5 Visit.
- ✓ Derive secondary PK parameters ($AUC_{0\text{-}24h}$ and C_{av}) of 230 SMA patients to evaluate risdiplam exposure.
- ✓ Investigate relationships between risdiplam exposure and pharmacodynamic (PD) markers SMN protein and SMN2 mRNA.

The PPK analyses and all simulations were performed using NONMEM version 7.4. The estimation method First Order Conditional Estimation (FOCE) with interaction implemented in NONMEM was used in PPK modelling. Perl-speaks-NONMEM (PsN) version 4.9.3 was used for bootstrap analyses. All graphical analyses were performed using R version 4.0.3 with RStudio version 1.2.1335.

A population PK modelling had previously been performed for a total of 13,030 observations of 551 subjects (61 healthy subjects and 490 SMA patients) of either of the six clinical studies BP29840, BP39054, BP39055, BP39056, BN40703 or BP41361. The selected PPK model comprises a three transit compartment absorption model connected to a systemic linear two-compartmental PK model. Inter-individual variability (IIV) was estimated for the absorption transit rate (k_{tr}), the apparent clearance (CL/F) and the apparent central volume of distribution (V_c/F). Proportional residual errors were separately estimated for venous and capillary samples. Time-varying body weight (power model structure with estimated allometric exponents) and a factor of CL/F for healthy adults were included as covariates of the model. In addition, a maturation function with time-varying age consists of a sigmoidal model with $Frac_{birth}$, a fraction of CL/F at birth, was also implemented to CL/F. Time-varying body weight effect with fixed allometric coefficient of 1.0 was included for V_c/F and V_p/F. The summary of the population PK parameter estimates are summarized in the table below. This model was used as the initial reference PPK model for the PK analysis with data from Study BP39055.

Table 3. Summary of the Reference Population PK Model of Risdiplam

Parameter	Unit	Estimate	RSE (%)	95%CI	95%CI*
Fixed Effects					
CL/F	L/h	2.44	2.91	2.3-2.58	2.27-2.64
ktr	/h	5.29	2.39	5.04-5.54	5.01-5.63
Vc/F	L	87.6	1.30	85.4-89.8	85.0-89.3
Q/F	L/h	0.644	6.58	0.561-0.727	0.572-0.832
Vp/F	L	102	9.99	82-122	53.0-137
Covariate Effects					
Effect of WT on CL/F and Q/F		0.249	10.0	0.2-0.298	0.180-0.305
Effect of WT on Vc/F and Vp/F		1 FIX	NA	NA	NA
Factor for CL/F of healthy adults		0.495	11.8	0.381-0.61	0.384-0.641
$Frac_{birth}$ – CL/F		0.112	16.6	0.0758-0.149	0.0746-0.162
Age_{50} – CL/F (y)		1.47	13.0	1.1-1.85	1.10-2.05
Random Effects					
CL/F (CV)		0.0607 (24.6%)	7.15	0.0522-0.0692	0.0510-0.0688
ktr (CV)		0.2570 (50.7%)	10.30	0.205-0.308	0.200-0.312
Vc/F (CV)		0.0762 (27.6%)	7.80	0.0645-0.0878	0.0641-0.0906
Error Model					
σ_1 proportional - venous (CV)		0.0592 (24.3%)	2.76	0.056-0.0624	0.0559-0.0623
σ_2 proportional – capillary (CV)		0.0836 (28.9%)	12.30	0.0634-0.104	0.0652-0.113
OFV = 84692.7428					

OFV = objective function, RSE = relative standard error of estimate; CV = coefficient of variation; NA = not applicable; WT = body weight.*bootstrap analyses with 200 replicates (77% were successful). Source [2].

The reference PPK model was fitted to the combined data set with and without parameter estimation step. The objective function value (OFV), precision of parameter estimates, goodness-of-fit (GOF) plots, prediction-corrected visual predictive check (pc-VPC) were examined to evaluate adequacy of the reference PPK model and necessity of parameter estimation step for the updated risdiplam PK data set.

Individual secondary PK parameters such as $AUC_{0\text{-}24h}$ and average concentration from the first dose to the Year 5 Visit (C_{av}) were derived using the post-hoc PK parameters of the PPK model, patients actual demographics and risdiplam dosing records. The cumulative AUC was calculated within NONMEM for each subject and $AUC_{0\text{-}24h}$ was extracted at specific time points for evaluation of exposure. The C_{av} was derived by dividing the cumulative AUC from the first dose until up to the Year 5 Visit.

Exploratory PKPD analysis

The pharmacodynamics (PD) of risdiplam was evaluated by quantifying SMN protein and SMN2 mRNA in blood collected from SMA patients who participated in Study BP39055 and compared with the pooled data of Studies BP39054 and BP39056. The relationship between risdiplam exposure and SMN protein was explored using estimated $AUC_{0\text{-}24}$ derived using the post-hoc PK parameters of the final PK model, patients actual demographics and risdiplam dosing records. Time-matched plasma concentrations of risdiplam were used for investigating the relationship with SMN2 mRNA since an instantaneous reaction of the SMN2 mRNA to the plasma concentration of risdiplam was observed in the study with healthy volunteers where extensive and matching PK and PD profiles over time had been collected.

6.2. Results

Population Pharmacokinetics

Data from 552 subjects, consisting of 61 healthy subjects (studies BP29840 and BP41361) and 491 SMA patients (studies BP39054, BP39055, BP39056 and BN40703) were available in the data base as of 2nd of October 2023 and included in the population PK analysis, corresponding to a total of 15,375 plasma samples for measurement of risdiplam. From these, 1742 samples were from Study BP39055, being available as of 2nd of October 2023. After database cleaning, a total of 14,997 observations including 471 capillary blood samples (3.1%) were available for the analysis. During analysis, additional 36 observations were excluded and therefore a total of 14961 observations were included in the final analysis.

The demographics of the patients at the time of the first dose are summarized in the table below.

Table 4. Summary of Demographic Data at the First Dose

	BP29840 (N=26)	BP39054 (N=173)	BP39055 (N=230)	BP39056 (N=62)	BN40703 (N=26)	BP41361 (N=35)	All (N=552)
Age (years)							
Mean	26.3	17.7	10.8	0.451	0.0754	42.2	14.0
Median [Min, Max]	24.0 [18.0, 44.0]	15.0 [1.14, 61.0]	9.85 [2.22, 25.4]	0.466 [0.184, 0.581]	0.0658 [0.0411, 0.110]	40.2 [22.1, 56.2]	11.7 [0.0411, 61.0]
Body weight (kg)							
Mean	79.0	41.6	32.3	6.78	4.05	80.9	36.3
Median [Min, Max]	79.7 [50.4, 95.3]	39.0 [9.20, 109]	27.6 [9.80, 109]	6.63 [4.14, 10.6]	4.02 [3.08, 5.75]	79.7 [52.5, 103]	31.0 [3.08, 109]
Sex							
Male	26 (100%)	95 (54.9%)	113 (49.1%)	25 (40.3%)	10 (38.5%)	20 (57.1%)	289 (52.4%)
Female	0 (0%)	78 (45.1%)	117 (50.9%)	37 (59.7%)	16 (61.5%)	15 (42.9%)	263 (47.6%)
SMA-Type							
Healthy	26 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	35 (100%)	61 (11.1%)
Type 1	0 (0%)	15 (8.7%)	0 (0%)	62 (100%)	0 (0%)	0 (0%)	77 (13.9%)
Type 2	0 (0%)	107 (61.8%)	165 (71.7%)	0 (0%)	0 (0%)	0 (0%)	272 (49.3%)
Type 3 ambulatory	0 (0%)	36 (20.8%)	57 (24.8%)	0 (0%)	0 (0%)	0 (0%)	93 (16.8%)
Type 3 non-ambulatory	0 (0%)	15 (8.7%)	8 (3.5%)	0 (0%)	0 (0%)	0 (0%)	23 (4.2%)
Presymptomatic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	26 (100%)	0 (0%)	26 (4.7%)
Race							
White	21 (80.8%)	142 (82.1%)	166 (72.2%)	35 (56.5%)	22 (84.6%)	14 (40.0%)	400 (72.5%)
Black or African American	2 (7.7%)	1 (0.6%)	2 (0.9%)	0 (0%)	0 (0%)	19 (54.3%)	24 (4.3%)
Asian	2 (7.7%)	9 (5.2%)	36 (15.7%)	18 (29.0%)	3 (11.5%)	1 (2.9%)	69 (12.5%)
Others	1 (3.8%)	21 (12.1%)	26 (11.3%)	9 (14.5%)	1 (3.8%)	1 (2.9%)	59 (10.7%)

The maximum plasma concentration and trough concentration at around Year 5 visit per individual patient of Study BP39055 is summarized in the table below.

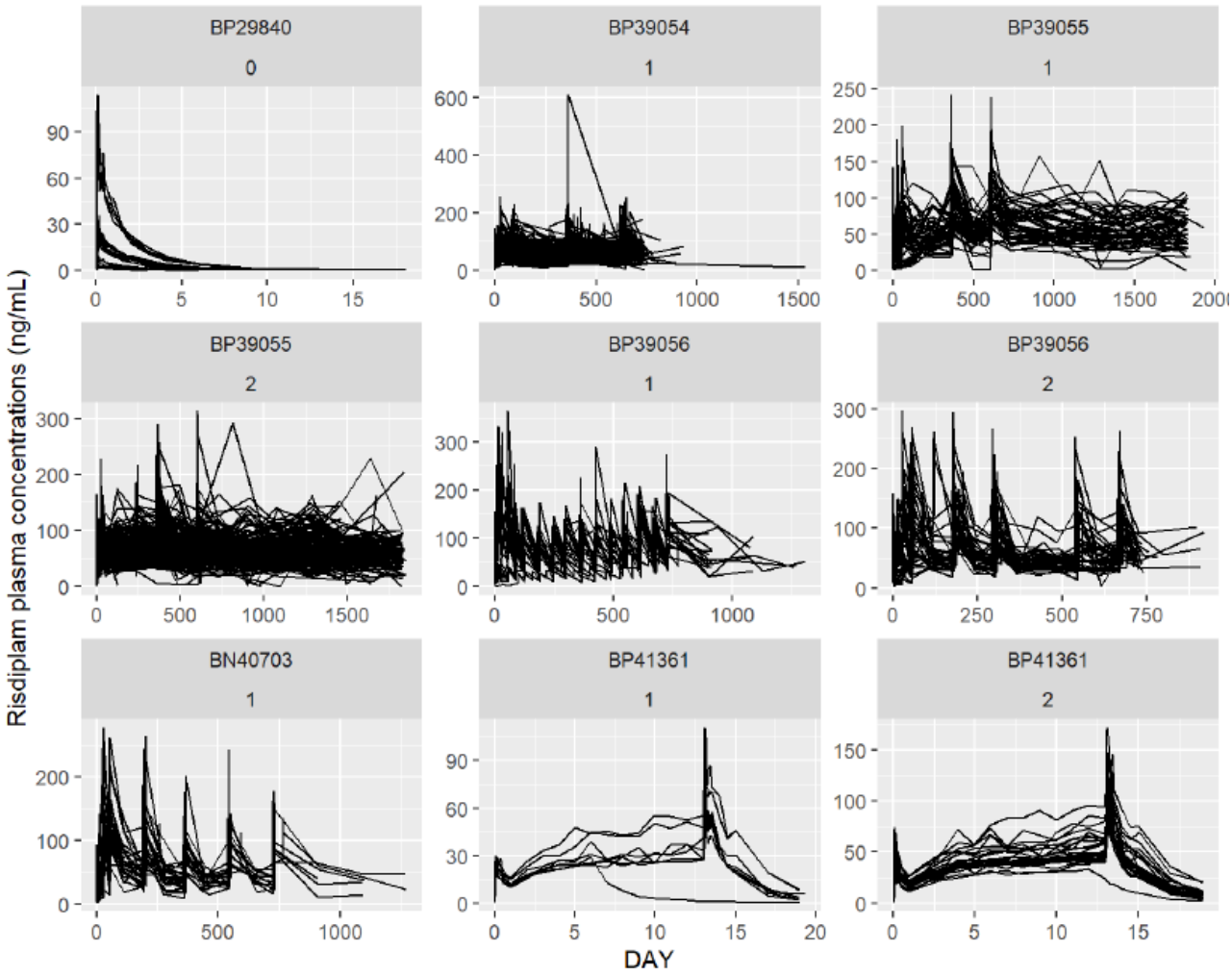
Table 5. Summary of the Maximum Observed and Trough Plasma Risdiplam Concentrations of SMA Patients of Study BP39055

	Maximum Plasma Concentration (ng/mL)[a]		Trough Plasma Concentration (ng/mL)[b]	
Part	1 (n=51)	2 (n=179)	1 (n=49)	2 (n=107)
Mean	142	140	55.9	59.3
Median [range]	137 [58.2, 242]	140 [42.7, 313]	54.1 [21.3, 108]	57.2 [4.50, 229]

[a]Maximum observed concentration throughout the observation period. [b]Risdiplam concentration determined in the last predose sample collected from each patient who had at least 1400 days of risdiplam treatment duration.

The individual plasma concentration time profiles included in the PPK analysis are shown in the figure below.

Figure 3. Risdiplam Concentration versus Time since First Dose By Study on Linear Scale

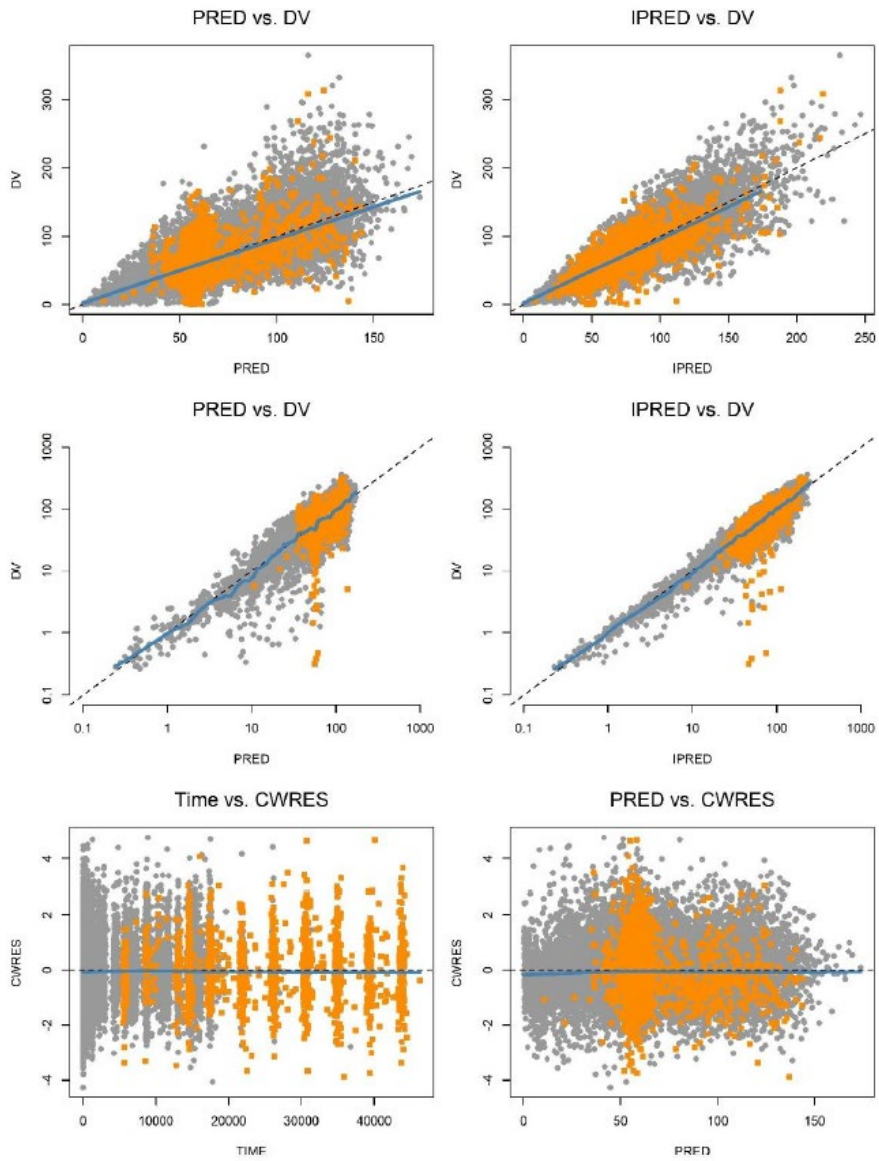


Study numbers are indicated in the headers.

The reference PPK model was fitted to the updated PPK data set including newly collected data of Study BP39055 up to Year 5 Visit. Adequacy of the reference PPK model to predict risdiplam PK, focusing on the SMA patients of Study BP39055, was examined.

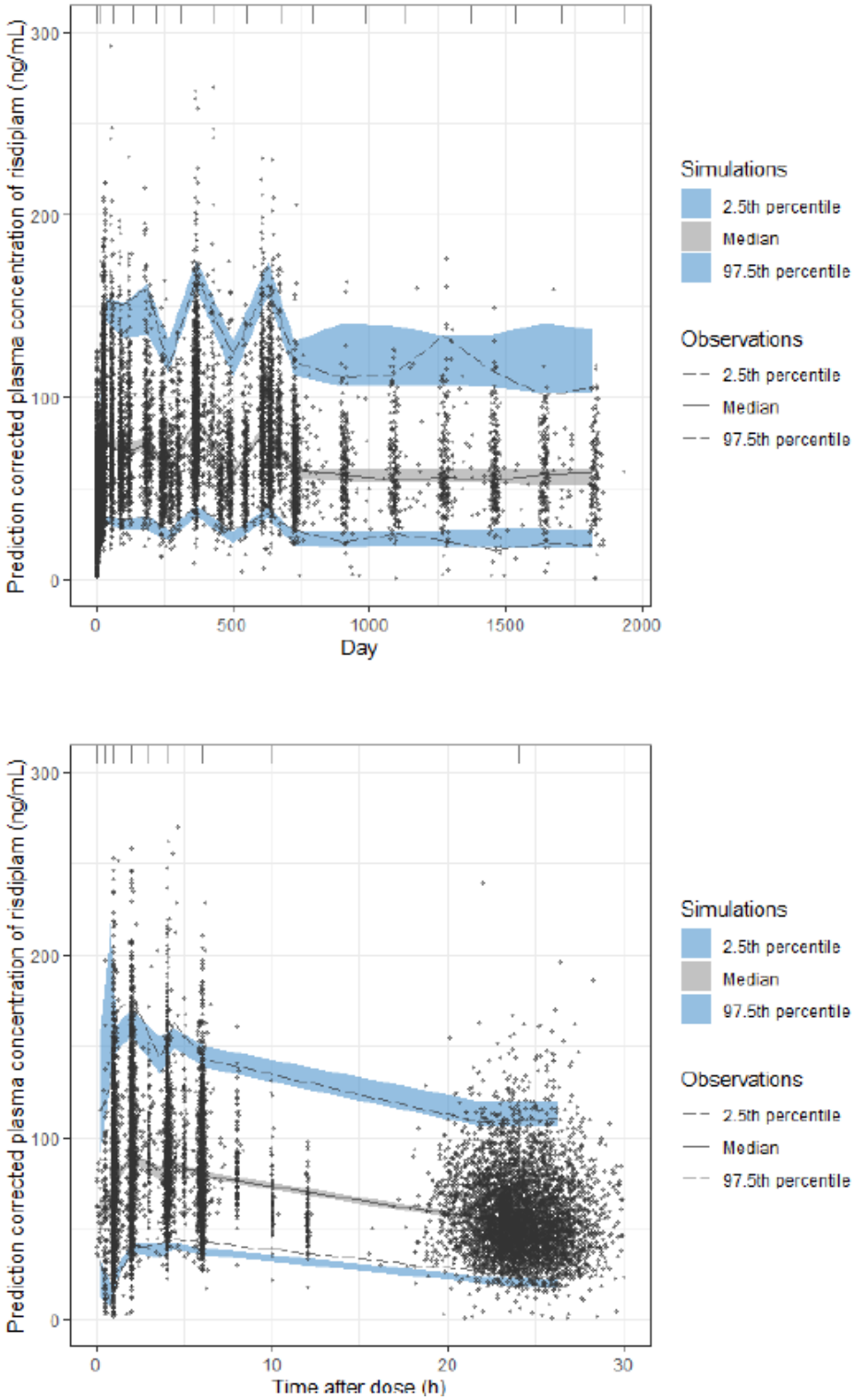
The Goodness-of-Fit (GOF) and prediction corrected Visual Predictive Check (pc-VPC) of the reference PPK model for the updated data set are shown in figures below. Both models showed good consistency between DV and PRED, as well as IPRED with most of them being homogenously distributed around the identity line. The distribution of CWRES 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 new data collected from Study BP39055 also showed consistency in GOFs. The pc-VPC showed ability of the models to adequately predict central tendency and inter-individual variability for all populations (Figure 4) as well as for Study BP39055 patients (Figure 5).

Figure 4. Goodness-of-Fit Plots of the Reference PPK Model of Risdiplam for the Updated Dataset Including Data of Year 5 Visit of Study BP39055



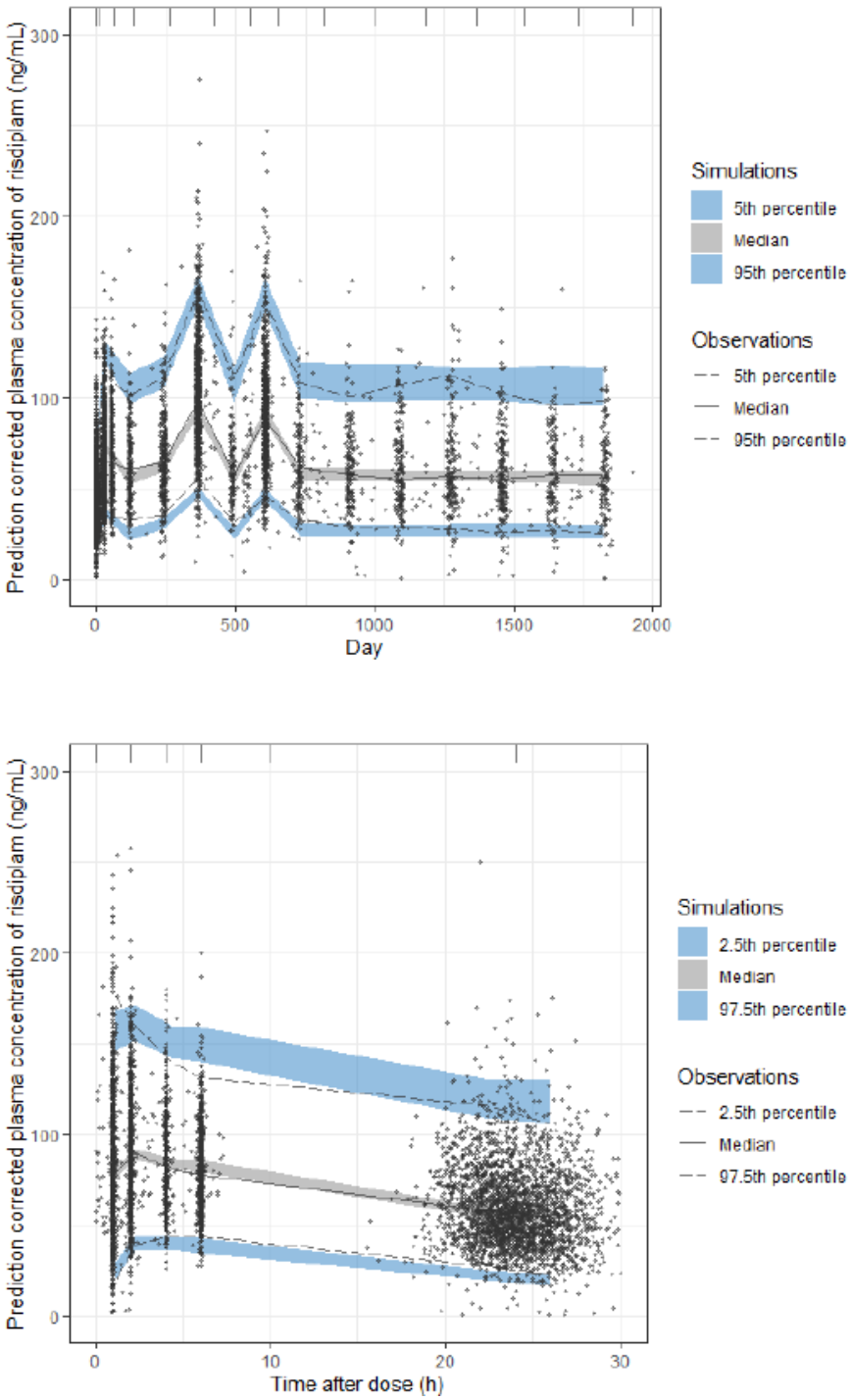
Note: DV – Observed risdiplam concentrations [ng/mL], PRED (IPRED) – Population (individual) predicted risdiplam concentrations [ng/mL], CWRES – conditional weighted residual. Gray and blue lines indicate identity line and smooth, respectively. Data points shown in dark orange are new data collected from Study BP39055 up to Year 5 Visit.

Figure 5. Prediction Corrected Visual Predictive Check of the Reference PPK Model of Risdiplam for the Updated Dataset Including Data of Year 5 Visit of Study BP39055: All Populations



Note: pc-VPC with time after the first dose (top) and time after last dose (bottom) are shown. Individual observations corrected by the respective prediction are shown with solid circles. Blue areas are 95% prediction intervals of the 2.5th, median and 97.5th percentiles of predictions. Dotted and solid lines show 2.5th and 97.5th, and median of the observations, respectively.

Figure 6. Prediction Corrected Visual Predictive Check of the Reference PPK Model of Risdiplam for the Updated Dataset Including Data of Year 5 Visit of Study BP39055: SMA Patients of Study BP39055 only

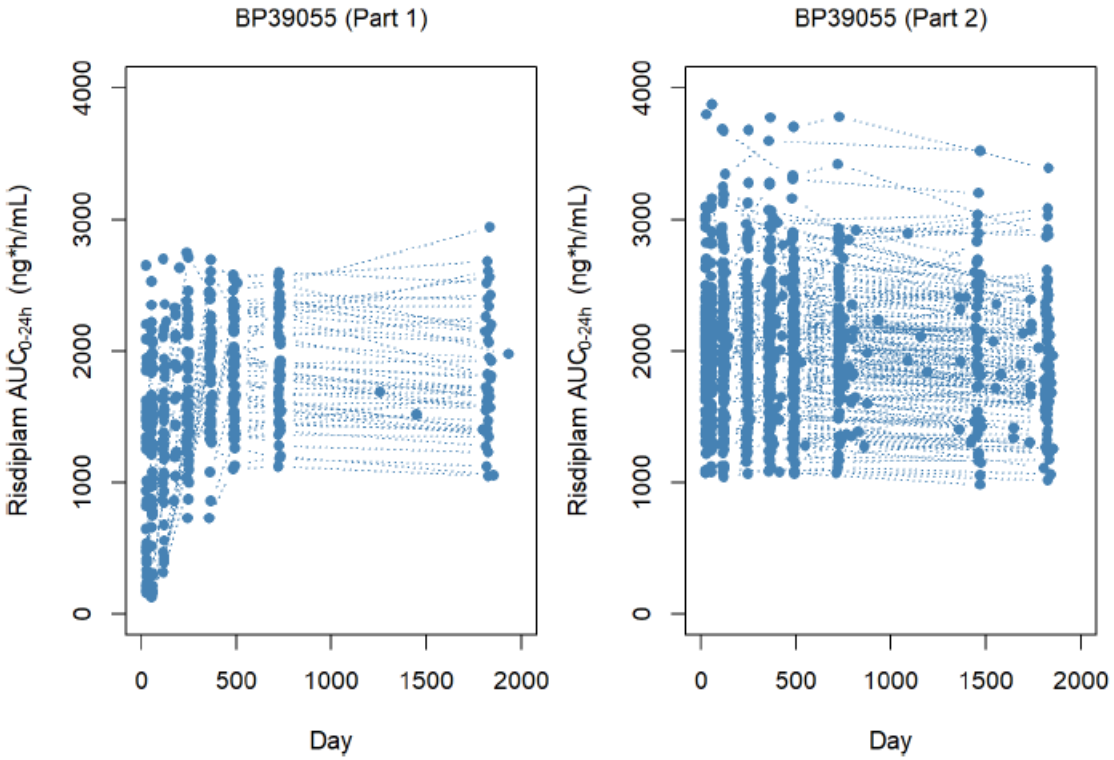


Note: pc-VPC with time after the first dose (top) and time after last dose (bottom) are shown. Individual observations corrected by the respective prediction are shown with solid circles. Blue areas are 95% prediction intervals of the 2.5th, median and 97.5th percentiles of predictions. Dotted and solid lines show 2.5th and 97.5th, and median of the observations, respectively.

Individual secondary PK parameters, $AUC_{0\text{-}24h}$ and average concentration from the first dose to Year 5 Visit (C_{av}), were derived using the post-hoc PK parameters, patients actual demographics and risdiplam dosing records.

The individual $AUC_{0\text{-}24h}$ by time course of the SMA patients of Study BP39055 between Day 28 and the last risdiplam dosing including Year 5 Visit are shown in the figure below. The $AUC_{0\text{-}24h}$ by time courses of patients in Part 1 are shown on the left, and the time course of the patients in Part 2 are shown on the right. Consistent risdiplam exposure during the treatment period was noted in both Parts 1 and 2.

Figure 7. Individual Risdiplam $AUC_{0\text{-}24h}$ of SMA Patients of Study BP39055 on Day 28 to Year 5 Visits



Risdiplam $AUC_{0\text{-}24h}$ and C_{av} are summarized by Part and dose in the table below. The median $AUC_{0\text{-}24h}$ of all SMA patients in Study BP39055 at Year 5 Visits was 1830 ng•h/mL and the median C_{av} was 81.2 ng/mL.

Table 6. Summary of Risdiplam $AUC_{0\text{-}24h}$ and C_{av} at Year 5 Visit of the SMA Patients of Study BP39055

	Part 1			Part 2			All
Dose	**0.25 mg/kg (n=5)**	**5 mg (n=44)**	**Total (n=49)**	**0.25 mg/kg (n=7)**	**5 mg (n=153)**	**Total (n=160)**	**(n=209)**
Age (years)							
Median [range]	8.00 [8.00, 9.00]	13.5 [8.00, 30.0]	13.0 [8.00, 30.0]	9.00 [8.00, 16.0]	15.0 [7.00, 30.0]	15.0 [7.00, 30.0]	14.0 [7.00, 30.0]
Body weight (kg)							
Median [range]	16.7 [14.5, 17.8]	36.5 [18.5, 73.0]	35.9 [14.5, 73.0]	16.4 [13.2, 19.2]	40.8 [18.5, 112]	40.0 [13.2, 112]	38.7 [13.2, 112]
$AUC_{0\text{-}24h}$ (ng•h/mL)							
Mean	2200	1760	1800	2540	1910	1940	1910
Median	2430	1700	1700	2450	1860	1880	1830
[5th -95th]	[1690, 2600]	[1140, 2500]	[1160, 2590]	[2050, 3000]	[1190, 2850]	[1200, 2890]	[1180, 2880]
C_{av} (ng/mL)							
Mean	83.3	74.1	75.0	105	82.8	83.7	81.7
Median	92.9	72.7	72.9	100	82.8	83.7	81.2
[5th -95th]	[61.1, 100]	[50.9, 106]	[51.5, 105]	[89.6, 118]	[50.3, 123]	[50.4, 122]	[50.5, 119]

Note: Age and body weight were at Year 5 Visit. Data from Year 5 Visit were not available from 21 patients who withdrew from the study with less than 1400 days of observations.

Exploratory PKPD analysis

SMN Protein

The SMN protein data at baseline and Year 5 Visit of the SMA patients of Study BP39055 are summarized in the table below. The SMN protein as absolute values and fold change from baseline on Day 28 or later was plotted against the time-matched risdiplam AUC_{0-24} estimated for each visit of PD sampling as shown in the figure below. The PKPD relationship of Study BP39055 patients was compared with the SMA patients of Studies BP39054 and BP39056. Large variability was noted in the risdiplam AUC and SMN protein relationships.

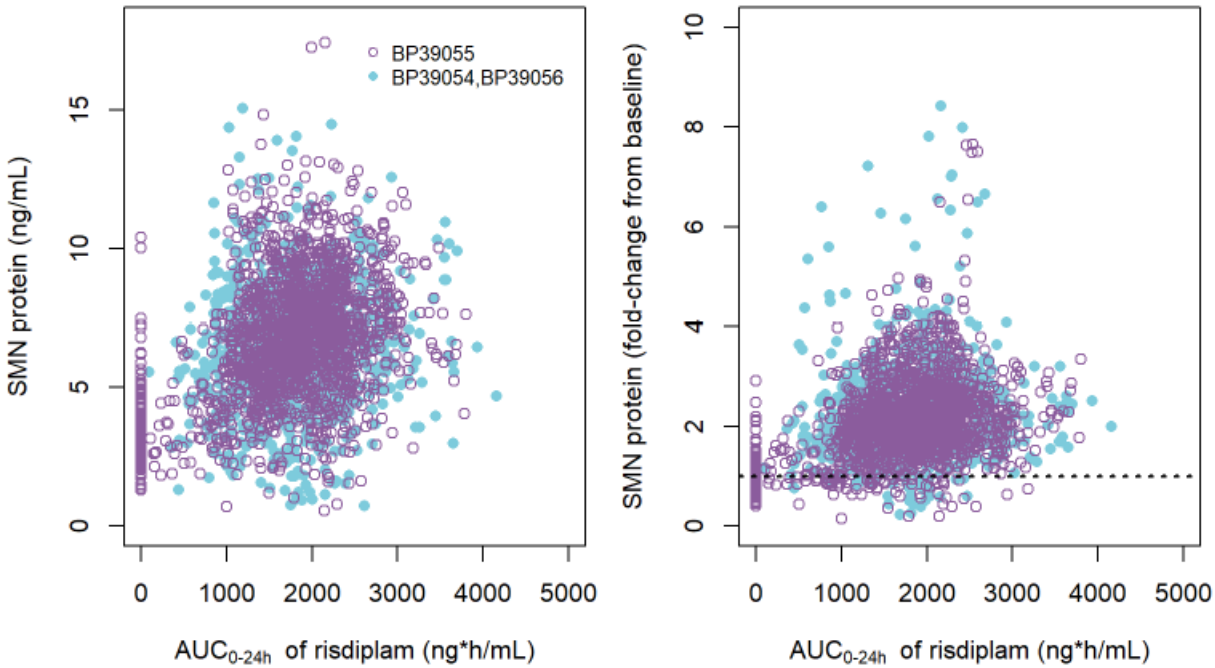
Overall, there was no obvious difference in risdiplam AUC and SMN protein relationships between SMA patients of Study BP39055 and two other studies.

Table 7. Summary of SMN protein at Baseline and Year 5 Visit of Study BP39055

Values	Absolute value at baseline (n=220)	Absolute value at Year 5 Visit (n=209)	Fold-change from baseline (n=200)
Median [range]	3.37 [0.570, 9.48]	7.61 [0.640, 14.3]	2.25 [0.182, 8.34]

Patients who withdrew from the study before 1400 days of treatment were not included in the summary.
SMN protein <0.4 ng/mL were not included in the analysis [1].

Figure 8. Relationship between Risdiplam AUC0-24h and SMN Protein Compared between BP39055 vs. BP39054 and BP39056 Study SMA Patients: 28 Days After First Dose and Onwards

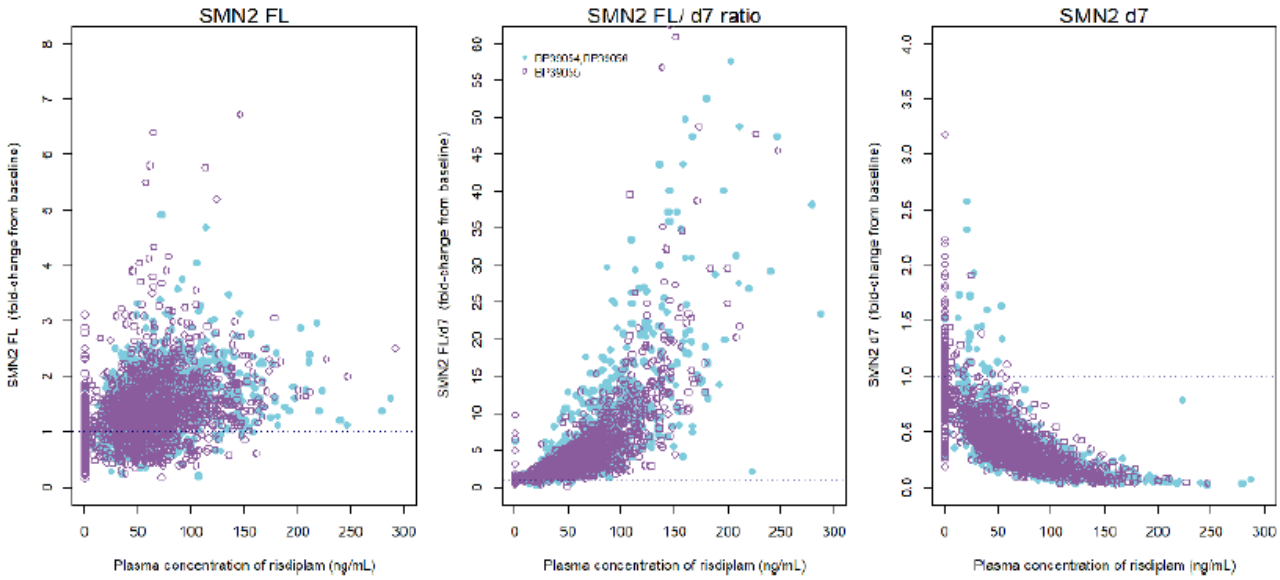


SMN2 mRNA

The relationship between plasma risdiplam concentration and fold-change from the baseline for SMN2 mRNA full-length (SMN2FL mRNA), SMNΔ7 mRNA and the ratio of SMN2FL/ SMNΔ7 mRNA are graphically shown in the figure below. The observed increase in full-length SMN2 mRNA, and the corresponding

decrease in Δ7mRNA, were both well correlated with the time-matched plasma concentration of risdiplam, and no obvious difference in the relationship was seen between BP39055 vs. BP39054 and BP39056 SMA patients.

Figure 9. Fold Change from Baseline in SMN2 mRNA versus Time-Matched Risdiplam Plasma Concentration in BP39055 vs. BP39054 and BP39056 Study SMA patients



Dashed lines indicate 1 (i.e., no change). Time-matched risdiplam plasma concentrations were available in 97.9% of the SMN2 mRNA samples and included in the analyses.

6.3. Discussion

Total of 6060 plasma risdiplam concentration data were available from 230 SMA patients of Study BP39055 by Year 5 Visit at CCOD of 2nd of October 2023. Since PPK model development dated June 2020 (reference PPK model), additional of 1742 samples were collected from the SMA patients and included in the PK analysis. The reference PPK model developed previously predicted the plasma concentration of risdiplam in the updated dataset including these newly collected samples from Study BP39055. The median of estimated individual $AUC_{0\text{-}24h}$ and C_{av} at Year 5 Visit were 1830 ng•h/mL and 81.2 ng/mL, respectively. These values are consistent with the Month 12 Visit of Part 2 where $AUC_{0\text{-}24h}$ and C_{av} of 2050 ng•h/mL and 83.7 ng•h/mL were reported, respectively. A sustainable risdiplam exposure along with growth and maturation of the SMA patients by the approved body weight and age-based dosing algorithm was observed.

Given the final results derived from Study BP39055, the Applicant has updated section 5.2 (pharmacokinetic properties) of the approved SmPC.

The relationship between risdiplam $AUC_{0\text{-}24h}$ and SMN protein were highly variable, and an obvious correlation was not seen within the exposure range with $AUC_{0\text{-}24h}$ values being mostly between 1000-3000 ng.h/m. Risdiplam concentration-dependent shift in SMN2 mRNA splicing was observed. Neither relationship between risdiplam concentration – SMN protein or – SMN2 mRNA were different between SMA patients of Study BP39055 vs. BP39054 and BP39056 patients.

7. Clinical Efficacy aspects

7.1. Methods – analysis of data submitted

This submission pertains to the assessment of Study BP39055 (SUNFISH), which was a PAM class 3.

Study BP39055 was a two-part, operationally seamless, multicenter, randomized, placebo-controlled, double-blind study designed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in patients with later onset (Type 2 and Type 3) SMA.

The study consisted of an exploratory dose-finding part (Part 1) and a confirmatory part (Part 2) that started after the dose had been selected in Part 1. The two parts of the study were independent, had their own objectives and eligibility criteria, and were analyzed separately. Part 1 patients did not roll over into Part 2. The study design is depicted in Figure 1 (see above in clinical pharmacology section).

This variation presents final data at the clinical cutoff date (CCOD) of 02 October 2023, which corresponds to the last patient last visit (LPLV). Results are presented for patients in Part 1, who had received up to 5 years of risdiplam treatment, and patients in Part 2, including those originally randomized to risdiplam who continued to receive risdiplam for 5 years and those originally randomized to placebo who switched to risdiplam at Month 12 and received risdiplam for 4 years.

Study dates: First Patient randomized in Part 1: 19-Oct-2016; First Patient randomized in Part 2: 09-Oct-2017; Last patient last visit: 02-Oct-2023

Number of patients (planned and analyzed): Part 1 (2:1 active placebo): minimum of 36 (planned); 51 (actual) (35 initially allocated to risdiplam; 16 to placebo). Part 2 (2:1 active placebo): 168 (planned); 180 (actual) (120 allocated to risdiplam; 60 to placebo).

Table Summary of Studies Contributing to Efficacy Evaluation

Study No (Phase)	Population	Study Design	Number of Patients	Dose, Route, and Regimen	CCOD	Median Exposure Time
BP39055 (Phase II/ III)	Part 1: Patients with Type 2 and Type 3 SMA (ambulant and non-ambulant) Part 2: Patients with Type 2 and non-ambulant Type 3 SMA	Seamless, multicenter, two-part study as follows: Part 1: A double-blind, placebo-controlled, randomized, exploratory dose-finding study to select the dose for Part 2. Part 2: A double-blind, randomized, placebo-controlled, parallel design study to investigate the efficacy, safety and tolerability, PK, and PD of risdiplam in patients with Type 2 and non-ambulant Type 3 SMA After 24 months patients in Part 1 and Part 2 had the opportunity to join an open-label extension for at least 3 years.	Part 1: 51 patients in 2 age groups, 2–11 years of age (n = 31) and 12–25 years of age (n = 20) Part 2: 180 patients aged 2–25 years	OD oral administration Part 1 Initial doses Age 12–25 years: PBO, risdiplam 3 mg or 5 mg Age 2–11 years: PBO, risdiplam 0.02, 0.05, 0.15 or 0.25 mg/kg. Minimum of 12-week placebo-controlled treatment, after which patients on PBO switched to risdiplam at the dose tested in their cohort. After the dose was selected for Part 2, all patients switched to the pivotal dose. Part 2 Pivotal dose 0.25 mg/kg (BW <20 kg); 5 mg (BW ≥20 kg); PBO. 24-month treatment period; patients on PBO switched in a blinded manner to active treatment after 12 months of treatment. OLE: pivotal dose for 3 years.	2 October 2023 (LPLV)	Part 1: 1826 days Part 2: 1815 days

BW = body weight; CCOD = clinical cutoff date; LPLV = last patient last visit; OD = once daily; PBO = placebo; PD = pharmacodynamic; PK = pharmacokinetic; SMA = spinal muscular atrophy; OLE = open-label extension.

Study Design and Analysis Plan

The BP39055 study design (overall design, study inclusion and exclusion criteria, and patient disposition) has been presented in section 6.1.

The objectives for the study were:

Part 1

Primary:

To evaluate the safety, tolerability, PK and PD of risdiplam in patients with Type 2 and Type 3 (ambulant or non-ambulant) SMA, and to select the dose for Part 2 of the study.

Secondary:

There were no secondary objectives for Part 1 of the study.

Exploratory:

To investigate the PK/PD relationship of risdiplam by PK/PD modeling (PD toinclude SMN2 mRNA and SMN protein).

To explore the effect of risdiplam on motor function, respiratory function, and pre-specified AEs (in terms of proportion of patients experiencing them) and patient-reported quality of life measures, in line with the secondary objectives of Part 2.

Part 2

Primary:

To evaluate efficacy of risdiplam compared to placebo in terms of motor function in Type 2 and non-ambulant Type 3 SMA patients, as assessed by the change from baseline in the total score of the 32-item Motor Function Measure (MFM32) at 12 months.

Secondary:

To investigate the PK/PD relationship of risdiplam by PK/PD modeling (PD to include SMN2 mRNA and SMN protein).

To investigate the efficacy of 12-month treatment with risdiplam in terms of motor function as assessed by the Hammersmith Functional Motor Scale Expanded (HFMSE), Revised Upper Limb Module (RULM), and responder analyses of the MFM32.

To investigate the efficacy of 12-month treatment with risdiplam in terms of respiratory function as assessed by sniff nasal inspiratory pressure (SNIP) and, in patients aged 6 years and older, by maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), forced vital capacity (FVC), forced expiratory volume in the first second (FEV1), and peak cough flow (PCF).

To investigate the proportion of patients who experience a pre-specified disease-related adverse event (AE) by Month 12.

To investigate the efficacy of 12-month treatment with risdiplam in terms of global health status as assessed by the Clinical Global Impression of Change (CGI-C).

To investigate the efficacy of 12-month treatment with risdiplam in terms of patient-reported and caregiver-reported independence, as measured by the SMA Independence Scale (referred to as SMAIS-Upper Limb Module [SMAIS-ULM] throughout).

To investigate the safety and tolerability of risdiplam treatment.

Exploratory:

To investigate efficacy of risdiplam treatment beyond 12 months in terms of motor function as assessed by the MFM32, the HFMSE, and the RULM.

To investigate efficacy of risdiplam treatment beyond 12 months in terms of respiratory function as assessed by SNIP, MIP, MEP, FVC, FEV1, and PCF.

To investigate the proportion of patients who experience pre-specified disease-related AEs beyond Month 12 of treatment.

To investigate the efficacy of risdiplam beyond 12 months in terms of patient-reported and caregiver-reported independence, as measured by the SMAIS.

Other exploratory objectives of the study were:

To assess the impact of risdiplam treatment and conduct economic modeling on caregiver resource use and health-related quality of life using the Work Productivity and Activity Impairment: Caregiver (WPAI:CG) and the 5-level EQ-5D version (EQ-5D-5L), respectively.

To explore the correlation of motor function and pulmonary function measures (as appropriate) with in vivo SMN2 mRNA and SMN protein in blood.

To assess the taste of the risdiplam oral solution.

Further information on patients:

Part 1:

Prior diseases and concomitant medication

In Part 1, all 51 patients had received prior medications (i.e., before the first dose of study drug).

All 51 patients received at least one concomitant medication in the study.

The most frequently reported concomitant medications (>= 20% of patients) includedtropicamide (51 patients [100%]), salbutamol (33 patients [64.7%]), colecalciferol (16 patients [31.4%]), and influenza vaccine (14 patients [27.5%]).

Previous and concomitant SMA-Related Surgeries and Procedures

In Part 1, 14 patients (27.5%) had undergone at least one previous SMA-related surgery and procedure.

A total of 29 concurrent SMA-related surgeries or procedures were reported by 17 patients (33.3%). Surgical and medical procedures included spinal fusion surgery (5 patients [9.8%]), gastrostomy (4 patients [7.8%]), spinal operation (3 patients [5.9%]), arthrodesis, scoliosis surgery, spinal implantation, and tenotomy (2 patients [3.9%] each); and gastrointestinal tube insertion, muscle release, joint stabilization, and gastrostomy tube removal (1 patient [2.0%] each).

Part 2:

Summary of SMA Disease Baseline Characteristics, Intent-to-Treat Patients

Patient Baseline Characteristics	Risdiplam (N = 120)	Placebo [a]/Risdiplam (N = 60)	Total (N = 180)
Age at screening, years, median (range)	9 (2–25)	9 (2–24)	9 (2–25)
Gender, Female, n (%)	61 (50.8%)	30 (50.0%)	91 (50.6%)
Age of onset of initial symptoms, months, mean (SD)	14.1 (8.4)	18.5 (21.1)	15.5 (14.1)
SMA type, n (%)			
TYPE II	84 (70.0%)	44 (73.3%)	128 (71.1%)
TYPE III	36 (30.0%)	16 (26.7%)	52 (28.9%)
SMN2 copy number, n (%)			
2	3 (2.5%)	1 (1.7%)	4 (2.2%)
3	107 (89.2%)	51 (85.0%)	158 (87.8%)
4	10 (8.3%)	8 (13.3%)	18 (10.0%)
Scoliosis, n (%)			
Yes	76 (63.3%)	44 (73.3%)	120 (66.7%)
> 40° curvature	34 (28.3%)	23 (38.3%)	57 (31.7%)
MFM32 total score, mean (SD) [b]	45.48 (12.09) [#]	47.35 (10.12) [$]	46.11 (11.46)
RULM total score, mean (SD) [b]	19.65 (7.22) [^]	20.91 (6.41) [&]	20.06 (6.97))
HFMSE total score, mean (SD) [b]	16.10 (12.46)	16.62 (12.09)	16.27 (12.30)
SMAIS-ULM total score, mean (SD)*	25.83 (8.29) *	26.92 (8.70) [$]	—
Patients with HFMSE total score < 10, n (%)	49 (40.8%)	25 (41.7%)	74 (41.1%)

HFMSE=Hammersmith Functional Motor Scale – Expanded; MFM32=32-item Motor Function Measure; RULM=Revised Upper Limb Module; SMA=spinal muscular atrophy; SMAIS-ULM=SMA Independence Scale-Upper Limb Module; SMN=survival of motor neuron.

[a] Patients in the placebo arm received placebo for 12 months followed by risdiplam treatment for 4 years.

[b] MFM32, RULM, and HFMSE scores are baseline prior to first dose of study treatment, placebo or risdiplam.

[#] N = 115; [$] N = 59; [^] N = 119; [&] N = 58; * N = 116.

A total of 41.1% of patients (74/180) had an HFMSE score below 10, scoliosis was present in 120 patients (66.7%); of whom 57 patients (31.7%) had severe scoliosis.

Prior medical conditions of Part 2 patients were described in the Update CSR (1105946).

Concurrent medical conditions were reported in 105 patients (58.3%). The most frequently reported medical conditions were in the SOCs Musculoskeletal and connective tissue disorders (26.1%), and Respiratory, thoracic and mediastinal disorders (16.1%). The most frequently (≥ 5% of patients) reported medical conditions by PTs were scoliosis (16.1%), constipation (6.7%), joint dislocation, joint contracture, and obesity (5.6% each), and seasonal allergy (5.0%).

In Part 2, 176 (97.8%) patients had received prior medications (i.e., before the first dose of study drug).

In Part 2, 178 (99.4%) patients received at least one concomitant medication in the study.

The most frequently reported concomitant medications (>= 20% of patients) included paracetamol (113 patients [63.1%]), ibuprofen (92 patients (51.4%]), amoxicillin (49 patients [27.4%]), sodium chloride supplementation (44 patients [24.6%]), exercise / physical therapy (43 patients [24.0%]), influenza vaccine (41 patients [22.9%]), azithromycin, tozinameran (39 patients [21.8%] each), amoxicillin and clavulanate potassium (37 patients [20.7%] each).

59 patients (32.8%) had undergone at least one previous SMA-related surgery and procedure. Fifty-five patients (30.0%) had at least one previous SMA surgical or medical procedure. The previous SMA surgical or medical procedure reported in ≥ 2 patients included: scoliosis surgery in 25 patients [13.9%]; spinal fusion surgery in 19 patients [10.6%], osteotomy and spinal operation in 6 patients each [3.3%], spinal implantation in 4 patients [2.2%], gastrointestinal tube insertion, gastrostomy, medical device removal, tenotomy in 3 patients each [1.7%], airway secretion clearance therapy, arthrodesis, hip surgery, spinal support in 2 patients each [1.1%].

A total of 123 concurrent SMA-related surgeries or procedures were reported by 62 patients (34.6%). Surgical and medical procedures reported in >= 2 patients included scoliosis surgery (25 patients [14.0%]), spinal fusion surgery (17 patients [9.5%]), spinal operation (8 patients [4.5%]), osteotomy (4 patients [2.2%]), arthrodesis, spinal implantation, urethral repair (3 patients [1.7%] each), spinal X-ray, spinal osteoarthritis, X-ray of pelvis and hip, cast application, mechanical ventilation, medical device removal, and spinal support (2 patients each [1.1%]).

7.2. Results

Part 1

Exposure to study treatment

In the all exposure to risdiplam treatment period, the median duration of exposure to risdiplam was 1826 days (min-max: 287-1931 days) for all patients. Median exposure to the pivotal dose was 1621 days (min-max: 287 - 1854 days). Cumulative exposure to risdiplam was 249.0 patient-years.

Dose intensity was defined as the total number of doses actually received divided by the total number of planned doses, expressed as a percentage. Median dose intensity in the all exposure to risdiplam treatment period was 99.89% (min-max: 80.0%-100.0%) and 98.0% of patients had a dose intensity >= 80%. Nine patients received a dose above the 10% limit of the planned dose.

Fourteen patients received <= 10% below the planned dose (defined as partial dose) on at least one occasion. Thirty-five patients missed one or more risdiplam doses with a median of 4 missed doses (min-max: 1-23 doses).

The data from Part 1 show stabilization or improvement in motor function from baseline to Week 260 (Year 5) with risdiplam treatment across this broad Type 2 and ambulant and non-ambulant Type 3 SMA population, as assessed by the 32-item Motor Function Measure (MFM32), Revised Upper Limb Module (RULM), and Hammersmith Functional Motor Scale Expanded (HFMSE). Key Part 1 efficacy results at Week 260 are summarized below:

- The mean (SD) change from baseline in MFM32 total score (excluding patients who performed the MFM20 at any time point) following 5 years (Week 260) on treatment was 1.38 (6.87). Overall, 67.5% of patients achieved a change from baseline ≥0 and 40.0% of patients achieved an improvement of ≥3 in MFM32 total score.
- The mean (SD) change from baseline in RULM total score was 1.28 (5.00) at Week 260. Overall, 63.8% of patients achieved a change from baseline ≥0 and 40.4% of patients achieved an improvement ≥2 in RULM total score.
- The mean (SD) change from baseline in HFMSE was −0.79 (5.24) at Week 260. Overall, 51.1% of patients achieved a change from baseline ≥ 0 points and 34.0% of patients experienced an improvement of ≥ 2 points in HFMSE total score.

Part 2

Exposure to Study Treatment

In the all exposure to risdiplam treatment period, the median duration of exposure to risdiplam was 1815 days (min-max: 100 - 1856) for all patients. Cumulative exposure to risdiplam was 799.2 patient-years. Median dose intensity in the all exposure to risdiplam treatment period was 99.80% (min-max: 90.1%-124.0%) and all patients had a dose intensity >= 80%. Seven patients received a dose above the 10% limit of the planned dose and 20 patients received <= 10% below the planned dose (defined as partial dose) on at least one occasion. A total of 119 patients missed one or more risdiplam doses with a median of 6 missed doses (min-max: 1-151 doses). A patient had a dose interruption of 151 days due to a suspected relationship of risdiplam treatment with AE of urinary occult blood positive.

Efficacy results

- In Part 2 of the study, risdiplam treatment of up to 5 years (Week 260) resulted in stabilization of motor function, as assessed by the MFM32, and improvement or stabilization of upper-limb function, as assessed by the RULM, in a broad and heterogeneous population of patients with Type 2 and non-ambulant Type 3 SMA. Improvements in the caregiver-reported SMA Independence Scale-Upper Limb Module (SMAIS-ULM) and stabilization in the patient-reported SMAIS-ULM were also observed, indicating greater or maintained independence in completing daily activities. Taken together, these results indicate the continued benefit of treatment with risdiplam. Key Part 2 efficacy results are summarized below.
- In patients treated with risdiplam from the start of the study:
- The mean (SD) change from baseline in MFM32 total score was −0.08 (7.38) at Week 260. Of these patients, 52.1% (49/94) achieved a change of ≥ 0 and 35.1% (33/94) achieved an improvement ≥3 in MFM32 total score.
- The mean (SD) change from baseline in RULM total score was 2.11 (5.50) at Week 260. Of these patients, 63.3% (62/98) achieved a change of ≥ 0 and 48.0% (47/98) achieved an improvement ≥2 in RULM total score.
- The mean (SD) change from baseline in HFMSE total score was −0.77 (6.96) at Week 260. Of these patients, 48.4% (46/95) achieved a change of ≥ 0 and 30.5% (29/95) achieved an improvement ≥2 in HFMSE total score.
- The mean (SD) change from baseline in the caregiver-reported SMAIS-ULM total score was 2.65 (5.86) at Week 260. In the patient-reported (≥ 12 years old) SMAIS-ULM total score, the mean (SD) change from baseline was 0.94 (4.22) at Week 260.

In patients initially assigned to placebo who switched to risdiplam at Month 12:

- The mean (SD) change from baseline in MFM32 total score was −1.86 (5.85) at Week 208. Of these patients, 47.1% (24/51) achieved a change of ≥ 0 and 19.6% (10/51) achieved an improvement ≥3 in MFM32 total score.
- The mean (SD) change from baseline in RULM total score was 0.77 (3.89) at Week 208. Of these patients, 67.3% (35/52) achieved a change of ≥ 0 and 38.5% (20/52) achieved an improvement ≥2 in RULM total score.
- The mean (SD) change from baseline in HFMSE total score was −2.64 (5.91) at Week 208. Of these patients, 34.0% (17/50) achieved a change of ≥ 0 and 22.0% (11/50) achieved an improvement ≥2 in HFMSE total score.

- The mean (SD) change from baseline in the caregiver-reported SMAIS-ULM total score was 2.73 (7.06) at Week 208. In the patient-reported (≥ 12 years old) SMAIS-ULM total score, the mean (SD) change from baseline was −0.68 (3.78) at Week 260.

Across the study, the results were more favorable in the youngest age group (2–5 years of age) and the patients who received risdiplam from the start of the study.

7.3. Discussion

Study BP39055 (SUNFISH) was purposely designed to recruit a broad patient population representative of the wide spectrum of later-onset SMA patients seen in clinics. The study included patients aged 2–25 years with Type 2 (73% and 71% in Parts 1 and 2, respectively) and Type 3 SMA (28% in Part 1 [ambulant and non-ambulant] and 29% in Part 2 [non-ambulant]) in dynamic progression given the age range. Patients had a disease duration of up to 23 years at study enrollment and consequently displayed typical features of advanced SMA disease and a multitude of SMA-related comorbidities at baseline, with very low motor function scores and scoliosis.

Multiple scales (MFM32, RULM, and HFMSE) were used to assess motor function in this broad and heterogeneous population. Unfortunately, and as discussed in previous assessments of the study interim reports, not all patients performed MFM32 at all visits, since a few have had MFM20 performed. The MFM32 captures a range of ability, including items relating to distal fine motor movements of the hands to more complex gross motor function activities. The upper limb assessments in the MFM32 are primarily not assessed by the HFMSE. The RULM is designed to assess upper limb motor function in SMA, which is of particular relevance to wheelchair-bound patients who rely on upper limb function for daily living. The HFMSE is designed to capture functional change in stronger SMA patients (Mercuri et al. 2019) and thus a floor effect may be expected in a profoundly weak study population such as the population enrolled in Study BP39055 (SUNFISH), where 45.1% and 41.1% of patients in Parts 1 and 2, respectively, had an HFMSE score <10 at baseline.

SMA is a progressive disease and, in the absence of a control arm after the Month 12 primary analysis or external control data for each scale for these 5–year, long-term efficacy data, it is difficult to contextualize appropriately the results. Especially because the available natural history data is getting older, and supportive care has significantly improved, as can be seen by the previous and concomitant procedures performed in the study patients.

The results show a clear deviation from natural history though, for the majority of the patients. Notwithstanding, mean MFM32 values show a tendency to a halt in progression rather than an improvement. A modest but significant improvement has only been observed in about 1/3 of the patients (35%). This improvement has been more significant in the upper limbs though, and this is relevant in non ambulant patients.

To contextualize, the slope of change with the MFM32 has been described as −0.86 points per year in patients with Type 2 SMA and −0.55 points per year in Type 3 (Vuillerot et al. 2013). With the RULM, an overall progressive decline in upper limb function over 24 months has been observed. The negative changes were most notable in patients with Type 2 SMA who retained the ability to sit (mean change −1.62 points) and in non-ambulant patients with Type 3 SMA (mean change −0.94 points) (Coratti et al. 2022). Natural history of Type 2 patients followed longitudinally for approximately 5 years with the HFMSE has shown the inflexion point in the trajectory of progression to be at 5 years of age with a decrease in HFMSE total scores of approximately 2 points per year between the ages of 5 and 13 years (Mercuri et al. 2019). In Type 3 patients, the decline can be observed after 7 years of age with an estimated slope of the curve of progression of −2.59 HFMSE points (Coratti et al. 2020). Collectively, these studies evidenced the progression of SMA when there was no effective intervention. In light of the

patients' expected motor function decline inferred from these natural history data, the results obtained in SUNFISH provide evidence for the benefit of 5 years of treatment with risdiplam.

Patients treated initially with placebo in Part 2 of the study who were treated for 4 years with risdiplam showed less benefit than patients treated for 5 years. This lag in response has been reported in other studies of SMA treatments (Darras et al. 2019).

8. Clinical Safety aspects

8.1. Methods – analysis of data submitted

The report presents a summary of results from Study BP39055 up to the clinical cutoff date (CCOD) of 2 October 2023, which corresponds to the last patient last visit (LPLV) for the study. The study, enrolled 51 patients in Part 1 and 180 patients in Part 2, for whom safety data is provided.

Please see sections 6.1 and 7.1 for further information on the study design and conduct.

8.2. Results

Part 1

With up to 5 years of treatment, risdiplam has been rather well tolerated and safety remains consistent with its known safety profile. No new safety signals were identified. There were no deaths, and no patient withdrew from the study due to adverse events (AEs). Further relevant safety findings are reported below:

During the all exposure to risdiplam treatment period, 1026 AEs were reported in 50 patients (98.0% of the 51 patients in total) who experienced at least one AE. The most commonly reported AEs (≥ 20% of patients) were in the SOCs Infections and infestations (84.3%), General disorders and administration site conditions (72.5%), Gastrointestinal disorders (62.7%), Respiratory, thoracic and mediastinal disorders (54.9%), Skin and subcutaneous tissue disorders (35.3%), Injury, poisoning and procedural complications (33.3%), Musculoskeletal and connective tissue disorders (29.4%), and Nervous system disorders (23.5%).

The most commonly reported AEs that occurred in ≥15% of all patients by preferred term (PT) were pyrexia (64.7%), vomiting (39.2%), cough (37.3%), upper respiratory tract infection (35.3%), nasopharyngitis (31.4%), COVID-19 (27.5%), gastroenteritis (27.5%), oropharyngeal pain (25.5%), influenza (23.5%), headache (19.6%), pharyngitis, (17.6%), abdominal pain (17.6%), upper respiratory tract inflammation (15.7%), and rash (15.7%).

Overall, there was a decrease in the rate of AEs per 100 patient years (PY) during the all exposure to risdiplam treatment period, which stabilized after the second year. Overall, there was also a decrease in the rate of serious adverse events (SAEs) per 100 PY over time.

AEs resolved for most patients (38 patients, 74.5%). Most AEs resolved without change to the study medication. Nine patients (17.6%) had 15 unresolved AEs. Three patients (5.9%) had nine AEs for which outcome was reported as unknown.

Analysis of the SOCs which include AEs representing possible effects on epithelial tissues showed that there was no pattern suggestive of epithelial effects of risdiplam.

Ten AEs in the SOC Eye disorder were reported in 8 patients (15.7%). All events were non-serious (highest toxicity Grade 2), were reported as unrelated to study medication by the investigator and

resolved without change to risdiplam treatment, except for 2 patients with 2 unresolved AEs (1 not clinically significant, 1 not related to study treatment). Ophthalmological assessments did not show any clinically significant adverse findings at the last visit compared with baseline.

Thirteen patients (25.5%) reported 24 AEs which were assessed as related to study treatment by the investigator.

More patients in the younger age group (2-11 years) reported AEs in the SOCs Infections and infestations (the most common of which were upper respiratory tract infection [48.4%] and nasopharyngitis [41.9%]), respiratory, thoracic and mediastinal disorders (the most common of which was cough [45.2%]), and Injury, poisoning, and procedural complications (the most common of which were femur fracture [16.1%] and fall [12.9%]), whereas in the older age group (12-25 years) more AEs were reported in the SOC Reproductive system and breast disorders (dysmenorrhea [20.0%])

Most AEs were Grade 1–2 in severity. Seventeen Grade 3–4 AEs were reported in 11 patients (21.6%). Each of these Grade 3-4 AEs resolved except for 1 case of scoliosis.

Seventeen patients (33.3%) reported a total of 26 SAEs. No SAE was considered related to study treatment by the investigator and all SAEs resolved.

Overall, 12 AEs that led to study medication dose interruption were reported in 8 patients (15.7%) during the all exposure to risdiplam treatment period. All these events resolved and did not recur following re-initiation of risdiplam.

There were no adverse events of special interest (AESIs) reported in study Part 1.

Adverse Events of the Skin and Other Events Potentially Linked to Effects on Epithelial Tissue:

Analysis of SOCs which include AEs representing possible effects on epithelial tissues showed that there was no pattern suggestive of effects of risdiplam on epithelial tissues. In the all exposure to risdiplam treatment period, 35 AEs in the SOC Skin and subcutaneous disorders were reported in 18 patients (35.3%). The most commonly reported AEs experienced by at least 2 patients were rash (8 patients), erythema (4 patients), eczema (3 patients), and alopecia, dry skin and palmar erythema (2 patients each). AEs had resolved for the majority of the patients. The AE outcome was reported as unknown for four AEs (erythema, palmar erythema, acne and skin exfoliation), and reported as unresolved for one AE (hypertrichosis). All AEs were non-serious (Grade 1-2). No change was made to the study treatment in response to the AEs. One event of hypertrichosis in one patient had not resolved by Week 260, and was assessed as unrelated by the investigator.

Ophthalmology Monitoring:

Due to retinal toxicity observed in the chronic toxicology study conducted in monkeys, a comprehensive panel of ophthalmological assessments was performed including imaging to detect structural changes of the retina, as well as visual function testing to detect potential functional impairment in central or peripheral vision. All 51 patients in the all exposure to risdiplam treatment period of Part 1 had at least one post-baseline ophthalmology visit. A total of 43 patients (84.3%) had 992 ophthalmological findings during the risdiplam treatment period. Overall, the fundus examination assessments did not show any findings consistent with risdiplam-induced retinal toxicity and did not show evidence of any other pathological findings associated with risdiplam treatment.

Tanner Staging:

A summary of Tanner staging results is provided. By the end of study Part 1, 23 patients 2-11 years old and 11 patients 12-25 years old had a post-baseline Tanner staging. No patients had delayed puberty (Tanner stage < II at age 13 years for females, and age 14 years for males).

Review of all available laboratory results, vital signs, and ECGs did not show any clinically significant adverse findings compared with baseline.

Part 2

A summary of AEs for Part 2 of the study in all patients exposed to risdiplam (n=179) as of LPLV (02 October 2023) is presented.

With up to 5 years of treatment, risdiplam continued to be adequately tolerated and safety remains consistent with its known safety profile. No new safety signals were identified. There was one death (due to suicide by poisoning) reported as not related to study treatment, and no patient withdrew from the study due to AEs. One death (Grade 5) was reported during study Part 2. The cause of death was an AE of toxicity to various agents unrelated to risdiplam treatment (the investigator provided further information that the cause of death was suicide by poisoning).

Further relevant safety findings are reported below:

During the all exposure to risdiplam treatment period, 2800 AEs were reported in 177 patients; the percentage of patients with at least 1 AE was 98.9%.

The most commonly reported AEs (≥ 20% of patients) occurred in the SOCs Infections and infestations, Gastrointestinal disorders, Respiratory, thoracic and mediastinal disorders, General disorders and administration site conditions, Skin and subcutaneous tissue disorders, Injury, poisoning and procedural complications, Nervous system disorders, Musculoskeletal and connective tissue disorders, and Renal and urinary disorders. Those that occurred in ≥15% of all patients by PT were upper respiratory tract infection (41.9%), nasopharyngitis (40.8%), pyrexia (34.1%), COVID-19 (33.0%), headache (26.3%), vomiting (25.7%), diarrhoea (25.1), cough (20.1%), gastroenteritis (16.2%), and pneumonia (16.2%).

Overall, there was a decrease in the rate of AEs per 100 PY during the all exposure to risdiplam treatment period in the second year and then a stabilization from third year onwards. Overall, the rate of SAEs per 100 PY during the all exposure to risdiplam treatment period remained relatively consistent over time with a decrease in Year 3 coinciding with the Coronavirus Disease 2019 (COVID-19) lockdown.

Most AEs had resolved by Week 260. Seventy-five patients (41.9%) had 144 unresolved AEs and 7 patients (3.9%) had 12 AEs for which outcome was reported as unknown.

Analysis of the SOCs which include AEs representing possible effects on epithelial tissues showed that there was no pattern suggestive of epithelial effects of risdiplam. In the all exposure to risdiplam treatment period, 150 AEs in the SOC Skin and subcutaneous disorders were reported in 72 patients (40.2%), of which 15 AEs were assessed by investigators to be related to study treatment. None of the events were serious or led to a change in study medication. All events resolved or were resolving by Week 260, except for 14 AEs reported by 11 patients with outcome unresolved and 2 AEs experienced by one patient for which outcome was unknown.

Twenty-six eye AEs, 25 in the SOC Eye disorders and 1 AE in the SOC neoplasms, were reported in 26 patients (12.3%). All AEs of eye disorders were non-serious, all were Grade 1 except 7 Grade 2 AEs, all were reported as unrelated to study treatment by the investigator except 2 related AEs (1 not clinically significant, 1 resolved), and all resolved except 3 Grade 1 AEs which had not resolved. Ophthalmological assessments did not show any clinically significant adverse findings at the last visit compared with baseline. No intracranial hypertension was reported.

All AEs of eye disorders were non-serious, all were Grade 1 except 7 Grade 2 AEs (2 conjunctivitis allergic, 2 dry eye in same patient, 1 lacrimation increased, 1 keratitis, 1 eyelid cyst), all were reported

as unrelated to study treatment by the investigator except 2 related AEs, and all resolved except 3 Grade 1 AEs (dry eye patient, eye naevus patient, retinal tear patient) and 1 Grade 2 AE (keratitis patient) which had not resolved. There was no change to risdiplam therapy for any of the AEs. Ophthalmological assessments were without clinically significant changes at the last visit compared to baseline.

Overall, 21 patients (11.7% of patients) reported 25 AEs from the SOC of Eye disorders and 1 patient (0.6% of patients) reported 1 AE relating to the eyes coding to the SOC neoplasms (a Grade 1 AE of eye naevus), which was small thus per investigator and per central reader could have been overlooked at baseline; reported as unrelated and unresolved. The event was seen in slit lamp assessments from Week 17 and was stable through Week 70. No abnormal slit lamp findings were reported at Week 78, Week 104 and at the study completion visit Week 260. The naevus was potentially overlooked again due to its small size.

Thirty-seven patients (20.7%) reported 121 AEs which were assessed as related to study treatment by the investigator. Thirteen SAEs reported for two patients from the same site were considered related to study treatment by the investigator. The 10 related (assessment by investigator) AEs of haematuria concerning 10 patients were all reported from two sites. All patients were non-ambulatory at screening. In each of the cases, therapy with risdiplam was maintained. Nine out of 10 AEs were reported as Grade 1 and no treatment was received. In one Grade 2 haematuria AE, the patient received treatment. There was no pattern of latency with therapy with risdiplam and the event onset date ranged from study Day 365 to study Day 1191. Two patients had blood in urine at baseline, during the placebo arm of the treatment as well as the treatment with risdiplam. The blood in urine results showed no clear pattern and fluctuated between absent, trace, positive and strong positive; and were accompanied by protein in urine in some instances.

The majority (109/179, 60.9%) of patients reported AEs that were Grade 1–2 in severity, 67 patients (37.4%) reported 200 Grade 3–4 AEs.

Sixty-eight patients (38.0%) reported a total of 173 SAEs. All but 5 SAEs had resolved/improved.

Thirty-two patients (17.9%) reported 82 AEs that led to study drug dose interruption during all exposure to risdiplam treatment period.

There were no AESIs reported in study Part 2.

Review of all available laboratory results, vital signs, and ECGs did not show any clinically significant adverse findings compared with baseline.

Safety in Special Groups and Situations

Intrinsic Factors

The safety profile was not evaluated for any intrinsic factor.

Extrinsic Factors

No relevant extrinsic factors were identified for this patient population based on the currently available data.

Drug Interactions

No new data pertaining to drug-drug or drug-food interactions was collected from Study BP39055.

Use In Pregnancy and Lactation

No pregnancies nor lactation were reported during the study.

Overdose

The number of patients who received >10% above the planned dose (defined as an overdose) was 9 in Part 1 and 7 in Part 2 across all patients, over 5 years of treatment, in Study BP39055 (SUNFISH). No cases of overdose were associated with any AEs due to risdiplam treatment.

Drug Abuse

There was no safety data from Study BP39055 to suggest any potential for risdiplam to cause dependence.

Withdrawal and Rebound

There was no new data from Study BP39055 to suggest that risdiplam has any effect on withdrawal or rebound.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

There was no new data from Study BP39055 to suggest an effect on ability to drive or operate machinery or impairment of mental ability.

Post Marketing Data

Risdiplam is currently approved in over 100 international markets (including U.S. and E.U.) for the treatment of SMA. Since the International Birth Date (07 August 2020) through 6 August 2023 (data lock point for the PBRER 1122884), an estimated cumulative total of 10,885 patients have received risdiplam from marketing experience (European Economic Area n = 3597; Rest of the World n = 4128; U.S. = 2513). Exposure was similar between the sexes (male n = 5119; female n = 5119; unknown n = 0). The information that became available did not alter the known benefit-risk profile of risdiplam and the benefit-risk profile of risdiplam in the authorized indication remains favorable. Refer to the PBRER 1122884, submitted on 13 October 2023 (procedure no: EMEA/H/C/PSUSA/00010925/202308) for more details.

8.3. Discussion

The MAH has presented the safety results of up to 5 years of follow up. The safety profile is similar to what was already known for risdiplam. Specifically, no new signals have been identified, neither for new AE type nor for a different frequency or time to event occurrences. Of note, the safety concerns related to this PAM and previously suspected from nonclinical data have not been confirmed with this long-term exposure of risdiplam.

9. Request for supplementary information

9.1. Major objections

None

9.2. Other concerns

Clinical aspects

Pharmacokinetics

Question 1

1. Given the final results derived from Study BP39055 (PKPD report 1129700, dated February 2024), the applicant is suggested to update section 5.2 (pharmacokinetic properties) of the approved SmPC.

10. Assessment of the responses to the request for supplementary information

10.1. Major objections

None

10.2. Other concerns

Clinical aspects

Pharmacokinetics

Question 1
Given the final results derived from Study BP39055 (PKPD report 1129700, dated February 2024), the applicant is suggested to update section 5.2 (pharmacokinetic properties) of the approved SmPC.

Summary of the MAH's response
Per request, Section 5.2 of the SmPC was updated specifically with the estimated exposure after 5 years of treatment as well as the mean C_{max}.

Assessment of the MAH's response
The applicant has updated section 5.2 of SmPC with results from SUNFISH study following 5 years of treatment. The mean exposure is 1940 ng.h/mL and mean C_{max} is 140 ng/mL.

This issue is considered as resolved.

Conclusion

☐Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☒No need to update overall conclusion and impact on benefit-risk balance