05 September 2024
EMA/CHMP/321325/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Evrysdi

International non-proprietary name: Risdiplam

Procedure No. EMEA/H/C/005145/II/0027

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	08 Jul 2024	08 Jul 2024	☐
☐	CHMP Rapporteur Assessment Report	12 Aug 2024	12 Aug 2024	☐
☐	CHMP members comments	26 Aug 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	29 Aug 2024	n/a	☐
☐	Start of written procedure	03 Sep 2024	03 Sep 2024	☐
☒	Opinion	05 Sep 2024	05 Sep 2024	☐

Table of Contents

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 20 June 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 BP39056 (FIREFISH) listed as a category 3 study in the RMP; this is 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.

The requested variation proposed no amendments to the Product Information.

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

The MAH has presented the final report for study BP39056 (FIREFISH). This was a two-part, operationally seamless, open-label, multi-center study designed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in infants with Type 1 spinal muscular atrophy (SMA).

The Part 2 primary efficacy objective was to assess the efficacy of risdiplam measured as the proportion of infants sitting without support after 12 months of treatment, as assessed in the gross motor scale of the Bayley Scales of Infant and Toddler Development - Third Edition (BSID-III), defined as sitting without support for 5 seconds.

The primary endpoint was met. The clinical value of this primary endpoint has been thoroughly discussed as limited. Notwithstanding, the other endpoints globally support the primary endpoint results, and some have significant clinical meaning, such as the ability to swallow, keep sitting for 30 seconds and ability to stand.

Regarding safety, and although seven deaths have been reported in the early part of the study, these are expected in the natural history of the disease and did not seem related to the treatment.

In conclusion, both the efficacy and safety data observed support the persistent effect of risdiplam up to 5 years of follow-up, with some milestones being acquired after three years of treatment.

No update to SmPC is considered needed at this point.

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	None

Submission of the final report from study BP39056 (FIREFISH) listed as a category 3 study in the RMP; this is 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.

☒is recommended for approval.

Amendments to the marketing authorisation

The variation leads to no amendments to the terms of the Community Marketing Authorisation.

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

Submission of the final report from study BP39056.

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

5. Introduction

The objective of this variation is to provide the final results from study BP39056 (FIREFISH), a two-part seamless, open-label, multi-center study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of risdiplam (RO7034067) in infants with Type 1 Spinal Muscular Atrophy. As an additional pharmacovigilance activity in the RMP (category 3 study), this study was to address the below safety concerns for risdiplam: long-term safety and effect on epithelial tissues. Given that the MAH foresees a minimal impact on the content of the RMP and the benefit/risk profile of risdiplam remains favourable, the MAH proposes to update the RMP as part of a submission at a later date, hence an updated RMP (module 1.8.2) has not been submitted. The updated CSR of Study BP39056, was submitted as a type II, C.I.4 variation in August 2021.

6. Clinical Pharmacology aspects

6.1 Methods – analysis of data submitted

The PK and PD data in the current submission is based on the final data from Study BP39056 at the clinical cutoff date of 22 December 2023, which corresponds to the last patient last visit after 5 years in the study. Study results are presented in the Population Pharmacokinetic, Pharmacokinetic and Pharmacodynamic Analyses Report for Risdiplam (code 1131437, dated May 2024).

The objective of report 1131437 was to describe risdiplam PK of the 62 patients with Type 1 SMA of Study BP39056 at Year 5 Visit, until a clinical cutoff date (CCOD) of 22 December 2023. A PPK model previously developed using the pooled data set of Studies BP29840, BP39054, BP39055, BP39056, BN40703 and BP41361 served as the reference PPK model in the present analysis.

Specifically, the analysis was performed to:

- Evaluate the previously developed population PK model against the updated data collected from Study BP39056 up to Year 5 Visit.
- Derive secondary PK parameters ($AUC_{0\text{-}24h}$ and C_{av}) of 62 SMA patients to evaluate risdiplam exposure.
- Investigate relationships between risdiplam exposure and pharmacodynamic (PD) markers SMN protein and SMN2 mRNA.

Concentrations of risdiplam were quantified in human plasma using a validated liquid chromatography tandem mass spectrometry (LS-MS/MS) method. The calibration range was 0.250 to 250 ng/mL in plasma. For samples with a concentration higher than the upper limit of the calibration range, the sample was re-analyzed after dilution, and the dilution factor applied for calculation of the concentration.

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.

The reference PPK model was 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 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 (ktr), the apparent clearance (CL/F) and the apparent central volume of distribution (Vc/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 Fracbirth, 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 Vc/F and Vp/F. The summary of the population PK parameter estimates are summarized in Table 1. This model was used as the reference PPK model to initiate the present PK analysis.

The reference PPK model was fitted to the combined data set 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 to adapt the model for the updated risdiplam PK data set.

Table 1. 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%)	10.3	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 [1].

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.

6.2 Results

Demographics

The demographics, risdiplam dosing history and plasma concentrations of risdiplam collected from 552 subjects, consisting of 61 healthy subjects (BP29840 and BP41361) and 491 SMA patients (BP39054, BP39055, BP39056 and BN40703) were available in the data base as of 22 December 2023 and included in the population PK analysis. The demographics of the patients at the time of the first dose are summarized in Table 2.

Table 2. 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%)

Plasma Concentrations

A total of 15,654 plasma samples for measurement of risdiplam concentrations were collected from 552 subjects who participated in Studies BP29840, BP39054, BP39055, BP39056, BN40703 and BP41361. There were additional 278 samples available from Study BP39056 as of CCOD of 22 December 2023 since the PPK modelling of risdiplam conducted in 2021. After excluding 424 samples, the remaining 15,230 observations including 476 capillary blood samples (3.1%) were available for the analysis.

The maximum plasma concentration and trough concentration at around Year 5 visit per individual patient of Study BP39056 is summarized in Table 3. The individual plasma concentration time profiles included in the PPK analysis are shown in Figure 1 (linear scale) and Figure 2 (semi-log scale).

Table 3. Summary of the Maximum Observed and Trough Plasma Risdiplam Concentrations of SMA Patients of Study BP39056 (FIREFISH)

	Maximum Plasma Concentration (ng/mL)[a]		Trough Plasma Concentration (ng/mL)[b]	
Part	1 (n=21)	2 (n=41)	1 (n=16)	2 (n=33)
Mean	201	193	61.1	65.6
Median [range]	187 [18.7, 364]	195 [67.7, 296]	58.8 [36.4, 102]	63.1 [15.1, 134]

[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 4 years of risdiplam treatment.

Figure 1. Risdiplam Concentration *versus* Time since First Dose by Study on Linear Scale

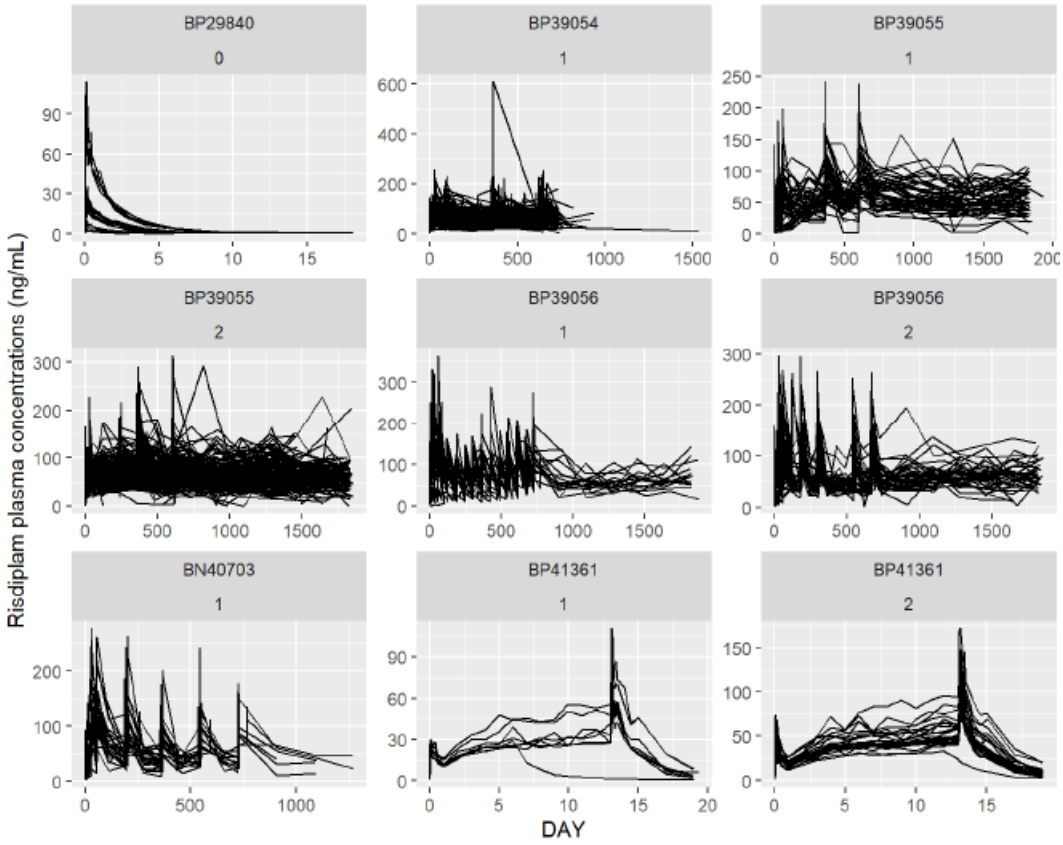
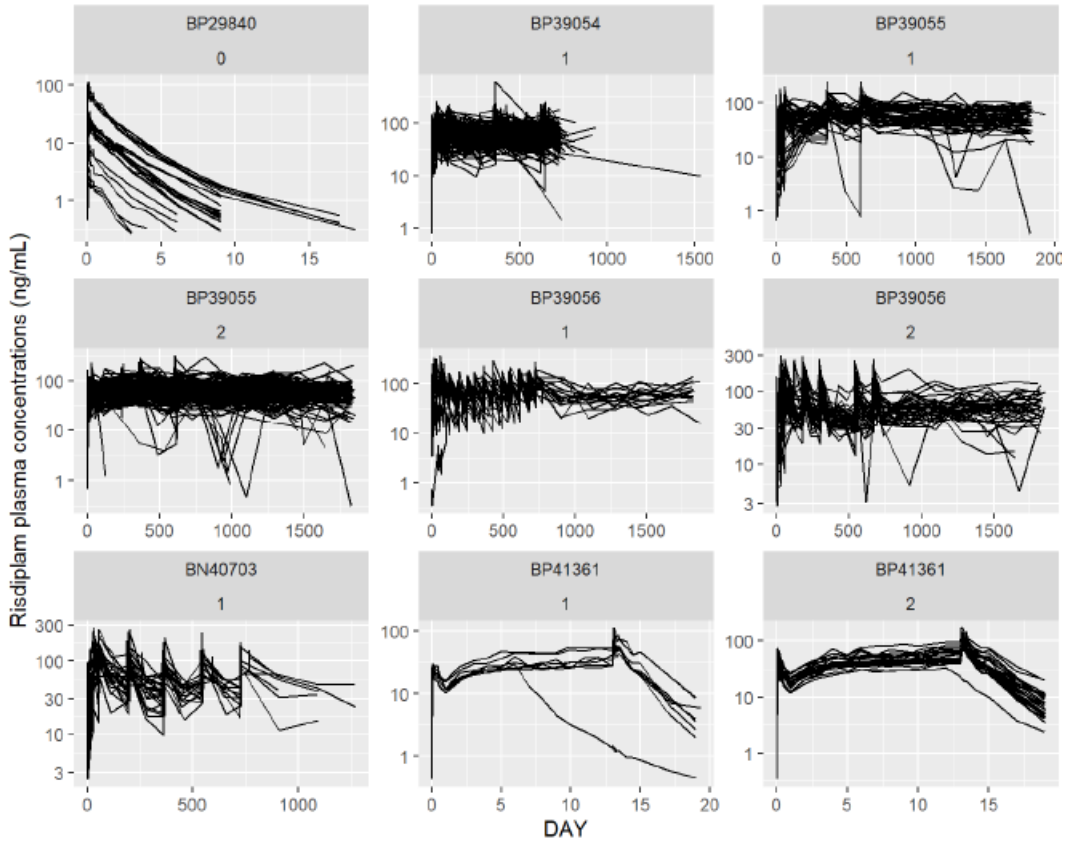


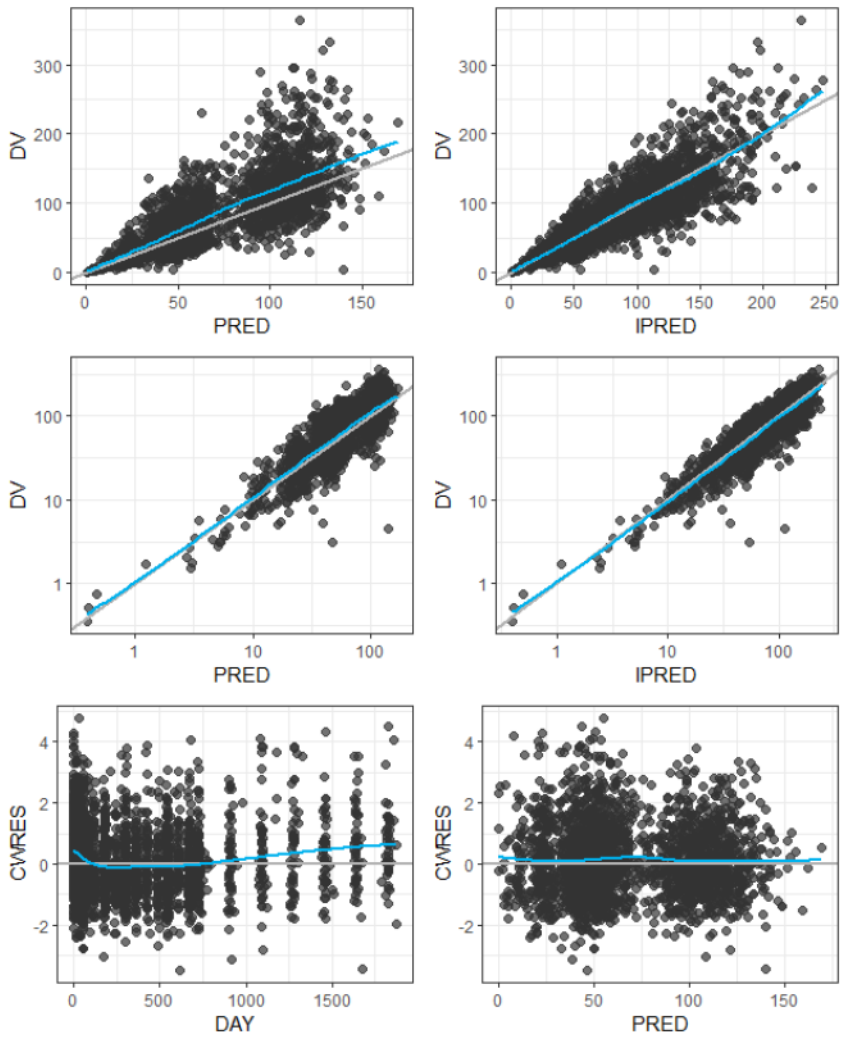
Figure 2. Risdiplam Concentration *versus* Time since First Dose by Study on Semi-Log Scale



The reference PPK model (Table 1) was fitted to the updated data set including newly collected data of Study BP39056 up to Year 5 Visit. Adequacy of the reference PPK model to predict risdiplam PK, focusing on the SMA patients of Study BP39056, was examined.

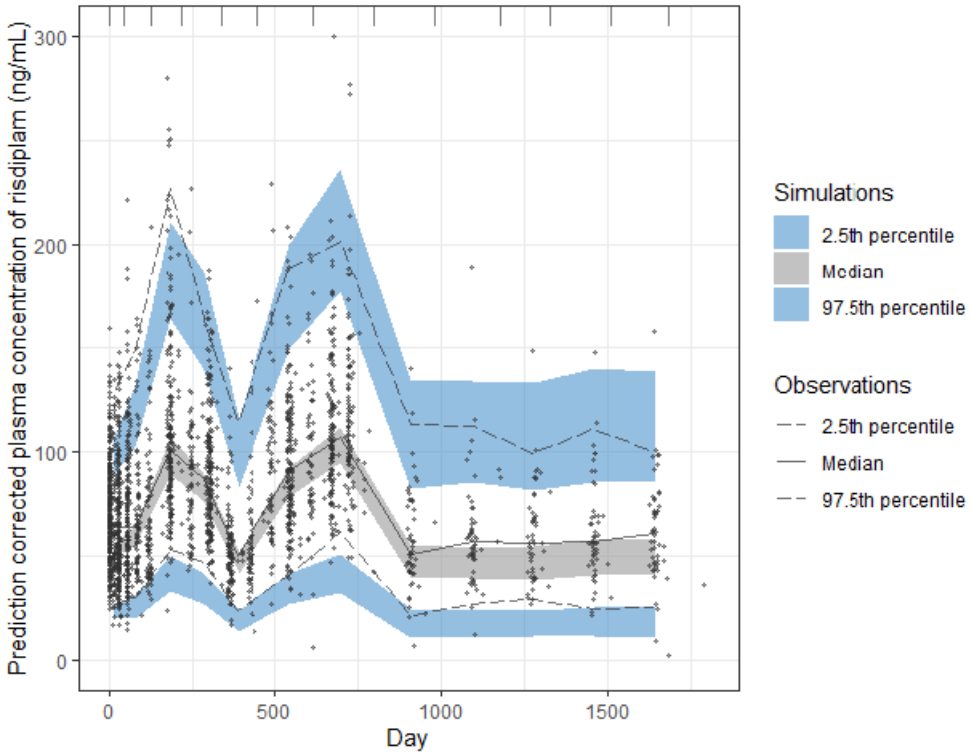
The GOFs and pc-VPC of the reference PPK model for Study BP39056 data are shown in Figure 3 and Figure 4, respectively. These plots for Study BP39056 showed a tendency for slight under prediction of risdiplam concentrations of the patients with Type 1 SMA.

Figure 3. Goodness-of-Fit Plots of the Reference PPK Model of Risdiplam for Study BP39056 data up to Year 5 Visit



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.

Figure 4. Prediction Corrected Visual Predictive Check of the Reference PPK Model of Risdiplam for the Updated Dataset Including Data of Year 5 Visit of Study BP39056: SMA Patients of Study BP39056 only



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 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.

In order to improve model predictions, inclusion of covariate effect of Type 1 SMA on clearance and volume of distribution was examined. Addition of the covariate effect on CL/F and Vc/F for the patients with Type 1 SMA significantly reduced OFV, and inclusion of the same covariate effects of CL/F on Q/F, and the covariate effect of Vc/F on Vp/F further decreased OFV. The estimated effect for Type 1 SMA was 18.4% lower CL/F and Q/F, and 20.4% lower Vc/F and Vp/F compared to subjects without Type 1 SMA (Table 4). The model parameters were well estimated with RSE <28% and good consistency with the bootstrap analysis supported robustness of the parameter estimates. Shrinkage for CL/F, ktr and Vc/F were 2.44, 25.5 and 9.45%, respectively, indicating an ability to reliably estimate individual post-hoc parameters.

Table 4. Summary of the Updated Population PK Model of Risdiplam

Parameter	Unit	Estimate	RSE (%)	95%CI	95%CI*
Fixed Effects					
CL/F	L/h	2.48	2.61	2.35-2.6	2.35-2.57
ktr	/h	5.44	2.30	5.19-5.68	5.14-5.75
Vc/F	L	91.8	1.42	89.2-94.3	89.3-94.3
Q/F	L/h	0.552	7.89	0.467-0.637	0.477-0.657
Vp/F	L	127	20.70	75.6-179	94.4-183
Covariate Effects					
Effect of WT on CL/F and Q/F		0.237	11.50	0.184-0.291	0.181-0.292
Effect of WT on Vc/F and Vp/F		1 FIX	-	-	-
Factor for CL/F of healthy adults		0.500	12.30	0.38-0.621	0.399-0.630
$Frac_{birth}$ – CL/F		0.0823	27.20	0.0384-0.126	0.0384-0.123
Age_{50} – CL/F (y)		1.06	12.40	0.802-1.32	0.826-1.34
Effect of Type 1 SMA on CL/F and Q/F		-0.184	14.90	-0.238- -0.13	-0.235- -0.137
Effect of Type 1 SMA on Vc/F and Vp/F		-0.204	14.30	-0.261- -0.147	-0.268- -0.141
Random Effects					
CL/F (CV)		0.0603 (24.6%)	6.94	0.0521-0.0685	0.0518-0.0685
ktr (CV)		0.254 (50.4%)	8.89	0.21-0.299	0.206-0.312
Vc/F (CV)		0.0681 (26.1%)	7.69	0.0579-0.0784	0.0589-0.0769
Error Model					
σ_1 proportional - venous (CV)		0.0638 (25.2%)	2.68	0.0605-0.0672	0.0608-0.0671
σ_2 proportional – capillary (CV)		0.0795 (28.2%)	12.2	0.0605-0.0984	0.0648-0.0954

OFV = objective function, RSE = relative standard error of estimate; CV = coefficient of variation; NA = not applicable; WT = body weight.*bootstrap analyses with 200 replicates

GOF plots of the updated PPK model for all subjects and for Study BP39056 patients are shown in Figure 5 and Figure 6, respectively. Good consistency between DV and PRED, as well as IPRED was shown with most of them being homogeneously distributed around the identity line. Improvement in PRED and CWRES distributions for Study BP39056 data compared to the reference PPK model (Figure 3) was shown in Figure 6. The pc-VPC showed the ability of the model to adequately predict central tendency and inter-individual variability of all subjects as well as the patients with Type 1 SMA as shown in Figure 7 and Figure 8, respectively. The individual secondary PK parameters of the patients with Type 1 SMA of Study BP39056 were estimated using the post-hoc parameters of the updated PPK model.

Figure 5. GOF Plots of the Updated Model for the Dataset including Study BP39056 Year 5 Visit: All Patients

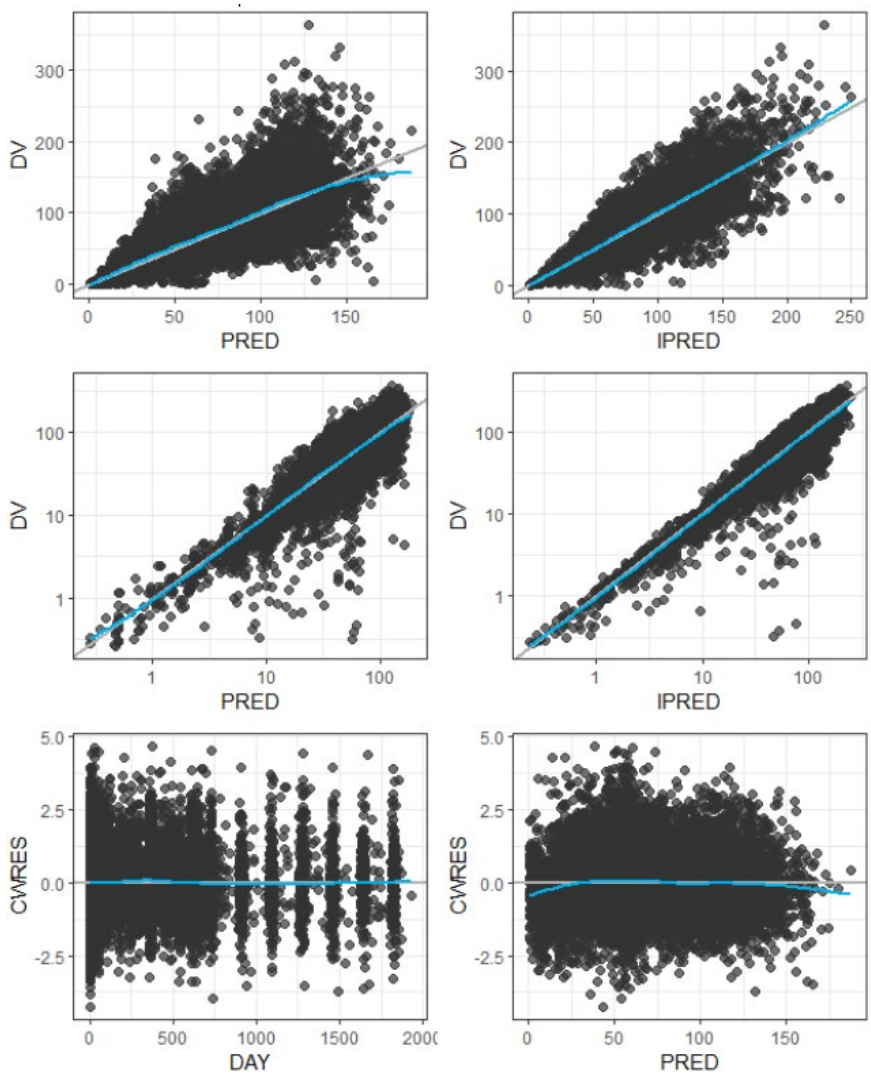


Figure 6. GOF Plots of the Updated Model for the Dataset including Study BP39056 Year 5 Visit: Study BP39056 Patients Only

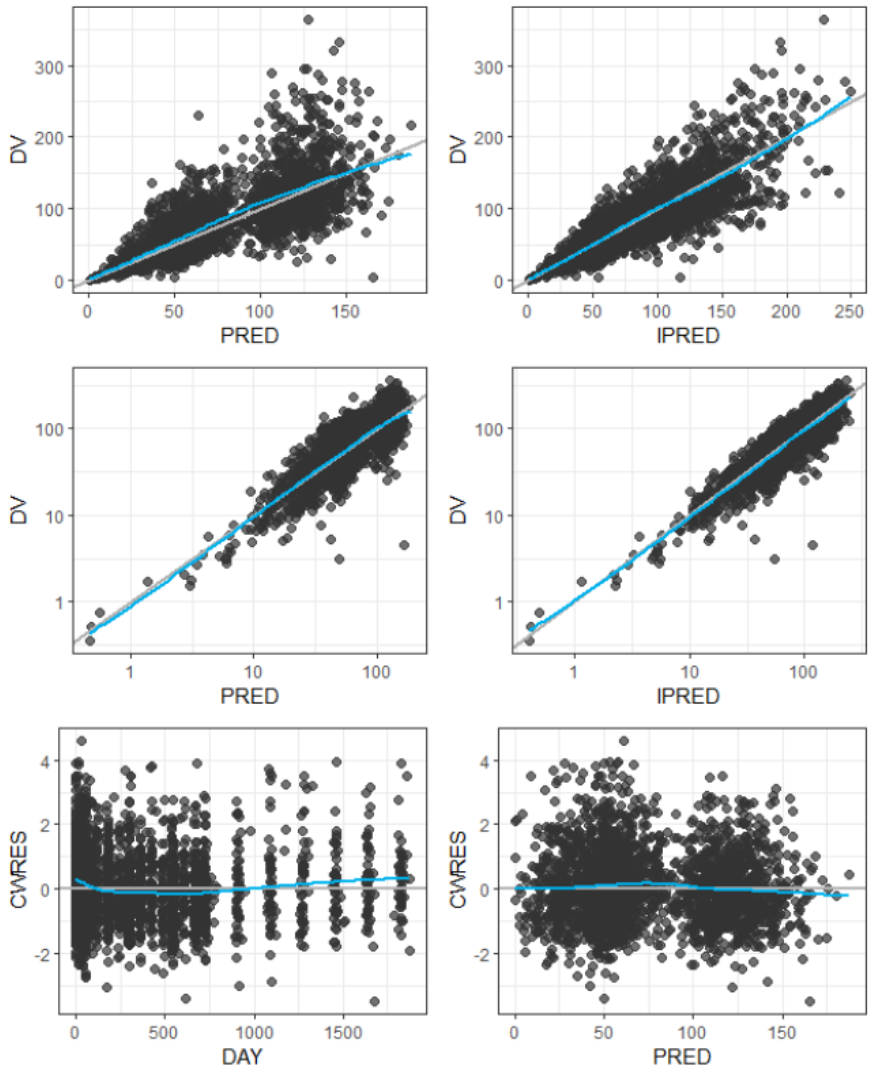


Figure 7. Prediction Corrected Visual Predictive Check of the Reference PPK Model of Risdiplam for the Updated Dataset Including Data of Year 5 Visit of Study BP39056: All Subjects

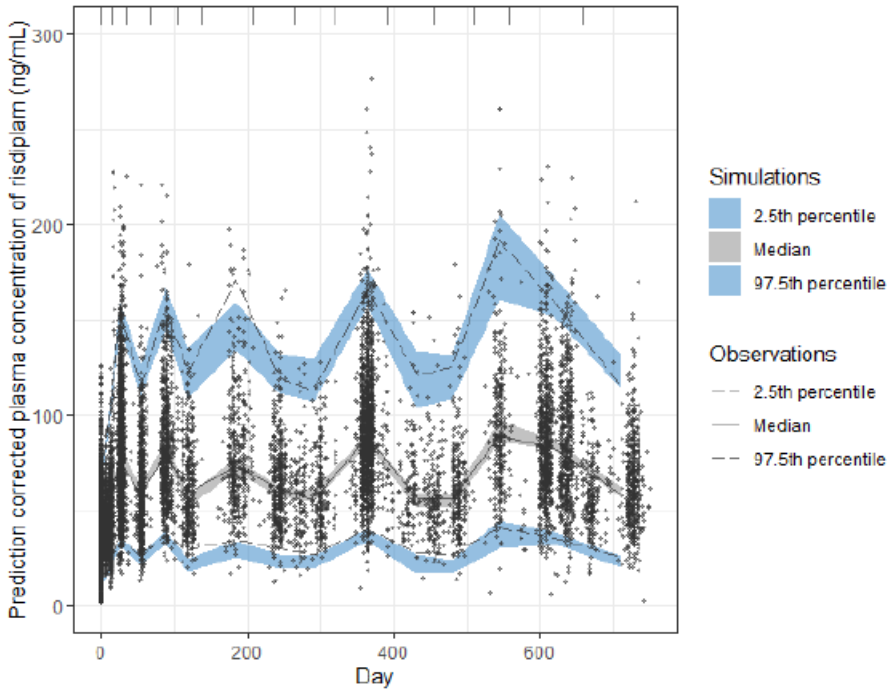
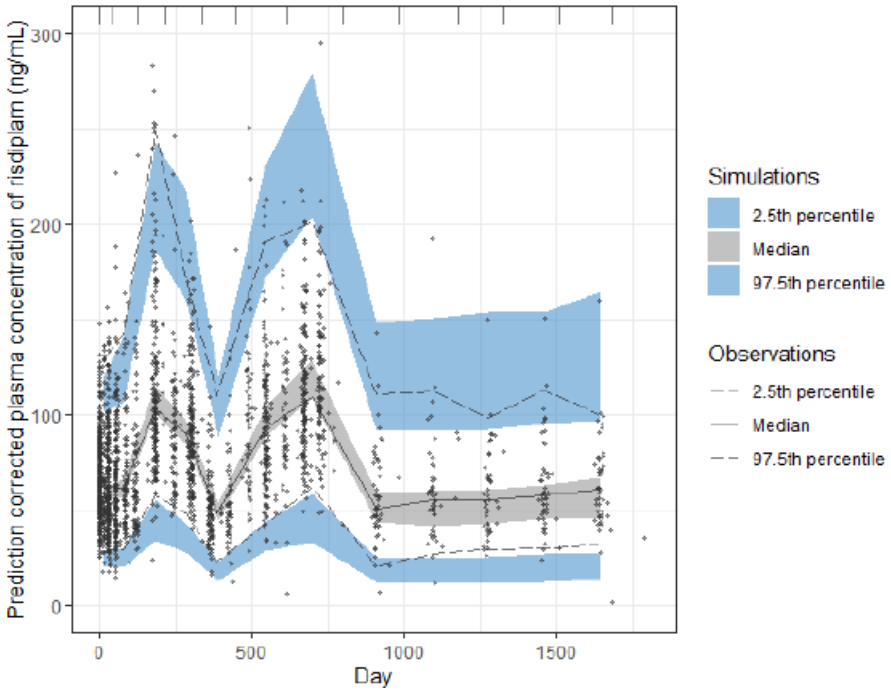


Figure 8. Prediction Corrected Visual Predictive Check of the Reference PPK Model of Risdiplam for the Updated Dataset Including Data of Year 5 Visit of Study BP39056: Study BP39056 Patients Only



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

The individual $AUC_{0\text{-}24h}$ –time course of the SMA patients of Study BP39056 between Day 28 and the last risdiplam dosing including Year 5 Visit are shown in Figure 9. Consistent risdiplam exposure during the treatment period was noted in both Parts 1 and 2 between Years 2 and 5 Visit. Risdiplam $AUC_{0\text{-}24h}$ and

C_{av} are summarized by Part in Table 5. The median AUC_{0-24h} of all patients with Type 1 SMA in Study BP39056 at Year 5 Visits was 2530 ng•h/mL and the median C_{av} was 92.9 ng/mL.

Figure 9. Individual Risdiplam AUC_{0-24h} of SMA Patients of Study BP39056 on Day 28 to Year 5 Visits

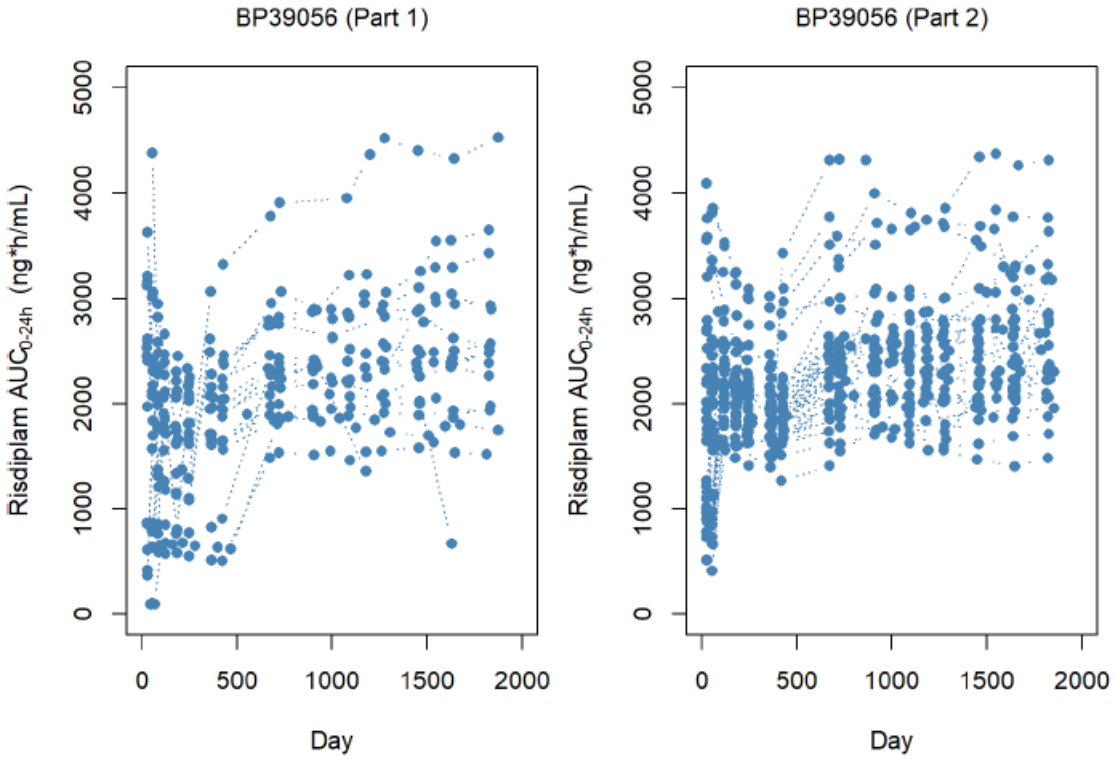


Table 5. Summary of Risdiplam AUC_{0-24h} and C_{av} at Year 5 Visit of the SMA Patients of Study BP39056

Dose	Part 1 (n=15)	Part 2 (n=35)	Total (n=50)
Age (years)			
Median [range]	5.50 [5.30, 5.70]	5.40 [4.90, 5.60]	5.50 [4.90, 5.70]
Body weight (kg)			
Median [range]	14.4 [12.4, 22.4]	15.2 [9.00, 33.0]	15.0 [9.00, 33.0]
AUC_{0-24h} (ng•h/mL)			
Mean	2620	2630	2630
Median [5th, 95th]	2500 [1670, 3910]	2560 [1820, 3670]	2530 [1720, 3710]
C_{av} (ng/mL)			
Mean	95.2	96.2	95.9
Median [5th, 95th]	96.3 [58.0, 132]	92.6 [71.9, 144]	92.9 [63.5, 144]

Age and body weight were at Year 5 Visit. Data from Year 5 Visit were not available from 12 patients who withdrew from the study with less than 4.5 years of observations. Individual parameters of all patients at Year 5 Visit or the latest visit are reported in Appendix 6.

Exploratory PKPD analyses of pharmacodynamic markers

The pharmacodynamics (PD) of risdiplam was evaluated by quantifying SMN protein and SMN2 mRNA in blood collected from SMA patients who participated in Studies BP39054, BP39055, and BP39056. In total 3912 SMN protein and 7047 mRNA samples from 466 SMA patients were available as of 22 December 2023. For SMN protein, the PKPD relationship was explored using estimated $AUC_{0\text{-}24h}$ derived using the post-hoc PK parameters of the updated PPK model, patient's actual demographics and risdiplam dosing records. Time-matched plasma concentrations of risdiplam were used for investigating the PKPD relationship with SMN2 mRNA.

SMN Protein

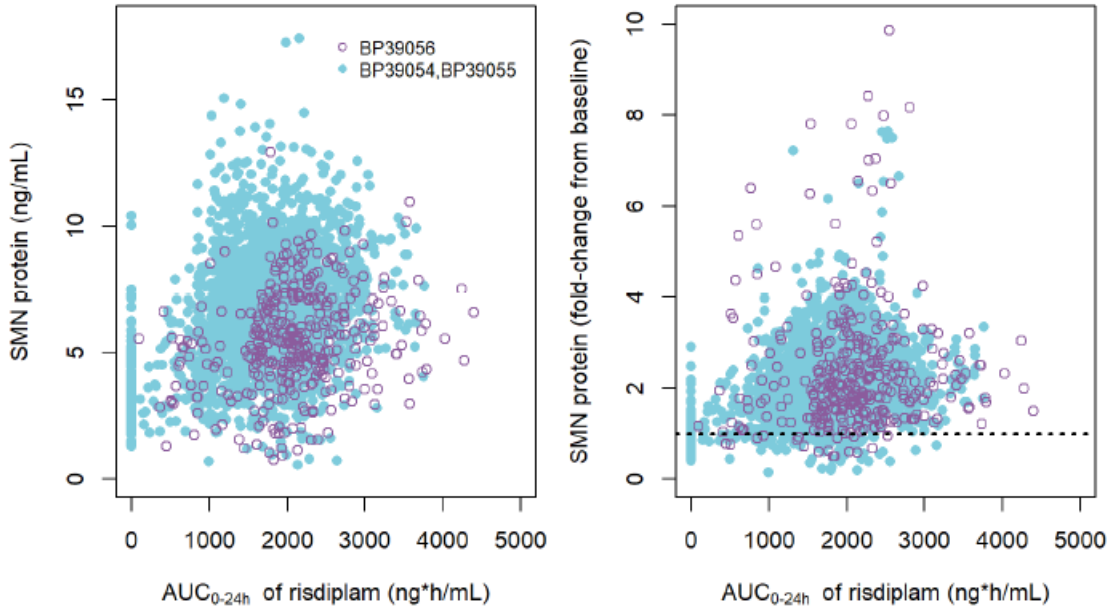
The SMN protein data at baseline and Year 5 Visit of the SMA patients of Study BP39056 are summarized in Table 6. The SMN protein as absolute values and fold change from baseline on Day 28 or later was plotted against the time-matched risdiplam $AUC_{0\text{-}24h}$ as shown in Figure 10. The PKPD relationship of Study BP39056 patients was compared with the SMA patients of Studies BP39054 and BP39055. 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 BP39056 and two other studies.

Table 6. Summary of SMN protein at Baseline and Year 5 Visit of Study BP39056

Values	Absolute value at baseline (n=60)	Absolute value at Year 5 Visit (n=46)	Fold-change from baseline (n=44)
Median [range]	2.78 [0.423, 6.40]	4.96 [1.22, 12.9]	1.88 [0.678, 9.87]

Patients who withdrew from the study before 4 years of treatment were not included in the summary. SMN protein <0.4 ng/mL were not included in the analysis [1].

Figure 10. Relationship between Risdiplam $AUC_{0\text{-}24h}$ and SMN Protein Compared between BP39056 vs. BP39054 and BP39055 Study SMA Patients: 28 Days After First Dose and Onwards

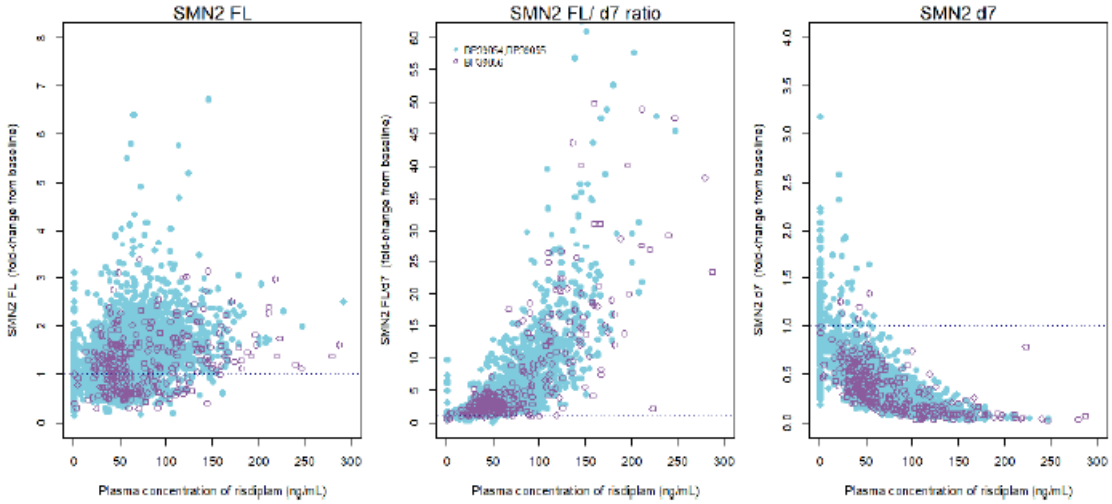


Dashed lines indicate 1 (i.e., no change). Time-matched $AUC_{0\text{-}24h}$ was available in 95.4% of the SMN protein samples and included in the analysis.

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 Figure 11. 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 BP39056 vs. BP39054 and BP39055 SMA patients.

Figure 11. Fold Change from Baseline in SMN2 mRNA versus Time-Matched Risdiplam Plasma Concentration in BP39056 vs. BP39054 and BP39055 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

A total of 2431 plasma risdiplam concentration data were available from 62 patients with Type 1 SMA of Study BP39056 by Year 5 Visit until CCOD of 22nd December 2023, which included 278 samples collected after the PPK modelling of risdiplam conducted in 2021. The reference PPK model developed previously generally well predicted the plasma concentrations of risdiplam obtained from all 525 subjects, however a trend to under-predict plasma risdiplam concentrations in the patients with Type 1 SMA in Study BP39056 was noted. The objective of the analyses was to estimate individual secondary PK parameters and the minor bias shown for the patients with Type 1 SMA by the reference PPK model was not expected to have impact on the estimation.

Nevertheless, covariate effects of Type 1 SMA was explored to correct the minor bias in population predictions. Inclusion of covariate effect of Type 1 SMA estimated 18.4% lower CL/F and Q/F, and 20.4% lower Vc/F and Vp/F than the subjects without Type 1 SMA which improved the predictions. Clinical relevance of these covariate effects was considered marginal. The median of estimated risdiplam $AUC_{0\text{-}24h}$ of 2530 ng•h/mL and C_{av} of 92.9 ng/mL at Year 5 Visit by the updated PPK model were comparable with the estimates by the reference PPK model ($AUC_{0\text{-}24h}$ of 2380 ng•h/mL and Cav of 90.3 ng/mL), indicating negligible impact of these covariates on estimation of individual secondary PK parameters.

The patients with Type 1 SMA of Study BP39056 switched from 0.2 mg/kg to 0.25 mg/kg before Year 2 Visit and four of the patients started receiving 5 mg before Year 5 Visit. The adaption of risdiplam dose along with increase in age and body weight according to the approved dosing algorithm sustained consistent risdiplam exposure between Year 2 to Year 5 Visits. The median $AUC_{0\text{-}24h}$ and C_{av} from Year 2

and Year 5 Visits were 2230 to 2530 ng•h/mL, and 80.1 to 92.9 ng/mL, respectively, which were maintained within 20% difference in the 3 years of treatment duration.

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/mL. Risdiplam concentration-dependent shift in SMN2 mRNA splicing was observed. Neither relationship between risdiplam concentration – SMN protein or – SMN2 mRNA were different between the patients with Type 1 SMA of Study BP39056 vs. BP39054 and BP39055 patients.

7. Clinical Efficacy aspects

7.1 Methods – analysis of data submitted

This variation focusses on the analysis of efficacy results after 5 years of risdiplam treatment from Study BP39056 (FIREFISH), which was a two-part, operationally seamless, open-label, multi-center study designed to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in infants with Type 1 spinal muscular atrophy (SMA).

The efficacy evaluation presented in this SCE is based on final results from Study BP39056 at the clinical cutoff date (CCOD) of 22 December 2023, which corresponds to the date the last patient completed their last study assessment after 5 years in the study. The key features of this study are summarized in Table 7.

Table 7. Summary of Studies Contributing to Efficacy Evaluation

Study No (Phase)	Population	Study Design	Number of Patients	Dose, Route, and Regimen	CCOD	Median Exposure Time
BP39056 (Phase II/III)	Infants with Type 1 SMA aged 1□7 months at enrollment	Seamless, multi-center, two-part study: Part 1: Open-label dose escalation study to select the dose for Part 2 Part 2: Open-label study to assess the efficacy, safety, and tolerability of risdiplam After 24 months, patients in Part 1 and Part 2 had the opportunity to continue in an OLE for at least 3 years.	Part 1: 21 patients Part 2: 41 patients Part 1 Cohort 2 and Part 2 (Pivotal Dose Population): 58 patients	OD oral administration Part 1: Cohort 1: 0.08 mg/kg for at least 12 months, then increased to 0.2 mg/kg Cohort 2: 0.04□0.25 mg/kg, then the dose was adjusted for all infants to 0.2 mg/kg for infants < 2 years. Part 2: Pivotal dose: 0.2 mg/kg for infants <2 years Infants ε 2 years (Part 1, Part 2, OLE): 0.25 mg/kg for infants ε 2 years and <20 kg BW 5 mg for children ε 2 years and ε20 kg BW [a]	22 December 2023 (LPLV)	Part 1: 60.0 months (range: 0.6□61.7 months) Part 2: 60.0 months (range: 1.6□61.0 months) Part 1 Cohort 2 and Part 2 (Pivotal Dose Population): 60.0 months (range: 1.6□61.6 months)

BW=body weight; CCOD=clinical cutoff date; EOS=end of study; LPLV=last patient last visit; OD=once daily; OLE=open-label extension; SMA=spinal muscular atrophy.

[a] After a patient had completed 3 years in the OLE, the patient could continue in the study until EOS, provided that risdiplam was not commercially available for the patient.

Overview of Study Design

This is a seamless open-label, single-arm, multi-center clinical study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of risdiplam in Type 1 SMA infants. The study was conducted in two parts and followed by an open-label extension phase:

Exploratory Part 1: Part 1 is an open-label, dose escalation study in infants with Type 1 SMA aged 1 to 7 months (at time of enrollment). This exploratory part consists of at least 8 infants and up to 24 infants (if required) to assess the safety, PK and PD profile of risdiplam in infants and determine the dose for Part 2.

Confirmatory Part 2: Part 2 is an open-label, single-arm study in 40 infants with Type 1 SMA aged 1 to 7 months (at time of enrollment) to assess the efficacy of risdiplam at the dose selected in Part 1 over a 24-month treatment period, with the primary endpoint analyzed at 12 months of treatment.

In both Part 1 and Part 2, after 24 months of treatment patients enter an open-label extension phase.

In both Part 1 and Part 2, after a patient completes Week 104 it may be possible for the patient to be allocated to another site, following discussion and agreement by the Sponsor. If this occurs, the reallocation will not be considered a new enrollment in the study.

The study will progress in an operationally seamless manner from Part 1 into Part 2 after the dose selection decision has been taken.

End of Study

The EOS is defined as the date when the last patient last visit (LPLV) occurs. LPLV is expected to occur at the latest when the last patient enrolled in the study has completed 24 months in the treatment phase and 3 years in the open label extension.

The study will continue until the EOS, or as per local regulation, or per the Sponsor's decision to terminate risdiplam development. The length of the study will not exceed 5 years after the last patient is enrolled in the study.

After completion of 24 months of treatment, each patient enters the open-label extension phase for an additional 3 years. After a patient has completed 3 years in the open-label extension, the patient may continue in the study until EOS, provided that risdiplam is not commercially available in the patient's country.

Number of study centers and countries

Part 1: 7 investigational sites across 5 countries (United States [2], Belgium [1], France [1], Italy [2], Switzerland [1]).

Part 2: 14 investigational sites across 10 countries (Italy [4], China [2], Brazil [1], Croatia [1], France [1], Japan [1], Poland [1], Russian Federation [1], Turkey [1], and United States [1]).

Main inclusion / exclusion criteria

SMA, including:

- Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene.
- Clinical history, signs or symptoms attributable to Type 1 SMA.

This study included infants with Type 1 SMA aged between 1 month and 7 months (inclusive) at the time of enrollment. For the first 3 patients enrolled in Part 1, required age was between 5 and 7 months inclusive, and a minimum body weight of 7 kg was required for the first patient only.

Doses and study treatment has been described in the Clinical Pharmacology section.

Independent Review Committees

The roles of the external independent Data Monitoring Committee and Permanent Ventilation Adjudication Committee have been previously reported and understood in interim analyses.

SUMMARY OF OB JECTIVES AND ENDPOINTS

The primary objectives for the study were:

- Part 1: To evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in infants with Type 1 SMA, and to select the dose for Part 2.
- Part 2: To assess the efficacy of risdiplam measured as the proportion of infants sitting without support after 12 months of treatment, as assessed in the gross motor scale of the Bayley Scales of Infant and Toddler Development - Third Edition (BSID-III), defined as sitting without support for 5 seconds.

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

The secondary objectives for Part 2 were:

- To assess the safety and tolerability of oral treatment with risdiplam.
- To assess the pharmacokinetics of risdiplam.
- To assess the pharmacodynamic effects of risdiplam (SMN2 mRNA, SMN protein).
- To evaluate at 12 months of treatment with risdiplam the effect on motor development milestones, such as head control and rolling, as measured in the BSID-III gross motor scale.
- To evaluate at 24 months of treatment with risdiplam the effect on sitting without support for 5 seconds and further motor development milestones such as sitting without support for 30 seconds, crawling, standing alone, and walking, as measured in the BSID-III gross motor scale.
- To assess the achievement of motor milestones at 12 and 24 months of treatment with risdiplam, as measured by the Hammersmith Infant Neurological Examination (HINE) Module 2.
- To evaluate the proportion of infants who achieved a score of 40 or higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at 12 months of treatment.
- To evaluate the proportion of infants who achieved an increase of at least 4 points on their CHOP-INTEND score from baseline at 8 and 12 months of treatment.
- To evaluate the proportion of infants who achieved head control at 8, 12, and 24 months of treatment (defined as a score of 3 or higher for item 12 of the CHOP-INTEND).
- To assess the change from baseline in the total raw score of the BSID-III gross motor scale at 12 and 24 months of treatment.
- To assess the proportion of infants who achieved a reduction of at least 30 degrees in phase angle at 12 months of treatment measured by respiratory plethysmography.
- To evaluate the proportion of infants who did not require invasive or non-invasive respiratory support at 12 and 24 months of treatment.
- To assess at 12 and 24 months of treatment the proportion of infants who were alive without permanent ventilation, as defined by >=16 hours of non-invasive ventilation per day or intubation > 21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy.
- To assess the impact of treatment with risdiplam on time-to-event (death, permanent ventilation).
- To evaluate the proportion of infants with the ability to feed orally at 12 and 24 months of treatment.

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

The exploratory objectives for Part 2 of this study were:

- To explore the effect of treatment with risdiplam on parent/caregiver-related infant health status and impact on the parent/caregiver, as measured by the Infant Toddler Quality of Life Questionnaire™ Short Form 47 item at 12 and 24 months.

- To assess at 8, 12, and 24 months of treatment with risdiplam the ratio between the chest and head circumference.
- To explore the treatment effect on pre-specified disease-related adverse events by 12 and 24 months of treatment.
- To investigate the effect at 12 and 24 months of treatment with risdiplam on muscle electrophysiology, as assessed by compound muscle action potential.
- To explore the effect of treatment with risdiplam on the number of hospitalizations (for any reason) per patient-year and number of nights admitted to hospital per infant at 12 and 24 months of treatment.
- To evaluate at 24 months the effects of risdiplam on sustained sitting for those infants sitting at 12 months (defined as sitting without support for 5 seconds).
- To explore at 24 months the maintenance of the effects of risdiplam on respiratory function for those infants who achieved a reduction of at least 30 degrees in phase angle at 12 months.
- To explore at 12 months the effect of treatment with risdiplam on clinician-reported changes in infants' respiratory function and swallowing ability, as measured by the clinical domain level items.
- To assess at 12 and 24 months of treatment with risdiplam the change from baseline in weight and length/height percentiles.

7.2 Results

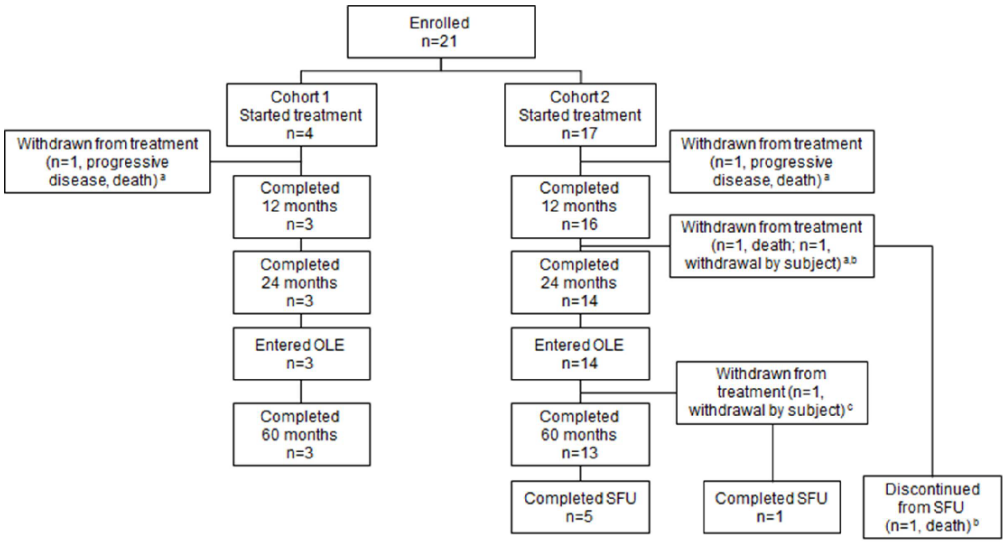
Study Population

Patient Disposition

Part 1

In Part 1, 26 patients were screened for enrollment, of whom 5 patients were screen failures. Reasons for screening failure are outlined in the Interim CSR (1087161). A total of 21 patients were enrolled at 7 sites in 5 countries, described in the Interim CSR (1087161).

Figure 1 Patient Disposition (ITT Population, Part 1 Patients)



OLE=open-label extension; SFU=safety follow-up.

Note: Cohort 1 includes the first 3 patients enrolled in the study who received Dose Level 1 for at least 12 months and the patient enrolled at Dose Level 1 who discontinued from the study on Study Day 19. Cohort 2 includes the infants enrolled at Dose Level 2 and the patient whose dose was escalated to Dose Level 2 on Study Day 83. Patients who completed the study or discontinued from the study early were to complete the SFU period. Continued access to risdiplam was offered to patients with no access to commercial risdiplam at the time patients completed the study until the end of the study.

[a] Three patients in Part 1 died from SMA-related respiratory complications that occurred while on treatment: One patient died on Study Day 21 after 18 days c treatment with risdiplam, one patient died on Study Day 236 after 7.7 months of treatment, and one patient died on Study Day 387 after 12.7 months of treatment.

[b] One patient entered SFU on Study Day 585 and died on Study Day 691 (approximately 3.5 months after stopping treatment).

[c] One patient withdrew on Study Day 1289, withdrawal by subject.

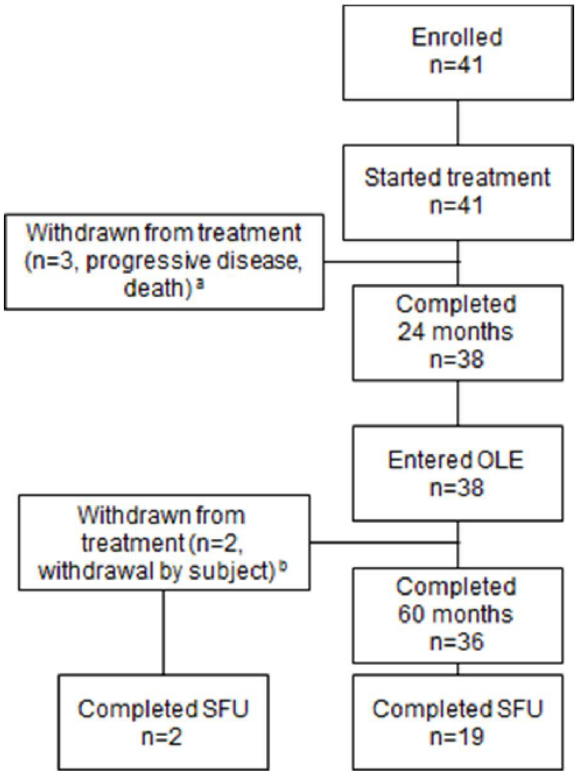
Part 2

In Part 2, 52 patients were screened for enrollment, of whom 11 patients were screen failures. Reasons for screening failure have been outlined in the Primary CSR (1100385). A total of 41 patients were enrolled at 14 sites in 10 countries, described in the Primary CSR (1100385). Before Month 12 of the study, 3 patients in Part 2 died of SMA-related complications.

These deaths have been described in the Primary CSR (1100385).

A total of 38 patients entered the open-label extension (OLE) phase and 36 patients completed 60 months of risdiplam treatment. By the end of the study, 21 patients had completed the SFU period, and 17 patients had opted for continued access to risdiplam.

Figure 2 Patient Disposition (ITT Population, Part 2 Patients)



OLE=open-label extension; SFU=safety follow-up.

Note: Patients who completed the study or discontinued from the study early were to complete the SFU period. Continued access to risdiplam was offered to patients with no access to commercial risdiplam at the time patients completed the study until the end of the study.

[a] Three patients died from SMA-related respiratory complications that occurred while on treatment: One patient died on Study Day 68 after 2.2 months of treatment with risdiplam; one patient died on Study Day 51 after 1.6 months of treatment with risdiplam; one patient died on Study Day 79 after 2.6 months of treatment with risdiplam.

[b] One patient withdrew on Study Day 870, withdrawal by subject. Another patient withdrew on Study Day 1816, "other-- withdrawal by subject."

Baseline disease characteristics

The baseline characteristics of patients (pooled Parts 1 and 2) were typical of a symptomatic Type 1 SMA population, with a median age of 1.5 months (range: 0.9-3.0 months) at symptom onset. The disease duration (time between onset of symptoms and first treatment) was >3 months in 42 patients (67.7%) and <=3 months in 20 patients (32.3%), for a median disease duration of 3.7 months (range: 1.0-6.0 months).

All patients had two SMN2 copies, as required by the study inclusion criteria. Median baseline scores for CHOP-INTEND (23.0), BSID-III (2.0), HINE-2 (1.0), and CMAP amplitude (0.2 mV) were low, as expected for this symptomatic patient population. Patients' 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 enrollment. The majority of patients (45/62; 72.6%) were receiving no pulmonary care at baseline; 13 patients (21.0%) were receiving non-invasive ventilation (bilevel positive airway pressure; BiPAP) support for < 16 hours/day, and 5 patients were receiving cough assistance (4 patients [6.5%] received it daily as a prophylactic therapy [not acute-illness related] and 1 patient [1.6%] received it because of an ongoing illness). There were no patients requiring awake assisted ventilation. It is not

possible to confirm if patients were receiving adequate standard of care for respiratory support in SMA (Finkel et al. 2018) at the time of the screening visit and baseline assessments.

Almost all patients (59/62; 95.2%) were able to swallow at baseline. The majority of patients (39/62; 62.9%) were fed exclusively by mouth, 2 patients (3.2%) were fed via a combination of oral and tube feeding, and 4 patients (6.5%) were fed via a feeding tube at baseline; information about feeding route at baseline was missing for 17 patients (27.4%).

Prior Medication

Prior and ongoing medications (i.e., those that were started prior to onset of risdiplam treatment and that were ongoing at the date of first dose) for Part 1 and Part 2 have been reported in the Primary CSR (1100385).

Concomitant Medication

In Part 1 and Part 2 combined, 61 of 62 patients (98.4%) received at least one concomitant medication for AEs, and 54 patients (87.1%) received concomitant medications that were not taken for AEs.

All 21 patients (100.0%) in Part 1 received concomitant medications for AEs on or after the date of the first dose of risdiplam. A total of 20 patients (95.2%) received concomitant medications on or after the date of the first dose of risdiplam that were not taken for AEs. The most common medications (taken by 4 patients [19.0%] or more), by medication class, were: ophthalmologicals (13 patients; 61.9%); vaccines (12 patients; 57.1%); vitamins (10 patients; 47.6%); nasal preparations (6 patients, 28.6%); all other therapeutic products, drugs for constipation, homeopathic preparation, immune sera and immunoglobulins, stomatologicals preparations, and antidiarrheals, intestinal anti-inflammatory/anti-infective agents (5 patients each; 23.8%); all other non-therapeutic products, cardiac therapy (included medications are also captured under other ATC classes that may reflect better the indication for which they were used), other dermatological preparations, otologicals, vasoprotectives, and cough and cold preparations (4 patients each; 19.0%).

A total of 40 patients (97.6%) in Part 2 received concomitant medications for AEs on or after the date of the first dose of risdiplam. These medications are discussed where relevant in the safety section. A summary of concomitant medications for AEs by PT is provided. A total of 34 patients (82.9%) received concomitant medications on or after the date of the first dose of risdiplam that were not taken for AEs. The most common medications (taken by >= 10% of patients), by medication class, were: vaccines (25 patients, 61.0%); ophthalmologicals (23 patients, 56.1%); vitamins (15 patients, 36.6%); other gynecologicals (8 patients, 19.5%, included medications are also captured under other ATC classes that reflect better the indication for which they were used); immune sera and immunoglobulins, other dermatological preparations (6 patients each, 14.6%); and urologicals (5 patients, 12.2%).

SMA-Related Surgeries and Procedures

After the date of first risdiplam dose, a total of 153 SMA-related surgeries or procedures have been performed in 34 patients (54.8%). This included 38 surgeries/procedures in 12 patients (57.1%) in Part 1 and 115 surgeries/procedures in 22 patients (53.7%) in Part 2.

Exposure to Study Treatment

All 62 enrolled patients received at least one dose of risdiplam.

In pooled Parts 1 and 2 (62 patients), the median exposure duration was 60.0 months (range: 0.6-61.7 months). Dose intensity was defined as the number of doses actually received divided by the expected number of doses, expressed as a percentage. The median dose intensity was 100.0% (range: 96.4%-100.0%). A total of 24 patients missed a maximum of 65 doses (median: 1.0).

Summary of Efficacy

Baseline in CHOP-INTEND Score and 90% CI by Visit (ITT Population, Part 2 Patients)

Time to Death

At 60 months following the start of risdiplam treatment, most patients in Part 2 were alive.

EFFICACY- POOLED PARTS 1 AND 2

In the pivotal dose population, the efficacy data up to 24 months of risdiplam treatment demonstrate clinically meaningful improvements in complex motor function. These improvements demonstrated at 24 months were generally sustained through the 60-month study duration, with some patients having further improvements, indicating long-term benefit for patients receiving risdiplam treatment.

An overview of efficacy findings from the Pivotal Dose ITT Population (n=58) after 12, 24, 36, 48, and 60 months of treatment, and survival and ventilation-free survival in the All Patients ITT Population (n = 62), are presented in Table 22.

Table 22 Summary of Efficacy Endpoints at Month 12, Month 24, and OLE Period (ITT Population, Part 1 Cohort 2 and Part 2 Patients)

Endpoint	Month 12 N=58	Month 24 N=58	OLE Period		
			Month 36 N=58	Month 48 N=58	Month 60 N=58
Motor Function and Development Milestones (Part 1 Cohort 2 and Part 2 [n=58])					
Proportion of patients sitting without support for 5 seconds (BSID-III) (90% CI)	32.8% (22.6%, 44.3%)	60.3% (48.7%, 71.2%)	60.3% (48.7%, 71.2%)	63.8% (52.2%, 74.3%)	62.1% (50.4%, 72.7%)
Proportion of patients sitting without support for 30 seconds (BSID-III) (90% CI)	19.0% (11.0%, 29.4%)	39.7% (28.8%, 51.3%)	58.6% (47.0%, 69.6%)	62.1% (50.4%, 72.7%)	58.6% (47.0%, 69.6%)
Proportion of patients who achieve a score of 40 or higher in the CHOP-INTEND (90% CI)	56.9% (45.3%, 68.0%)	74.1% (63.0%, 83.3%)	63.8% (52.2%, 74.3%)	69.0% (57.5%, 78.9%)	65.5% (54.0%, 75.8%)
Proportion of patients who achieve a score of 50 or higher in the CHOP-INTEND (90% CI)	15.5% (8.3%, 25.5%)	48.3% (36.9%, 59.8%)	44.8% (33.6%, 56.4%)	53.4% (41.9%, 64.8)	50.0% (38.5%, 61.5%)
Proportion of patients who achieve a score of 60 or higher in the CHOP-INTEND (90% CI)	0 (0%, 5.0%)	8.6% (3.5%, 17.3%)	12.1% (5.8%, 21.5%)	15.5% (8.3%, 25.5%)	19.0% (11.0%, 29.4%)
Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline (90% CI)	89.7% (80.6%, 95.4%)	87.9% (78.5%, 94.2%)	75.9% (64.9%, 84.8%)	77.6% (66.7%, 86.2%)	72.4% (61.2%, 81.9%)
Proportion of motor milestone responders as assessed by the HINE-2 [a] (90% CI)	77.6% (66.7%, 86.2%)	82.8% (72.5%, 90.3%)	74.1% (63.0%, 83.3%)	79.3% (68.6%, 87.6%)	77.6% (66.7%, 86.2%)
Proportion of patients who achieve head control as assessed by HINE-2					
Wobbles	29.3%	17.2%	6.9%	6.9%	6.9%
All the time maintained upright	46.6%	63.8%	63.8%	69.0%	69.0%
Proportion of patients able to roll as assessed by HINE-2					
Rolling to side	31.0%	31.0%	24.1%	20.7%	17.2%
Prone to supine	15.5%	6.9%	8.6%	6.9%	5.2%
Supine to prone	10.3%	39.7%	41.4%	46.6%	50.0%

Endpoint	Month 12 N=58	Month 24 N=58	OLE Period		
			Month 36 N=58	Month 48 N=58	Month 60 N=58
Proportion of patients able to stand as assessed by HINE-2					
Supports weight	13.8%	15.5%	5.2%	12.1%	8.6%
Stands with support	3.4%	12.1%	15.5%	8.6%	5.2%
Stands unaided	0	0	0	6.9%	6.9%
Proportion of patients able to walk as assessed by HINE-2					
Bouncing	1.7%)	1.7%	1.7%	10.3%	0
Cruising	0	1.7%	3.4%	12.1%	10.3%
Respiratory (Part 1 Cohort 2 and Part 2 [n=58])					
Proportion of patients who do not require invasive or non-invasive respiratory support (90% CI)	22.4% (13.8%, 33.3%)	22.4% (13.8%, 33.3%)	19.0% (11.0%, 29.4%)	20.7% (12.4%, 31.4%)	29.3% (19.6%, 40.7%)
Nutrition (Part 1 Cohort 2 and Part 2 [n=58])					
Proportion of patients with the ability to feed orally [b] (90% CI)	84.5% (74.5%, 91.7%)	82.8% (72.5%, 90.3%)	58.6% (47.0%, 69.6%)	77.6% (66.7%, 86.2%)	72.4% (61.2%, 81.9%)
Healthcare Utilization (Part 1 Cohort 2 and Part 2 [n=58])					
Number of hospitalizations per patient-year [c] (90% CI)	1.24 (1.00, 1.52)	0.92 (0.77, 1.08)	0.71 (0.60, 0.83)	0.63 (0.55, 0.73)	0.55 (0.47, 0.63)
Proportion of patients with no hospitalizations (90% CI)	48.3% (36.9%, 59.8%)	34.5% (24.2%, 46.0%)	25.9% (16.7%, 37.0%)	22.4% (13.8%, 33.3%)	22.4% (13.8%, 33.3%)
Survival and Ventilation-Free Survival (All Patients Part 1 and 2 [n=62])					
Proportion of patients alive without permanent ventilation (90% CI)	87.1% (78.1%, 92.6%)	83.8% (74.3%, 90.1%)	83.8% (74.3%, 90.1%)	80.5% (70.5%, 87.4%)	80.5% (70.5%, 87.4%)
Proportion of patients alive (90% CI)	91.9 (83.9, 96.1)	90.3 (81.9, 94.9)	90.3 (81.9, 94.9)	90.3 (81.9, 94.9)	90.3 (81.9, 94.9)

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; OLE=open-label extension.

[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 showed improvement than showed worsening.

[b] Includes patients who were fed exclusively orally (41 patients at Month 12, 41 patients at Month 24, 29 patients at Month 36, 41 patients at Month 48, and 37 patients at Month 60) and those who were fed orally in combination with a feeding tube (8 patients at Month 12, 7 patients at Month 24, 5 patients at Month 36, 4 patients at Month 48, and 5 patients at Month 60). Data are missing from 13 patients at Month 36.

[c] Hospitalizations include all hospital admissions observed by Month 12/24/36/48/60 which spanned at least two days.

This section presents an evaluation of response to risdiplam for patients who received the pivotal dose (patients in Part 1 Cohort 2 and Part 2). Additionally, survival and ventilation free survival results for all patients in Part 1 and Part 2 are provided.

- The proportion of patients in the pivotal dose population sitting without support for 5 seconds, as assessed by Item 22 of the BSID-III gross motor scale, was 32.8% (19 patients; 90% CI: 22.6%, 44.3%) at Month 12, 60.3% (35 patients; 90% CI: 48.7%, 71.2%) at Month 24, 60.3% (35 patients; 90% CI: 48.7%, 71.2%) at Month 36, 63.8% (37 patients; 90% CI: 52.2%, 74.3%) at Month 48, and 62.1% (36 patients; 90% CI: 50.4%, 72.7%) at Month 60.

- The proportion of patients in the pivotal dose population sitting without support for 30 seconds, as assessed by Item 26 of the BSID-III gross motor scale, was 19.0% (11 patients; 90% CI: 11.0%, 29.4%) at Month 12, 39.7% (23 patients; 28.8%, 51.3%) at Month 24, 58.6% (34 patients; 90% CI: 47.0%, 69.6%) at Month 36, 62.1% (36 patients; 90% CI: 50.4%, 72.7%) at Month 48, and 58.6% (34 patients; 90% CI: 47.0%, 69.6%) at Month 60.

- The proportion of patients standing alone, as assessed by Item 40 of the BSID-III gross motor scale, was 0% (0 patients; 90% CI: 0%, 5.0%) at Month 12, 0% (0 patients; 90% CI: 0%, 5.0%) at Month 24, 0% (0 patients; 90% CI: 0%, 5.0%) at Month 36, 5.2% (3 patients; 90% CI: 1.4%, 12.8%) at Month 48, and 6.9% (4 patients; 90% CI: 2.4%, 15.1%) at Month 60.

- The proportion of patients walking alone, as assessed by Item 42 of the BSID-III gross motor scale, was 0% (0 patients; 90% CI: 0%, 5.0%) at Month 12, 0% (0 patients; 90% CI: 0%, 5.0%) at Month 24, 0% (0 patients; 90% CI: 0%, 5.0%) at Month 36, 1.7% (1 patient; 90% CI: 0.1%, 7.9%) at Month 48, and 0% (0 patients; 90% CI: 0%, 5.0%) at Month 60.

- The number of patients who achieved an increase of at least 4 points from baseline in their CHOP-INTEND score was 52 patients (89.7%; 90% CI: 80.6%, 95.4%) at Month 12, 51 patients (87.9%; 90% CI: 78.5%, 94.2%) at Month 24, 44 patients (75.9%; 90% CI: 64.9%, 84.8%) at Month 36, 45 patients (77.6%; 90% CI: 66.7%, 86.2%) at Month 48, and 42 patients (72.4%; 90% CI: 61.2%, 81.9%) at Month 60.

- The proportion of patients achieving a CHOP-INTEND total score of 40 points or higher was 56.9% (33 patients; 90% CI: 45.3%, 68.0%) at Month 12, 74.1% (43 patients; 90% CI: 63.0%, 83.3%) at Month 24, 63.8% (37 patients; 90% CI: 52.2%, 74.3%) at Month 36, 69.0% (40 patients; 90% CI: 57.5%, 78.9%) at Month 48, and 65.5% (38 patients; 90% CI: 54.0%, 75.8%) at Month 60.

- The proportion of patients achieving a CHOP-INTEND total score of 50 points or higher, was 15.5% (9 patients; 90% CI: 8.3%, 25.5%) at Month 12, 48.3% (28 patients; 90% CI: 36.9%, 59.8%) at Month 24, 44.8% (26 patients; 90% CI: 33.6%, 56.4%) at Month 36, 53.4% (31 patients; 90% CI: 41.9%, 64.8%) at Month 48, and 50.0% (29 patients; 90% CI: 38.5%, 61.5%) at Month 60.

- The proportion of patients achieving a CHOP-INTEND total score of 60 points or higher, was 0% (0 patients; 90% CI: 0%, 5.0%) at Month 12, 8.6% (5 patients; 90% CI: 3.5%, 17.3%) at Month 24, 12.1% (7 patients; 90% CI: 5.8%, 21.5%) at Month 36, 15.5% (9 patients; 90% CI: 8.3%, 25.5%) at Month 48, and 19.0% (11 patients; 90% CI: 11.0%, 29.4%) at Month 60.

- The proportion of patients classified as motor milestone responders, as assessed by the HINE-2, was 77.6% (45 patients, 90% CI: 66.7%, 86.2%) at Month 12, 82.8% (48 patients; 90% CI: 72.5%, 90.3%) at Month 24, 74.1% (43 patients; 90% CI: 63.0%, 83.3%) at Month 36, 79.3% (46 patients; 90% CI: 68.6%, 87.6%) at Month 48, and 77.6% (45 patients; 90% CI: 66.7%, 86.2%) at Month 60.

- At Month 24, 10 patients (17.2%) could hold their head upright only intermittently (wobbles) and 37 patients (63.8%) could maintain their head upright all of the time. At Month 60, 4 patients (6.9%) could hold their head upright only intermittently (wobbles) and 40 patients (69.0%) could maintain their head upright all of the time.

- At Month 24, the majority of patients (70.7%; 41 patients) achieved some level of sitting: 3 patients (5.2%) were able to sit with support at hips, 7 patients (12.1%) sat by propping themselves up, 16 patients (27.6%) achieved a stable sit, and 15 patients (25.9%) were able to pivot (rotate) while sitting. At Month 60, 44 patients (75.9%) achieved some level of sitting: 4 patients (6.9%) were able to sit with support at hips, 6 patients (10.3%) sat by propping themselves up, 8 patients (13.8%) achieved a stable sit, and 26 patients (44.8%) were able to pivot (rotate) while sitting.

- At Month 24, 45 patients (77.6%) achieved some level of rolling: 18 patients (31.0%) could roll to a side, 4 patients (6.9%) could roll from prone to supine, and 23 patients (39.7%) could roll from supine to prone. At Month 60, 42 patients (72.4%) achieved some level of rolling: 10 patients (17.2%) could roll to a side, 3 patients (5.2%) could roll from prone to supine, and 29 patients (50.0%) could roll from supine to prone.

- At Month 24, 7 patients (12.1%) could crawl on elbows, 2 patients (3.4%) could crawl on outstretched hand, and 3 patients (5.2%) could crawl on hands and knees. At Month 60, 4 patients (6.9%) could crawl on elbows, 7 patients (12.1%) could crawl on outstretched hand, 6 patients (10.3%) could crawl flat on abdomen and 6 patients (10.3%) could crawl on hands and knees.

- At Month 24, 9 patients (15.5%) were able to support weight and 7 patients (12.1%) could stand with support; no patients could stand unaided. At Month 60 of treatment, 5 patients (8.6%) were able to support weight, 3 patients (5.2%) could stand with support, and 4 patients (6.9%) could stand unaided.

- At Month 24, 1 patient (1.7%) was able to bounce and 1 patient (1.7%) was able to cruise; no patients were able to walk independently. At Month 60 of treatment, no patients were able to bounce, 6 patients (10.3%) were able to cruise, and no patients were able to walk independently.

- For all patients in Part 1 and Part 2, at Month 60, the proportion of patients alive without permanent ventilation was 80.5% (90% CI: 70.5%, 87.4%). A total of 6 patients had died and 6 patients had met the endpoint of permanent ventilation. The median time to death or permanent ventilation was not evaluable.

- For all patients in Part 1 and Part 2, the proportion of patients alive at Month 60 was 90.3% (90% CI: 81.9%, 94.9%). The median time to death was not evaluable.

- The number of patients who did not require respiratory support was 13 (22.4%) at Month 12, 13 (22.4%) at Month 24, 11 (19.0%) at Month 36, 12 (20.7%) at Month 48, and 17 (29.3%) at Month 60.

- The number of patients able to feed orally was 49 (84.5%; 90% CI: 74.5%, 91.7%) at Month 12, 48 (82.8%; 90% CI: 72.5%, 90.3%) at Month 24, 34 (58.6%; 90% CI: 47.0%, 69.6%) at Month 36, 45 (77.6%; 90% CI: 66.7%, 86.2%) at Month 48, and 42 (72.4%; 90% CI: 61.2%, 81.9%) at Month 60.

- The number of patients with the ability to swallow was 50 (86.2%; 90% CI: 76.5%, 93.0%) at Month 12, 50 (86.2%; 90% CI: 76.5%, 93.0%) at Month 24, 45 (77.6%; 90% CI: 66.7%, 86.2%) at Month 36, 47 (81.0%; 90% CI: 70.6%, 89.0%) at Month 48, and 46 (79.3%; 90% CI: 68.6%, 87.6%) at Month 60.

- The median weight-for-age percentile was 24.8 (range: 0.0 to 97.7) at Month 12, 8.8 (range: 0.0 to 99.9) at Month 24, 9.1 (range: 0.0 to 100.0) at Month 36, 6.1 (range: 0.0 to 100.0) at Month 48, and 9.2 (range: 0.0 to 100.0) at Month 60. The number of patients in the 10th percentile or lower for age-adjusted weight was 15 at Month 12, 26 at Month 24, 29 at Month 36, 29 at Month 48, and 24 at Month 60.

- The median length/height-for-age percentile was 51.4 (range: 0.6 to 100.0) at Month 12, 40.6 (range: 0.0 to 99.5) at Month 24, 24.7 (range: 0.0 to 99.9) at Month 36, 19.6 (range: 0.0 to 93.8) at Month 48, and 15.7 (range: 0.1 to 99.5) at Month 60. The number of patients in the 10th percentile or lower for age-adjusted length/height was 8 at Month 12, 10 at Month 24, 16 at Month 36, 19 at Month 48, and 18 at Month 60.

- The median weight-for-length/height percentile was 17.9 (range: 0.0 to 96.1) at Month 12, 5.3 (range: 0.0 to 98.8) at Month 24, 4.3 (range: 0.0 to 98.2) at Month 36, 13.4 (range: 0.0 to 100.0) at Month 48, and was not evaluable at Month 60 (due to WHO Child Growth measuring standards including children only up to 5 years of age for this measure). The number of patients in the 10th percentile or lower for weight-for-length/height was 24 at Month 12, 31 at Month 24, 26 at Month 36, and 15 at Month 48.

- The median head circumference was 47.0 cm (range: 42.0 to 51.0 cm) at Month 12, 49.0 cm (range: 43.6 to 55.5 cm) at Month 24, 50.0 cm (range: 45.6 to 53.0 cm) at Month 36, 51.0 cm (range: 47.0 to 55.0 cm) at Month 48, and 52.5 cm (range: 43.5 to 57.0 cm) at Month 60. The number of patients in the 10th percentile or lower for head circumference was 3 at Month 12, 5 at Month 24, 5 at Month 36, 3 at Month 48, and was not evaluable at Month 60 (due to WHO Child Growth measuring standards including children only up to 5 years of age for this measure).

- The median chest circumference was 45.8 cm (range: 40.0 to 51.0 cm) at Month 12, 48.0 cm (range: 40.5 to 55.6 cm) at Month 24, 49.5 cm (range: 43.5 to 57.0 cm) at Month 36, 52.0 cm (range: 46.5 to 59.0 cm) at Month 48, and 54.0 cm (range: 43.0 to 61.0 cm) at Month 60.

- A total of 13 patients (22.4%) did not require any overnight hospitalization at any point during the study (i.e., hospital admissions for any reason that included at least one night in the hospital). Patients who were hospitalized were admitted for a median of 17 nights (range: 2.0164). These numbers also include planned and/or elective hospital admissions.

- The rate of hospitalizations decreased over time. There were 99 hospitalizations by Month 24, resulting in a rate of 0.92 (90% CI: 0.77, 1.08) hospitalizations per patient year. Between Month 24 and Month 60, there were 43 additional hospitalizations. Thus, overall, there were 142 hospitalizations by Month 60, resulting in a rate of 0.55 hospitalizations per patient-year (90% CI: 0.47, 0.63).

7.3 Discussion

Efficacy analyses evaluating the proportions of patients achieving motor function and development milestones (as assessed by the BSID-III, CHOP INTEND, and HINE 2), survival and ventilation-free survival, nutrition and swallowing, and healthcare utilization show moderate clinical improvements up to the first 24 months of risdiplam treatment.

The observed efficacy is in line with what is known from the short to medium term studies and the clinical practice that has been followed meanwhile.

The improvements demonstrated at 24 months were generally sustained through the 5-year study duration, with some patients having further small improvements.

Of note, only 3 children in 41 have gained the ability to stand independently, and this ability to walk independently has occurred after the year 3 of treatment.

The PRO endpoints show that there is a benefit which is sustained, but the quality of life of both parents / caregivers and child is still significantly affected by the disease. (On the ITQOL the median score for the Global behavior item at Month 60 was 60.0 (range: 0-100)).

In conclusion, these longer-term efficacy data provide relevant evidence of the continued benefit of risdiplam in patients with infantile-onset (Type 1) SMA.

8. Clinical Safety aspects

8.1 Methods – analysis of data submitted

The cumulative safety data is retrieved from Study BP39056 (FIREFISH). The FIREFISH study was a two-part, multicenter study to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of risdiplam in infants with infantile-onset (Type 1) spinal muscular atrophy (SMA).

The study was conducted in two parts and followed by a 3-year open-label extension phase.

- Exploratory Part 1: Part 1 was an open-label, dose escalation study in infants with Type 1 SMA aged 1 to 7 months (at time of enrollment). This dose-finding part assessed the safety, pharmacokinetic, and pharmacodynamic profile of risdiplam and determined the dose for Part 2.

  Once the dose for Part 2 was selected, all infants (including the first 4 infants enrolled at Dose Level 1) were given the possibility to continue receiving risdiplam at the dose selected for Part 2 as part of an extension phase until Month 24. Thereafter, the open-label extension (OLE) phase, beginning after 24 months of treatment, included regular monitoring of safety, tolerability and efficacy, and continued for an additional 3 years for each patient, as outlined below.

- Confirmatory Part 2: Part 2 was an open-label, single arm study in infants with Type 1 SMA aged 1 to 7 months (at time of enrollment) to assess the efficacy and safety of risdiplam at the dose selected in Part 1 over a 24-month treatment period, with the primary endpoint analyzed at 12 months of treatment.

The Part 1 comprised 7 investigational sites across 5 countries (United States [2], Belgium [1], France [1], Italy [2], Switzerland [1]) and Part 2 14 investigational sites across 10 countries (Italy [4], China [2], Brazil [1], Croatia [1], France [1], Japan [1], Poland [1], Russian Federation [1], Turkey [1], and United States [1]).

The administration of risdiplam was oral, once daily. The dose was adjusted throughout Part 1 based on the emerging PK data. Data from Part 1 were used to determine the starting dose levels for Part 2 [for infants >1 month old and <3 months old at enrollment: 0.04 mg/kg. For infants >=3 months old and <5 months old at enrollment: 0.08 mg/kg. For infants >=5 months old at enrollment: 0.2 mg/kg]. The dose was adjusted to 0.2 mg/kg for all patients (based on review of individual PK data for each infant enrolled in Part 1 and Part 2), in order to reach the target exposure defined in the protocol as a mean AUC of <=2000 ng.h/mL.

The duration of the study for each patient enrolled in Part 1 (not including the open-label extension [OLE]) was divided as follows:

- Treatment period: 24 months

The duration of the study for each patient enrolled in Part 2 (not including the OLE phase) was divided as follows:

- Treatment period: 24 months

The patient's treatment in the OLE continued for an additional 3 years, after completion of 24 months of treatment for a total of 5 years. After a patient had completed 3 years in the OLE, the patient could continue to receive study drug until the end of study (EOS), provided that risdiplam was not commercially available for the patient.

After the study completion or early withdrawal visit, patients had to complete a period of 52 weeks of follow-up. In version 6 of the protocol, this follow-up was replaced with a phone call 30 days after this visit.

After study completion, patients who were going to continue with risdiplam treatment and did not have access to commercial drug remained on study treatment until they gained access, or until the last patient last visit.

The results from the FIREFISH Study up to the clinical cutoff date (CCOD) of 22 December 2023, which corresponds to the date the last patient completed their last study assessment after 5 years in the study are presented. Full safety information from this study, which enrolled 21 patients in Part 1 and 41 patients in Part 2, is provided in the Final CSR, Study BP39056, Report 1126881.

By the end of the study, all patients were >=2 years of age and most weighed <20 kg and therefore received a dose of 0.25 mg/kg.

The overall key features of this study are summarized in the Table below.

Table - Summary of Studies Contributing to Safety Evaluation

Study No (Phase)	Study Design	Population	No. of Patients Evaluable for Safety	Dose, Route, and Regimen	CCOD	Median Exposure Time
BP39056 (Phase II/III)	Seamless, multicenter, two-part study: Part 1: Open-label dose escalation study to select the dose for Part 2 Part 2: Open-label study to assess the efficacy, safety, and tolerability of risdiplam After 24 months, patients in Part 1 and Part 2 had the opportunity to continue in an OLE for at least 3 years. [a]	Infants with Type 1 SMA aged 1-7 months at enrollment	Part 1: 21 infants Part 2: 41 infants	OD oral administration <u>Part 1</u> Cohort 1: 0.08 mg/kg for at least 12 months, then increased to 0.2 mg/kg. Cohort 2: 0.04□0.25 mg/kg, then the dose was adjusted for all infants to 0.2 mg/kg for infants < 2 years. <u>Part 2</u> Pivotal dose: 0.2 mg/kg for infants < 2 years Infants ε 2 years (Part 1, Part 2, OLE): 0.25 mg/kg for infants ε 2 years and <20 kg BW 5 mg for infants ε 2 years and ε 20 kg BW	22 December 2023 (LPLV)	Part 1 and Part 2 (pooled): 60.0 months

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

[a] After a patient had completed 3 years in the OLE, the patient could continue in the study until the end of study, provided that risdiplam was not commercially available for the patient.

Assessment of Safety

Safety assessments consisted of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs, ECGs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Safety Plan

The Safety Plan considers observations made in nonclinical investigations, including Good Laboratory Practice (GLP) toxicology studies in rats and cynomolgus monkeys, and the observations made in clinical trials. Hypothetical considerations are included in the interpretation of nonclinical and clinical data. The exposure cap of a mean $AUC_{0\text{-}24h,ss}$ 2000 ng.h/mL corresponds to the NOAEL in the 39-week toxicology study in cynomolgus monkey, i.e., the exposure level at which no adverse events were observed.

Only effects on the testes were observed at those exposure levels in another study in rats (effects on testes could not be assessed in cynomolgus monkey due to sexual immaturity of the animals (Risdiplam Investigator's Brochure)); parents of male subjects will be informed accordingly. In humans, the pachytene stage of meiosis is completed towards the end of fetal development. In this study, effects on the oocyte are not expected because premature infants will not be included. In juvenile and adult rat toxicity studies and in monkey toxicity studies, there was no effect on female reproductive organs or female fertility. Any effects on meiosis and oocyte maturation will be further investigated in a pre-postnatal toxicity study in rats (Risdiplam Investigator's Brochure).

Safety Monitoring

Based on observed toxicity in nonclinical studies (see Risdiplam Investigator's Brochure for details), the following safety monitoring plan has been compiled:

- Specialty medical doctors (ophthalmologist) will be identified who will be trained in risdiplam observed nonclinical toxicological findings prior to study start to follow-up quickly in case of any suspicious or actual adverse toxicity event.

- Ophthalmological assessments (see Section 4.6.1.8 for details)

- Stopping rules for individual patients have been defined that include criteria for treatment discontinuation in case of ophthalmic events (Section 5.2.4).

- Follow-up phone calls (as per the time-points in the SoA; Appendix 1, Appendix 2): parents or caregiver will be called by the Investigator or designee to monitor safety and tolerability when not attending the clinic. Assessments will include adverse events, concomitant medication review and significant life events.

Methods and Timing for Capturing and Assessing Safety Parameters: The Investigator is responsible for ensuring that all adverse events are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided. For each adverse event recorded on the Adverse Event eCRF, the Investigator made an assessment of seriousness, severity, and causality.

8.2 Results

- A total of 950 AEs were reported in 62 patients (100.0%). In pooled Parts 1 and 2, the most frequently reported AEs (.10% of patients), by SOC, were the following:
-

Infections and infestations (98.4% [61 patients])

General disorders and administration site conditions (69.4% [43 patients])

Gastrointestinal disorders (66.1% [41 patients])

Respiratory, thoracic, and mediastinal disorders (59.7% [37 patients])

Skin and subcutaneous tissue disorders (48.4% [30 patients])

Injury, poisoning, and procedural complications (25.8% [16 patients])

Metabolism and nutrition disorders (22.6% [14 patients])

Nervous system disorders (17.7% [11 patients])

Blood and lymphatic system disorders (14.5% [9 patients])

Eye disorders, investigations (12.9% [8 patients] each)

Congenital, familial, and genetic disorders, musculoskeletal and connective tissue disorders (11.3% [7 patients] each)

- The majority of AEs (906 of 950 AEs) resolved. By the end of the study, 35 AEs were not resolved, and the outcome of 2 AEs was unknown. The unresolved AEs, by SOC, were the following: gastrointestinal disorders (10 AEs); musculoskeletal and connective tissue disorders (9 AEs); renal and urinary disorders (4 AEs); injury, poisoning, and procedural complications, nervous system disorders (3 AEs each), congenital, familial and genetic disorders (2 AEs); cardiac disorders, eye disorders, respiratory, thoracic, and mediastinal disorders, skin and subcutaneous tissue disorders (1 AE each).
- The proportion of patients with Grade 3.5 AEs was 69.4% (43 patients with a total of 131 AEs). The proportion of patients with Grade 5 (fatal) AEs was 9.7% (6 patients with 7 AEs). The most common Grade 3.5 AEs by PT (. 5% of patients) were: pneumonia (40.3% [25 patients]), viral pneumonia (8.1% [5 patients]), respiratory distress (6.5% [4 patients]), and respiratory failure (6.5% [4 patients]).
- 6 patients (9.7%) died due to progressive disease and 1 patient (1.6%) died due to an AE of pneumonia.
- The SAE rate per 100 patient-years decreased over time. Rates of SAEs of pneumonia also decreased more than 2.fold between the first and second years of treatment. The most common SAEs by SOC (. 5% of patients) were: Infections and infestations (66.1% [41 patients]),

Respiratory, thoracic, and mediastinal disorders (29.0% [18 patients]), Metabolism and nutrition disorders (11.3% [7 patients]), Gastrointestinal disorders (9.7% [6 patients]). The most common SAEs by PT (. 5% of patients) were: Pneumonia (45.2% [28 patients]) Respiratory distress (9.7% [6 patients]), Viral pneumonia (8.1% [5 patients]), Respiratory failure (8.1% [5 patients], Respiratory tract infection (6.5% [4 patients]), Acute respiratory failure (6.5% [4 patients]).

- 1 patient (1.6%) experienced a Grade 5 AE of viral respiratory tract infection that led to discontinuation of study treatment.
- 5 patients (8.1%) experienced 5 AEs that led to dose modification or interruption of study treatment. Occurring in 1 patient for each, they were: Grade 4 hypoxia, Grade 3 diarrhea, Grade 3 pneumonia, Grade 1 vomiting, and Grade 1 pyrexia. All events resolved.
- There were no AEs of special interest.
- In the SOC Eye disorders, 9 AEs were reported in 8 patients (12.9%): conjunctival hyperaemia in 2 patients (3.2%); and macular cyst, retinal exudates, strabismus, heterophoria, subretinal fluid, eye movement disorder and astigmatism in 1 patient (1.6%) each. There was no change of risdiplam therapy due to the AEs. All AEs were assessed by the investigator as not related to risdiplam therapy. All AEs were mild except 2 moderate AEs (strabismus and heterophoria, both described in the Update CSR). All except 2 AEs resolved (heterophoria resolved with sequelae, described in the Update CSR), and astigmatism which did not resolve, new after the cutoff date of the Update CSR).
- 30 patients (48.4%) had at least one AE coding to the SOC Skin and subcutaneous tissue disorders. None of the 49 AEs were serious or led to a change in study medication.
- 41 patients (66.1%) had at least one AE coding to the SOC Gastrointestinal disorders. Most of the 120 AEs were non-serious and did not lead to a change in study medication. Analysis of the SOCs which include AEs representing possible effects on epithelial tissues showed that events were not suggestive of any effects of risdiplam on epithelial tissues.
- Hematological parameters were generally stable over time. High baseline eosinophil, lymphocyte, and platelet counts were observed in some patients that continued to be high throughout the study. None of the values were assessed as clinically significant by the investigator.
- Isolated shifts in laboratory parameters were observed, however these were not sustained over time and generally were not clinically significant. As expected for patients with SMA, most patients had creatinine values below the LLN throughout the study, including at baseline
- Shifts in vital signs were observed; however, there was no trend and the percentage of patients with shifts toward higher values and shifts toward lower values was similar and did not increase over time.
- The percentage of patients with shifts from baseline in ECG parameters did not increase over time.
- Fifty-eight of 62 patients (93.5%) had at least one post-baseline ophthalmology assessment. Fifty-seven patients (100%) were followed up with an SD-OCT assessment at 12 months, 48

patients (87.3%) at 24 months, 45 patients (83.3%) at 36 months, 50 patients (94.3%) at 48 months, and 46 patients (86.8%) at 60 months which was the longest follow-up.

- During the safety follow-up period, 2 patients reported 8 AEs. One patient experienced nasal congestion, pyrexia (Grade 1 each; resolved), salivary hypersecretion (Grade 3; did not resolve), and 3 SAEs of cardiac arrest, hypoxia, and obstructive airways disorder, which were fatal. The other patient experienced one Grade 3 AE of pneumonia and one Grade 1 AE of diarrhea; both of which resolved. No events were assessed as related to the study treatment by the investigator.
- During the continued access period, 4 patients reported a total of 8 AEs. All AEs were Grade 1.2 except for 1 AE of oesophagitis (Grade 3). All cases resolved. There were 3 patients who reported a total of 5 SAEs, including 2 SAEs of respiratory failure, and 1 SAE each of acute respiratory failure (these 3 SAEs were assessed as not related to study treatment by the investigator), oesophagitis, and oesophageal stenosis (both assessed as related to study treatment by the investigator). All SAEs were Grade 1.2 except for 1 SAE of oesophagitis (Grade 3). All cases either resolved, were resolving, or resolved with sequelae.

1.1.1.
Post marketing data

Risdiplam is currently approved in over 100 international markets (including the U.S. and E.U.) for the treatment of SMA. Since the International Birth Date (7 August 2020) through 6 February 2024 (data lock point for the PBRER 1128869), an estimated cumulative total of 14,341 patients have received risdiplam from marketing experience (European Economic Area [EEA] n = 4475; Rest of the World [RoW] n = 5402; U.S. n = 3773; Japan n = 691). Exposure was similar between the sexes (male n = 6716; female n = 6933 for EEA, RoW, and U.S.). 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 1128869, submitted on 12 April 2024 (procedure no: EMEA/H/C/PSUSA/00010925/202402) for more details.

8.3 Discussion

The results of the final analysis for Study BP39056 (FIREFISH) (which includes all efficacy and safety results for Part 1 and Part 2 from enrollment to the end of study after 5 years of treatment) was submitted by the MAH to fulfil the requirements of Article 46 of Regulation (EC) No 1901/2006. As an additional pharmacovigilance activity in the RMP (category 3 study), this study was to address the following safety concerns for risdiplam: long-term safety and effect on epithelial tissues. The MAH proposed to update the RMP as part of a submission at a later date, hence an updated RMP (module 1.8.2) has not been submitted. This will be further assessed by the PRAC.

Overall, results from the FIREFISH study show that risdiplam treatment for up to 5 years in symptomatic Type 1 SMA patients (the severe form of the disease), was well tolerated, and the safety remains consistent with its known safety profile. No new safety signals were identified.

In brief, results retrieved from 'All Patients Safety Population' show that all patients enrolled experienced at least 1 AE and there was a total of 950 AEs reported. AEs occurring in more than 10% of patients were pyrexia (64.5%), upper respiratory tract infection (62.9%), pneumonia (50.0%), constipation,

diarrhea, nasopharyngitis (25.8% each), COVID-19, rhinitis, vomiting (21.0% each), bronchitis, cough, influenza, respiratory tract infection (19.4% each), urinary tract infection (17.7%), teething (12.9%), and respiratory failure (11.3%). Overall, 131 Grade =>3 AEs were reported by 43 (69.4%) patients. For the majority of patients, Grade =>3 AEs were reported in SOCs infections and infestations (58.1%), respiratory, thoracic and mediastinal disorders (27.4%), and gastrointestinal disorders (11.3%).

The majority of AEs (909/950 AEs) were not considered by the investigator to be related to risdiplam. The most frequently reported treatment-related AE was hematuria (3 patients [4.8%]).

There were 7 deaths (11.3%) during the study; the cause of death was assessed as progressive disease for 6 patients and AE of pneumonia for 1 patient by the investigator.

There were 51 patients (82.3%) who experienced a total of 150 SAEs. All but 7 SAEs had resolved/improved (2 SAEs of pneumonia, 1 SAE of acute respiratory failure, 1 SAE of cardiac arrest, 1 SAE of respiratory failure, 1 SAE of respiratory tract infection, 1 SAE of respiratory tract infection viral. All were fatal and none were assessed as related to the study drug by the investigator). There were no new deaths reported in the study since the Primary CSR (1100385), after the 24-month clinical cutoff. One patient experienced an AE of respiratory tract infection viral (1.6%) which led to discontinuation of study treatment.

No events or findings suggestive of the non-clinical safety findings (risdiplam induced effects on epithelial tissues, retinal toxicity and hematological effects) were observed in these patients with infantile-onset (Type 1) SMA.

A review of all available safety laboratory results, vital signs, ECGs, and ophthalmological assessments did not show any clinically significant adverse findings compared with baseline.

According to the MAH post-marketing data, where an estimated cumulative total of 14,341 patients have received risdiplam did not alter the known benefit-risk profile of risdiplam, and the benefit-risk profile of risdiplam in the authorized indication remains favorable.