

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**213535Orig1s000**

**CLINICAL PHARMACOLOGY  
REVIEW(S)**

# Office of Clinical Pharmacology Review

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<b>NDA</b>	213535
<b>Link to EDR</b>	<a href="\\cdsesub1\\evsprod\\nda213535">\\cdsesub1\\evsprod\\nda213535</a>
<b>Submission Date</b>	09/24/2019
<b>Submission Type</b>	505 (b) (1), Priority Review
<b>Brand Name</b>	EVRYSDI™
<b>Generic Name</b>	Risdiplam
<b>Dosage Form and Strength</b>	Powder for Oral Solution: 60 mg, constituted to 0.75 mg/mL
<b>Route of Administration</b>	Oral
<b>Proposed Indication</b>	Treatment of [REDACTED] <sup>(b) (4)</sup> Spinal Muscular Atrophy (SMA)
<b>Applicant</b>	Genentech, Inc.
<b>Associated IND</b>	128972
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## **1. EXECUTIVE SUMMARY**

Genentech, Inc is seeking approval for risdiplam (EVRYSDI), an orally bioavailable, small molecule, survival of motor neuron 2 (SMN2) splicing modifier formulated as powder for oral solution for the treatment of spinal muscular atrophy (SMA) in [REDACTED] <sup>(b) (4)</sup> patients (2 months and older) via 505(b)(1) pathway.

SMA is an autosomal recessive neuromuscular disorder characterized by the progressive loss of spinal motor neurons leading to muscle weakness and eventually cause mortality. It is caused by a homozygous deletion (95% of cases) or mutation of the SMN1 gene which encodes SMN protein. In humans, there are two SMN genes, the SMN1 gene (produces functional, full length SMN protein) and its paralog SMN2 gene (produces less functional and unstable SMN protein due to loss of Exon 7 during SMN2 pre-mRNA splicing process). Due to loss of SMN1 gene, patients with SMA rely on SMN2 gene to produce SMN protein. The dysfunctional and unstable SMN protein in patients with SMA leads to the death of motor neurons resulting in decreases in motor strength and function, ultimately impairing a patient's ability to reach motor milestones. Risdiplam is expected to modulate SMN2 splicing, retain Exon 7 in SMN2 mRNA and thus increases the production of functional, full-length SMN protein from the SMN2 gene.

The application relies on safety and efficacy of risdiplam from two ongoing studies: SUNFISH and FIREFISH. The SUNFISH is a placebo-controlled study in late onset SMA patients ( $\geq 2$  to 25 years, Type 2 and Type 3 SMA). The FIREFISH is an uncontrolled study in infantile onset, pediatric patients with Type 1 SMA ( $>1$  month to 7 months at enrollment). Both SUNFISH and FIREFISH studies consist of two-parts. The Part 1 was a pharmacokinetics (PK), pharmacodynamics (PD), safety and dose ranging study, and Part 2 is an efficacy and safety study.

In SUNFISH study (N=180; 120 risdiplam and 60 placebo), following 12 months treatment, a significant improvement of change from baseline in Motor Function Measures 32 (MFM32) total score [primary efficacy endpoint] was observed with risdiplam 0.25 mg/kg once daily ( $\leq 20$  kg) / 5 mg once daily ( $>20$  kg) compared to placebo. In FIREFISH study (N=21), following 12 months treatment, an approximately 41% (7 out of 17) of infantile onset SMA patients were able to sit for 5 seconds without support when dosed with risdiplam 0.2 mg/kg once daily compared to 0.08 mg/kg once daily (sub-therapeutic dose). These studies demonstrated effectiveness in favor of risdiplam compared to placebo.

The primary objectives of this review are:

- 1) to evaluate the appropriateness of the proposed dosing recommendation of risdiplam in patients with SMA
- 2) to assess the effect of intrinsic and extrinsic factors on risdiplam pharmacokinetics, and
- 3) to evaluate the adequacy of labeling statements for risdiplam.

## 1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the information contained in this NDA and recommends approval from a clinical pharmacology perspective. The review focus with specific recommendations and comments are summarized below.

Review Summary	Recommendations and Comments
<b>Pivotal or supportive evidence of effectiveness</b>	Primary evidence of effectiveness in late onset SMA was established from a placebo-controlled study (SUNFISH) in patients with Type 2 and Type 3 SMA ( $\geq 2$ to 25 years), and in infantile onset SMA was established from an uncontrolled study (FIREFISH) in pediatric patients with Type 1 SMA ( $>1$ month to 7 months at enrollment).
<b>General dosing instructions</b>	<p>Administer orally, once daily based on age and body weight as described below:</p> <p>2 months to less than 2 years of age: 0.2 mg/kg 2 years of age and older weighing less than 20 kg: 0.25 mg/kg 2 years of age and older weighing 20 kg or more: 5 mg</p> <p>Administer risdiplam after a meal, and in children who are breastfed, administer after breastfeeding, at approximately the same time each day.</p>
<b>Dosing in patient subgroups (intrinsic and extrinsic factors)</b>	<p>Renal impairment is not expected to influence systemic exposures to risdiplam. No dose adjustment is required for patients with renal impairment.</p> <p>Risdiplam is predominantly metabolized in the liver. Hepatic impairment may potentially increase the exposures to risdiplam. A study in patients with mild and moderate hepatic impairment is currently ongoing. Given there is a lack of information to support dosing recommendation in patients with impaired hepatic function, the review team recommends avoid use of risdiplam in patients with impaired liver function.</p> <p>Drug-drug interaction liability with risdiplam is considered low except for drugs that are substrates of multidrug and toxin extrusion protein (MATE1 and MATE2-K) transporters. Risdiplam is an inhibitor of MATE1/2-K transporters <i>in vitro</i>. The review team recommends avoiding drugs that are MATE1/2-K substrates while taking risdiplam. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction if needed based on the labeling of the co-administered drug.</p>

<b>Labeling</b>	The labeling concepts proposed by the Applicant are generally adequate.
<b>Bridge between the to-be-marketed and clinical trial formulations</b>	The to-be-marketed formulation is the same as the one used in the pivotal efficacy study (SUNFISH).

## 1.2 Post-Marketing Requirements and Commitments

Two post-marketing studies are required to meet the clinical pharmacology requirements of this application. These studies include,

### 1) Hepatic impairment study

Risdiplam is mainly metabolized by flavin monooxygenase 1 and 3 (FMO1 and FMO3), and by CYPs 1A1, 2J2, 3A4 and 3A7. In a mass balance study in humans, approximately 53% of the administered dose (14% unchanged risdiplam) was excreted in the feces and 28% in the urine (8% unchanged risdiplam). This suggests that hepatic metabolism plays a major role in the disposition of risdiplam and impairment of hepatic function may increase its systemic exposures. Therefore, a hepatic impairment study is necessary to understand the impact of hepatic impairment on the PK of risdiplam.

The Applicant stated that a hepatic impairment study (BP40995) in subjects with mild and moderate liver impairment is currently ongoing. The results of this study should be submitted as a post-marketing study report.

### 2) Thorough QT (TQT) study

The PK/electrocardiogram (ECG) data available from the submitted clinical studies are at considerably lower exposures (Cmax) of risdiplam than those expected with therapeutic doses at the steady-state. Given the submitted data are not adequate to characterize the risk of QTc prolongation associated with the oral administration of risdiplam, the QT-IRT recommends that the sponsor characterizes the effect of risdiplam on the QTc interval in a dedicated study at clinically relevant exposures. Please refer to the QT-IRT review by Girish Bende, submitted in to DARRTS on 02-19-2020 for additional details.

## 2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

### 2.1 Pharmacology and Clinical Pharmacokinetics

**Mechanism of Action:** Risdiplam is a survival of motor neuron 2 (SMN2) - directed RNA splicing modifier designed to treat SMA caused by mutations in chromosome 5q that lead to SMN protein deficiency. Using *in vitro* assays and studies in transgenic animal models of SMA,

risdiplam was shown to increase exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts and production of full-length SMN protein.

### **Pharmacokinetics:**

Risdiplam showed a linear and dose proportional increase in maximum plasma concentration ( $C_{max}$ ) and area under the plasma concentration-time curve (AUC) in a single ascending dose study in healthy subjects over the dose range from 0.6 mg to 18 mg, and a multiple ascending dose study in patients with SMA over the dose range from 0.02 to 0.25 mg/kg. Risdiplam exposures reach steady state 7 to 14 days after once daily administration.

**Absorption:** Following oral administration, time to reach  $C_{max}$  ( $T_{max}$ ) ranges from 1 to 4 h. In the clinical efficacy/safety studies, risdiplam was mostly administered with a morning meal or after breastfeeding in breastfed infants.

### **Distribution:**

The apparent volume of distribution at steady state is 6.3 L/kg. Risdiplam is predominantly bound to serum albumin, without any binding to alpha-1 acid glycoprotein, with a free fraction of 11%.

**Metabolism:** Risdiplam is mainly metabolized by flavin monooxygenase 1 and 3 (FMO1 and FMO3), and to some extent by CYPs 1A1, 2J2, 3A4 and 3A7. The major metabolite is N-hydroxy risdiplam (M1). Risdiplam is the major circulating component (83% of total drug in the circulation) in plasma. The M1 metabolite is pharmacologically inactive.

**Excretion:** The mean terminal elimination half-life of risdiplam is approximately 50 h. Following administration of a radiolabeled dose of 18 mg, approximately 53% of the dose (14% unchanged risdiplam) was excreted in the feces and 28% in the urine (8% unchanged risdiplam). The apparent clearance (CL/F) of risdiplam is 2.1 L/h for a 14.9 kg patient.

## **2.2 Dosing and Therapeutic Individualization**

### ***2.2.1 General dosing***

The proposed dosing recommendation of risdiplam include, 2 months to <2 years of age: 0.2 mg/kg;  $\geq 2$  years of age (< 20 kg): 0.25 mg/kg;  $\geq 2$  years of age ( $\geq 20$  kg): 5 mg.

Administer risdiplam after a meal, and in children who are breastfed, administer after breastfeeding, at approximately the same time each day. These dosing recommendations were studied in pivotal efficacy trials.

### ***2.2.2 Therapeutic individualization***

No therapeutic individualization is required for risdiplam based on intrinsic or extrinsic factors. Intrinsic factors including gender, race and renal impairment are not expected to significantly affect risdiplam exposures. Hepatic impairment may potentially increase the exposures to risdiplam. A study in patients with mild and moderate hepatic impairment is currently ongoing. Given there is a lack of information to support dosing recommendation in patients with impaired

liver function, the review team recommends avoid use of risdiplam in patients with impaired liver function.

*In vitro* studies showed that risdiplam and its major metabolite (M1) are not inhibitors of major CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, CYP3A4/5) or transporters (human MDR1, BCRP, OATP1B1, OATP1B3, OAT 1 and 3) at clinically relevant concentrations. Also, risdiplam is not an inducer of CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4) *in vitro*.

No clinically relevant interactions were seen when strong CYP3A inhibitor, itraconazole was administered with risdiplam or when risdiplam was administered with CYP3A substrate, midazolam. Therefore, drug-drug interaction liability with risdiplam is considered low except for drugs that are MATE1/2-K substrates.

Risdiplam is an inhibitor of MATE1/2-K transporters *in vitro*. The review team recommends avoiding drugs that are MATE1/2-K substrates while taking risdiplam. If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction if needed based on the labeling of the co-administered drug.

## 2.3 Outstanding Issues

None.

## 2.4 Summary of Labeling Recommendations

The labeling concepts proposed by the Applicant are generally adequate. The reviewer recommends adding the following language in Section 7.

### 7.1 Effect of EVRYSDI on Substrates of Multidrug and Toxin Extrusion (MATE) Protein Transporters

(b) (4)

Avoid coadministration of EVRYSDI with MATE substrates (b) (4) If coadministration cannot be avoided, monitor for drug-related toxicities and consider dosage reduction if needed based on the labeling of the co-administered drug.

### 8.6 Hepatic Impairment

The safety and efficacy of EVRYSDI in patients with hepatic impairment have not been studied. Hepatic impairment may potentially increase the exposures to risdiplam. Avoid use of EVRYSDI in patients with impaired (b) (4) function.

### **3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW**

#### **3.1 Overview of the Product and Regulatory Background**

Risdiplam is developed as powder for oral solution (0.75 mg/ml) for the treatment of SMA in (b) (4) patients (b) (4).

The Agency granted orphan drug designation and fast track designation for risdiplam for the treatment of SMA on January 04, 2017 and April 05, 2017, respectively. (b) (4)

On April 30, 2019, the Agency agreed with the Sponsor for the rolling submission of risdiplam NDA. On July 19, 2019, the Agency held a pre-NDA meeting with the Sponsor to discuss the content and format of risdiplam NDA for the treatment of patients with SMA. On September 24, 2019, the initial part of risdiplam application was submitted to the Agency.

The clinical studies submitted in this application include,

- 1) a three-part PK study in healthy subjects consists of single ascending dose PK study, food effect study and clinical interaction with a strong 3A inhibitor, itraconazole in healthy subjects,
- 2) a mass balance study,
- 3) clinical drug interaction with CYP3A substrate, midazolam in healthy subjects,
- 4) a two-part study in patients with late-onset SMA [BP39055 (SUNFISH); Part 1 – dose-ranging PK, PD and safety study and Part 2 – safety and efficacy study],
- 5) a two-part study in patients with infantile-onset SMA [BP39056 (FIREFISH); Part 1 – dose-ranging PK, PD and safety study],
- 6) Safety and efficacy study in patients with all types of SMA who are under background therapies for SMA [BP39054 (JEWELFISH)].

#### **3.2 General Pharmacology and Pharmacokinetic Characteristics**

Pharmacology	
<b>Mechanism of Action</b>	Risdiplam modulates SMN2 pre-mRNA splicing process and thus allows inclusion of Exon 7 in SMN2 mRNA. The full-length SMN2 mRNA with Exon 7 produces functional and stable SMN protein.
<b>QT Prolongation</b>	The PK/electrocardiogram (ECG) data available from the submitted clinical studies are at considerably lower exposures (Cmax) of risdiplam than those expected with therapeutic doses at the steady-state. Given the submitted data are not adequate to characterize the risk of QTc prolongation associated with the oral administration of risdiplam, the QT-IRT recommends that the sponsor characterizes the effect of risdiplam on the QTc interval in a dedicated study at clinically relevant exposures. A TQT study is required as PMR. Please refer to the QT-IRT review by Girish Bende, submitted in to DARRTS on 02-19-2020 for additional details.

<b>General Information</b>	
<b>Bioanalysis</b>	Plasma concentrations of risdiplam and its metabolite, N-hydroxy risdiplam (M1) were measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Details are described in section 4.1.
<b>Healthy Volunteers vs. Patients</b>	Relatively similar PK between healthy subjects and patients with SMA.
<b>Dose Proportionality</b>	The PK is linear and dose-proportional over the dose range of 0.6 to 18 mg in a single ascending dose study in healthy subjects and 0.02 to 0.25 mg/kg once daily in a multiple ascending dose study in patients with SMA.
<b>Variability</b>	Inter-individual variability (%CV) in plasma C <sub>max</sub> of risdiplam ranges from 15-27% and AUC <sub>0-24h</sub> ranges from 8% to 25%.
<b>Absorption</b>	
T <sub>max</sub>	Following oral administration, T <sub>max</sub> for risdiplam occurs between 1 and 4 h. Risdiplam exposures reach steady state 7 to 14 days after once daily administration. In the clinical efficacy/safety studies, risdiplam was administered mostly with a morning meal or after breastfeeding in breastfed infants.
<b>Distribution</b>	
<b>Volume of Distribution</b>	The apparent volume of distribution at steady state is 6.3 L/kg.
<b>Protein Binding</b>	89%
<b>Substrate/Inhibitor of Transporter Systems</b>	Substrate of P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) transporters <i>in vitro</i> . Based on the mass balance study, the oral bioavailability of risdiplam is approximately 81%. Given the oral bioavailability of risdiplam is high (>80%), P-gp or BCRP inhibitors are not expected to result in clinically significant increase of risdiplam concentrations.  Risdiplam is an inhibitor of MATE1 and MATE2-K transporters at therapeutic concentrations <i>in vitro</i> . However, the clinical relevance of interaction with MATE1/2-K substrates is unknown. Risdiplam and its metabolite, M1 are not inhibitors of human organic cation transporter 2 (OCT2) and BCRP at therapeutic exposures.
<b>Elimination</b>	
<b>Terminal Elimination Half-Life</b>	The elimination half-life is approximately 50 h.
<b>Metabolism</b>	
<b>Metabolizing Enzymes</b>	Risdiplam is primarily metabolized by FMO1 and FMO3 and minimally metabolized by CYP1A1, 2J2, 3A4 and 3A7. The major metabolite is N-hydroxy risdiplam (M1), which accounts approximately 30% of the parent drug exposure in plasma in patients with SMA. M1 is pharmacologically inactive.

<b>Inhibitor/Inducer</b>	Risdiplam and its metabolite (M1) showed a time dependent inhibition of CYP3A <i>in vitro</i> at concentrations higher than the clinically relevant concentrations (concentrations that achieve half-maximal inactivation of CYP3A (KI) is greater than 10 times of Cmax). Furthermore, a clinical interaction study suggests that risdiplam did not significantly increase the systemic exposures to CYP3A substrate, midazolam (refer to Appendices 4.2). Therefore, CYP3A inhibition is considered to be clinically not relevant. The applicant also included an exploratory pediatric PBPK analysis, which was not considered essential to describe the CYP3A4-mediated DDI liability of risdiplam.  Both risdiplam and its metabolite, M1 are not inhibitors for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 or inducers for CYP3A, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6.
<b>Excretion</b>	
<b>Primary Excretion Pathways</b>	Following oral administration of a radiolabeled dose of 18 mg, approximately 53% of the dose (14% unchanged risdiplam) was excreted in the feces and 28% in the urine (8% unchanged risdiplam).

### 3.3 Clinical Pharmacology Review Questions

#### 3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

Both SUNFISH and FIREFISH studies provide the pivotal evidence of efficacy of risdiplam for the treatment of patients with SMA. The SUNFISH study is a placebo-controlled study in late onset SMA patients ( $\geq 2$  to 25 years, Type 2 and Type 3 SMA). The FIREFISH study is an uncontrolled study in infantile onset, pediatric patients with Type 1 SMA ( $> 1$  month to 7 months at enrollment). Both FIREFISH and SUNFISH studies consist of two-parts. The Part 1 is a PK, PD, safety and dose ranging study, and Part 2 is an efficacy and safety study.

In SUNFISH study (Part 2), the primary efficacy endpoint was change from baseline in Motor Function Measures 32 (MFM32) total score at Month 12. Following 12 months treatment with risdiplam [N=120; 0.25 mg/kg once daily ( $\leq 20$  kg) and 5 mg once daily ( $> 20$  kg)] or placebo [N=60], the improvement in MFM32 total score [least square mean (SE)] was 1.36 (0.38) for patients receiving risdiplam and -0.19 (0.52) for patients receiving placebo. The least square difference (95%CI) of the improvement in MFM32 total score was 1.55 (0.3, 2.8).

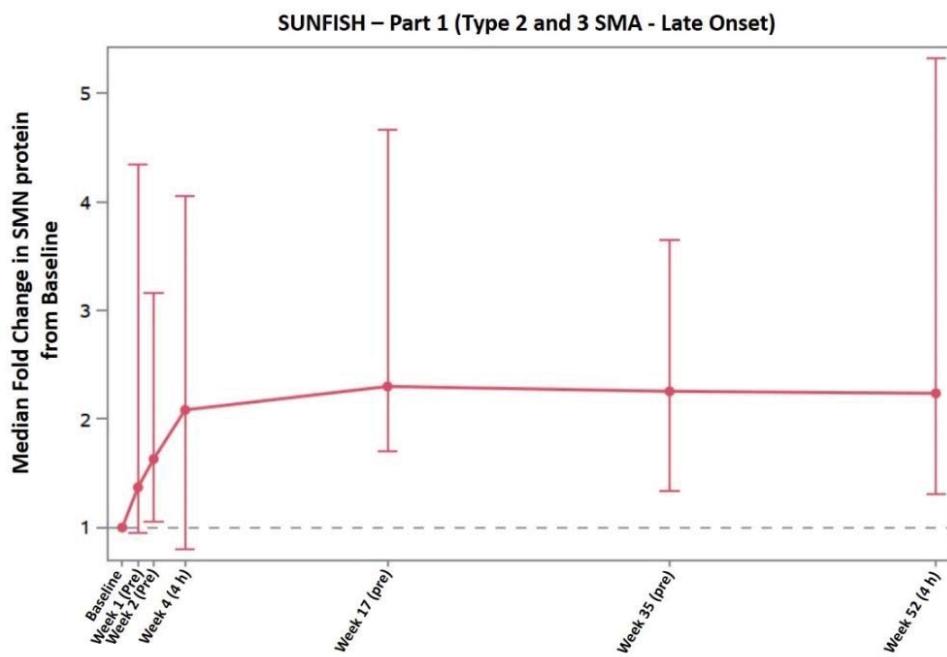
In FIREFISH study (Part 1), following 12 months treatment (N=21), an approximately 41% (7 out of 17) of infantile onset SMA patients who were able to sit for 5 seconds without support when dosed with risdiplam 0.2 mg/kg once daily compared to 0.08 mg/kg once daily (sub-therapeutic dose). Similarly, risdiplam 0.2 mg/kg treatment showed improvement in other motor function milestones, survival and ventilation free survival, respiratory measures, swallowing and

nutrition, and compound muscle action potential compared to 0.08 mg/kg dose. Refer to the clinical review by Dr. Rainer Paine from Division of Neurology I and the statistical review by Dr. Tristan Massie from Office of Biostatistics for additional details regarding the efficacy and statistical significance.

#### **Pharmacodynamic effect on serum SMN protein:**

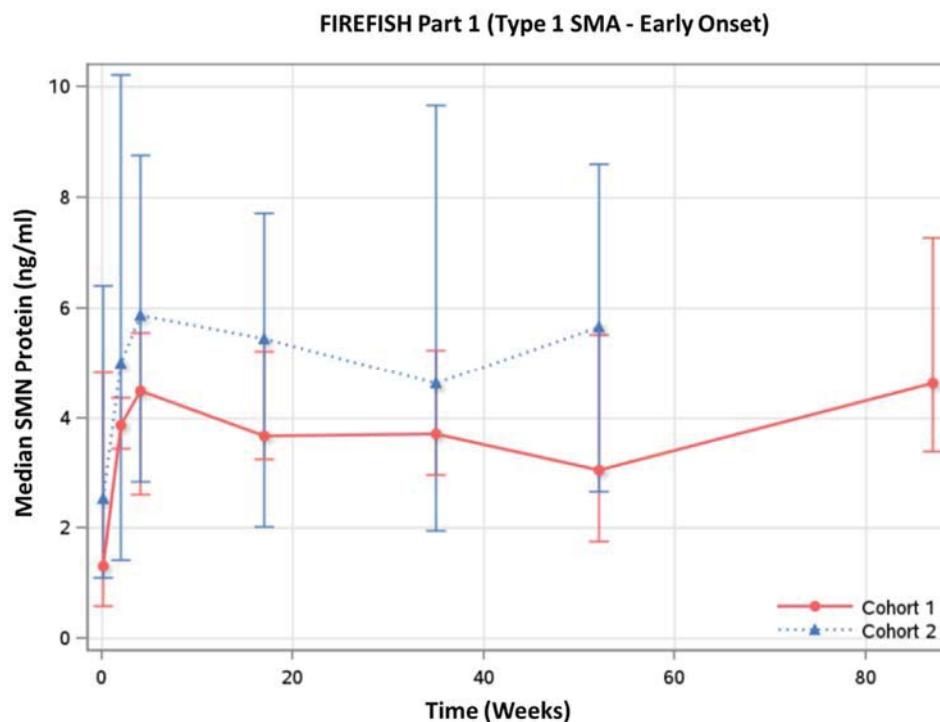
In Type 2 and Type 3 SMA patients (SUNFISH), risdiplam 0.25 mg/kg or 5 mg once daily showed approximately two-fold or greater median fold increase in blood SMN protein compared to baseline. The fold increase in SMN protein reaches its maximum after 4 weeks treatment and thereafter the magnitude of increase in SMN protein is maintained throughout the treatment period (Figure 1). In Type 1 SMA patients (FIREFISH), risdiplam showed a relatively similar or greater extent of increase in SMN protein levels from baseline compared to Type 2 and Type 3 SMA patients (Figure 2; Table 1).

**Figure 1. Effect of risdiplam on change from baseline in SMN protein in patients with late onset SMA**



Dose: 0.25 mg/kg / 5 mg once daily; N=20 except for week 2 (N=10) and week 52 (N=19); Error bars indicate minimum and maximum values. Source: Module 2.7.2; Summary of Clinical Pharmacology

**Figure 2. Effect of risdiplam on change from baseline in SMN protein in patients with early onset SMA**



Cohort 1 (N=4; Target AUC<sub>0-24h,ss</sub>: 700 ng/mL\*h): 0.00106 mg/kg single dose followed by 0.0106 mg/kg once daily for 1 month followed by 0.08 mg/kg once daily for 52 weeks followed by the dose was adjusted to 0.2 mg/kg

Cohort 2 (N=17; Target AUC<sub>0-24h,ss</sub>: ≤2000 ng/mL\*h): 0.2 mg/kg once daily. Dose was adjusted over 0.04 to 0.25 mg/kg to achieve target exposure. One of the subjects initially targeted to AUC<sub>0-24h,ss</sub>: 700 ng/mL\*h and after 2.7 months, the dose was adjusted to target AUC<sub>0-24h,ss</sub>: ≤2000 ng/mL\*h. Error bars indicate minimum and maximum values. Source: Module 2.7.2; Summary of Clinical Pharmacology

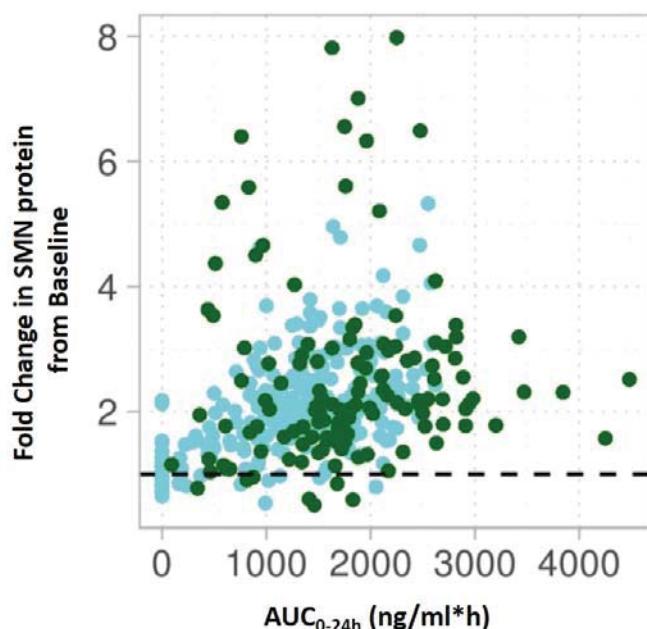
**Table 1. SMN protein levels in patients with SMA from Studies BP39056, BP39054 and BP39055**

SMN protein	BP39056	BP39054	BP39055
n	50	12	51
Last observation (Day)	244 [26 - 771]	182 [26.3 - 367]	364 [244 - 735]
Absolute SMN protein (ng/mL)	6.08 [1.31 – 9.29]	5.98 [2.98 – 7.75]	6.64 [1.18 – 11.2]
Fold-change from baseline	2.11 * [0.59 – 7.98]	2.19 [1.39 – 3.41]	2.22 [0.939 – 5.32]

Values indicated median (range); \* Baseline data missing for two patients; BP39056 – FIREFISH study (Type 1 SMA patients, age at the time of enrollment: ≥2 months to 7 months); BP39054 – JEWELFISH study (Type 1, 2 and 3 SMA patients, age ranges from 6 months to 60 years); BP39055 – SUNFISH study (Type 2 and 3 SMA patients, age ranges from 2 years to 25 years); Source: Module 2.7.2; Summary of Clinical Pharmacology

The exploratory analysis of exposure vs SMN protein levels suggests that increase in AUC<sub>0-24h</sub> is associated with an increase in SMN protein (Figure 3). The extent of increase in SMN protein levels did not reach plateau due to the exposure cap (AUC<sub>0-24h</sub> ≤2000 ng/ml\*h) defined in clinical studies based on the NOAEL observed in non-clinical studies. In non-clinical pharmacology studies, approximately 2 to 3-fold increase in SMN protein was associated with significant reduction in the manifestation of SMA disease characteristics and improvement in survival (Ref: Non-clinical review by Dr Edward J Fisher). Although literature reports <sup>1,2,3</sup> suggest that increase in SMN copy number (which leads to increase in SMN protein levels) is associated with a decrease in SMA phenotype, the relationship between blood SMN protein levels and achievement of motor milestones and other manifestations of SMA phenotype in humans is not known. Therefore, the adequacy of 2 to 3-fold increase in blood SMN protein levels in patients with SMA remains unclear.

**Figure 3. Effect of risdiplam exposure at steady state on SMN protein**



Source: Population PK/PD report; Module 5.3.3.5

### ***3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?***

Yes, the proposed dose and dosing regimen for risdiplam is appropriate for the intended patient population.

<sup>1</sup> Kolb and Kissel (2011) Arch Neurol 68:979-984;

<sup>2</sup> Netter's Neurology; Ferri's Netter Patient Advisor, 2nd edition;

<sup>3</sup> Butchbach (2016) Front Mol Biosci 3:7

Based on the animal toxicology findings, the average systemic exposure of risdiplam at steady state was capped to  $AUC_{0-24h, ss} \leq 2000 \text{ ng/ml*h}$  in clinical studies conducted in patients with SMA. In Part 1 of both SUNFISH and FIREFISH studies, PK was evaluated following administration of range of doses (refer to Appendices 4.3). Population PK model-based analyses suggest that age and body weight influence the PK of risdiplam. The clearance of risdiplam increases with increase in body weight up to 20 kg and thereafter clearance remains constant despite increase in body weight  $\geq 20$  kg. Therefore, weight-based dose was selected in subjects who weigh  $< 20$  kg and fixed dose was selected in subjects who weigh  $\geq 20$  kg. The studied doses include 0.2 mg/kg for subjects who are  $< 2$  years old, 0.25 mg/kg for subjects who are  $\geq 2$  years old but body weight  $< 20$  kg, 5 mg for subjects who are  $\geq 2$  years old but body weight  $\geq 20$  kg resulted in the average systemic exposure ( $AUC_{0-24h, ss}$ ) of approximately  $\leq 2000 \text{ ng/ml*h}$  (Table 2). Furthermore, the selected doses resulted in the median fold increase in blood SMN protein levels of approximately 2-fold or greater in patients with SMA. Although some subjects who showed  $AUC_{0-24h, ss}$  greater than  $> 2000 \text{ ng/ml*h}$ , the average systemic exposures achieved with the selected doses are in accordance with the toxicology based exposure cap, and acceptable safety and efficacy of risdiplam were observed in both late onset and early onset SMA patients (Refer to clinical review by Dr. Rainer Paine). Therefore, the Applicant's proposed dosing of risdiplam for the treatment of patients with SMA is acceptable.

**Table 2. PK parameters from Population PK analysis of JEWELFISH, SUNFISH and FIREFISH data**

Study	Dose	N	Age (years)	$AUC_{0-24h}$ (ng/ml*h)	$C_{max}$ (ng/ml)
<b>BP39054 (JEWELFISH)</b>	5 mg	12	21 [14-53]	1440 [1800-2170]	73.3 [42.4-111]
<b>BP39055 (SUNFISH)</b>	0.25 mg/kg	28	4.8 [3.2-11]	2286 [1660-3100]	178 [122-258]
	5 mg	89	12.8 [4.9-26.4]	1943 [830-3700]	134 [65-290]
<b>BP39056 (FIREFISH)</b>	0.08 mg/kg	4	0.54 [0.45-1.4]	1060 [646-1540]	60 [37.6-81.6]
	0.2 mg/kg	53	1.1 [0.37-2.1]	1930 [1100-3700]	117 [77.8-200]
	0.25 mg/kg	5	2.6 [2.1-2.7]	1770 [1280-2140]	114 [87.8-133]

Values in Age indicate median (range) and those in PK parameters indicate mean (range). Steady state values were estimated using data from subjects who received risdiplam treatment over at least 4 weeks or greater.

Source: Population PK/PD report; Module 5.3.3.5

### ***3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?***

No. Gender and race did not appear to affect the systemic exposures of risdiplam. Although age and body weight were found to influence the PK of risdiplam, these intrinsic factors were already accounted for doses studied in patients with SMA. Because only 8% of risdiplam is excreted unchanged in to urine, the renal impairment is not anticipated to significantly alter the exposures of risdiplam. Risdiplam is predominantly metabolized in the liver. The impaired liver function may potentially increase the systemic exposure to risdiplam. A study (BP40995) in patients with mild and moderate hepatic impairment is currently ongoing. As there is a lack of information to support dosing in subjects with liver impairment, the review team recommends avoid use of risdiplam in patients with hepatic impairment.

Based on the current information, alternate dosing regimen of risdiplam is not required for subpopulations based on intrinsic factors.

### ***3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?***

No. The Sponsor conducted a food effect assessment for risdiplam as part of a phase 1 study (BP29840) in a small number of healthy subjects (N=3). A high fat, high calorie meal did not appear to affect the exposures to risdiplam. Because of the smaller sample size, the food effect assessment for risdiplam from this study is considered exploratory. In the clinical efficacy/safety studies, risdiplam was mostly administered with a morning meal or after breastfeeding in breastfed infants. Therefore, the labeling should reflect the similar language (please refer to Appendices 4.2).

Based on *in vitro* assessments and follow up *in vivo* studies, the drug-drug interaction liability of risdiplam is considered low, except for drugs that are MATE1/2-K substrates.

*In vitro* studies showed that risdiplam is primarily metabolized by FMO1 and FMO3, and also metabolized by CYP3A4, CYP2J2, CYP1A1, CYP2C8 and CYP2C9. Risdiplam is a substrate of P-glycoprotein (P-gp) and breast cancer resistant protein (BCRP) transporters *in vitro*. Because the oral bioavailability of risdiplam is >80% in healthy subjects and *in vitro* passive permeability of risdiplam appears to be high (350 nm/s in LLC-PK1 cells and >300 nm/s in MDCKII cells), the clinical significance of efflux transporters such as P-gp and BCRP is expected to be low.

At clinically relevant concentrations, risdiplam and its major metabolite (M1) are not inhibitors of major CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6) or transporters (human MDR1, BCRP, OATP1B1, OATP1B3, OAT 1 and 3, OCT2) *in vitro*. Also, risdiplam is not an inducer of CYP enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19 or 3A4) *in vitro*. Risdiplam and its metabolite (M1) showed a time dependent inhibition of CYP3A *in vitro* at concentrations higher than the clinically relevant concentrations (*in vitro* KI for CYP3A is greater than 10 times of Cmax). Furthermore, no clinically relevant interactions were observed when clinical interaction studies

were conducted in adults using either strong CYP3A inhibitor, itraconazole or sensitive index CYP3A substrate, midazolam. This suggests that the drug interaction liability with risdiplam is expected to be low. This conclusion is expected to apply to both adults and pediatrics.

The Sponsor also included a physiologically-based PK (PBPK) analysis to explore whether the drug-drug interaction (DDI) results observed with risdiplam as a potential CYP3A4 inhibitor and midazolam, a sensitive CYP3A4 substrate, in adults is similar to those in pediatric subjects aged 2 months to 18 years. Note that the *in vivo* DDI study in adults demonstrated no clinically relevant CYP3A4 mediated interaction potential for risdiplam. The Applicant's PBPK analysis showed that risdiplam has low interaction potential for midazolam in pediatrics 2 months and above. Given the PBPK simulations showed a comparable DDI effect on midazolam in pediatrics and adults, the review team decided to include the *in vivo* DDI information in adults but not the language proposed by the applicant related to DDI between risdiplam and the CYP3A substrate midazolam in the pediatric population in Section 12.3 of the label.

Risdiplam is an *in vitro* inhibitor of multidrug and toxin extrusion protein (MATE1 and MATE2-K) transporters at therapeutic exposures. Therefore, risdiplam is anticipated to increase the systemic exposures of MATE1/2-K transporter substrates (cimetidine, metformin, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephadrine, fexofenadine). Given that MATE1 and MATE2-K transporter substrates are not frequently used in patients with SMA, the clinical relevance of this interaction is unknown. Furthermore, MATE1/2-K substrates were prospectively excluded from clinical studies conducted in patients with SMA. Therefore, while considering the drug interaction risks, the review team recommends avoid use of risdiplam with MATE1/2-K substrates. If coadministration cannot be avoided, appropriate monitoring for drug-related toxicities and dosage adjustment may be necessary based on the labeling of the co-administered drug.

## 4. APPENDICES

This section includes information on – (a) bioanalytical method validation and performance supporting all pharmacokinetic studies, and (b) brief description of study design and detailed pharmacokinetic results from the studies submitted in this application.

### 4.1 Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of risdiplam and its metabolite, N-hydroxy risdiplam (M1) were measured by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) [Validation report 1087035]. The summary of method performance is shown in Table 3 below. Additionally, it was found that:

- The precision and accuracy values of at least two-thirds of the overall QC samples were equal to or better than 15% (20% at the LLOQ) from the supporting bioanalytical reports.
- Risdiplam and N-hydroxy risdiplam were found to be stable in plasma after at least three freeze-thaw cycles at -75° C, at -20° C storage in human plasma over at least 33 days for (long term), bench-top stability in human plasma at 5° C for at least 6 h and processed sample stability at 8° C for at least 49 h.
- The QC sample accounting for dilution showed an acceptable precision ( $\leq 5\%$ ) and bias ( $\leq 5\%$ ). Carry over effects were observed in selected runs for risdiplam but not for N-hydroxy risdiplam. However, appropriate measures were taken to overcome the carry over effects.
- More than two-thirds of the incurred sample reanalysis (ISR) fell within 20% deviation.

**Table 3. Summary of bioanalytical methods and validation procedures for risdiplam and N-hydroxy risdiplam**

Bioanalytical Facility	Analytical method	Analyte	Sample volume ( $\mu\text{l}$ )	Analytical range (ng/ml)	Precision (CV%)	Accuracy (%)
(b) (4)	LC-MS/MS	Risdiplam	40	0.25-250	$\leq 11.0\%$	92.8-101.1
		N-hydroxy risdiplam	40	0.25-250	$\leq 6.5\%$	97.3-100.8

Source: Module 5.3.1.4; Bioanalytical Reports from all studies

Whole blood concentrations of SMN protein were measured using a validated sandwich immunoassay (SMN Elecsys research assay) [Validation report 1096681]. Because SMN protein was not available, the recombinant human SMN protein was used for the calibration. The analytical range of the assay is 0.03 to 50 ng/ml. The precision of the assay is  $\leq 6\%$ . Because the absolute nominal value of SMN protein is not available, the accuracy of the assay cannot be estimated. Following 8-fold dilution of QC samples, the precision is  $\leq 6\%$ . The post-processed stability is 8 h. The QC samples are stable at room temperature for 24 h and at 4° C for 48 h. The QC samples are stable after three freeze-thaw cycles at -80° C. The carry over effect assessment is not applicable to this method.

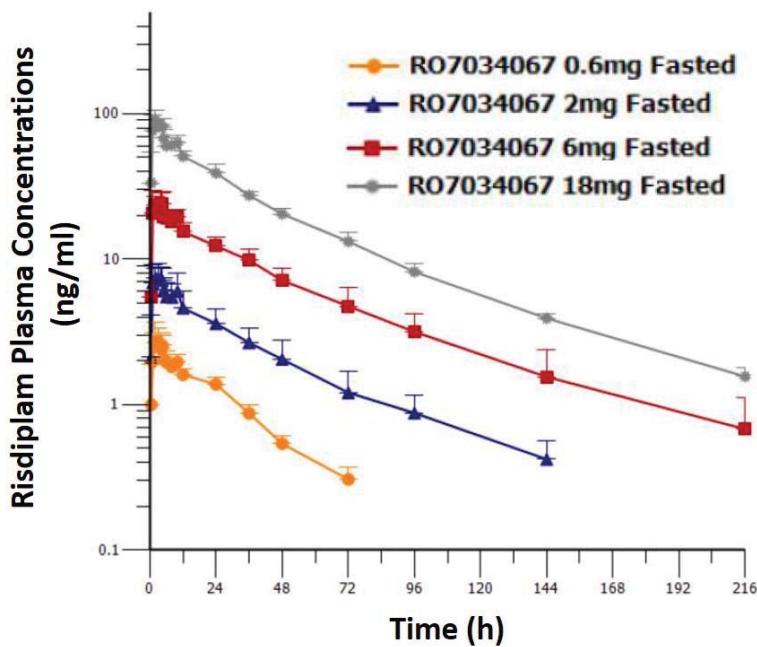
*Reviewer's comments: The bioanalytical methods for risdiplam and N-hydroxy risdiplam (M1 metabolite) satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development, and is acceptable. Given there is a lack of availability of absolute SMN protein, the recombinant SMN protein was used in the SMN Elecsys research assay for the calibration and assay validation. Furthermore, the relationship between blood SMN protein and the clinical improvement of motor milestones in humans is not known. Therefore, the interpretation of SMN protein levels in blood is considered only for exploratory purpose. The method of quantitation of whole blood SMN protein and the validation procedures appear to be reasonable.*

## 4.2 Clinical PK Assessment

### Pharmacokinetics:

In a single ascending dose (SAD) study in healthy subjects (Study BP29840), risdiplam showed a dose proportional increase in  $C_{max}$ ,  $AUC_{0-24h}$  and  $AUC_{inf}$  from 0.6 mg to 18 mg under fasted condition (Figure 4; Table 4). The apparent plasma terminal elimination  $t_{1/2}$  was approximately 50 h. Furthermore, pharmacokinetics of risdiplam in Japanese healthy subjects (Study NP39625) is similar to those observed in primarily Caucasian healthy subjects (Study NP39625).

**Figure 4. Average plasma concentration-time profile of risdiplam following single oral administration in healthy subjects. Error bars indicate standard deviation (SD).**



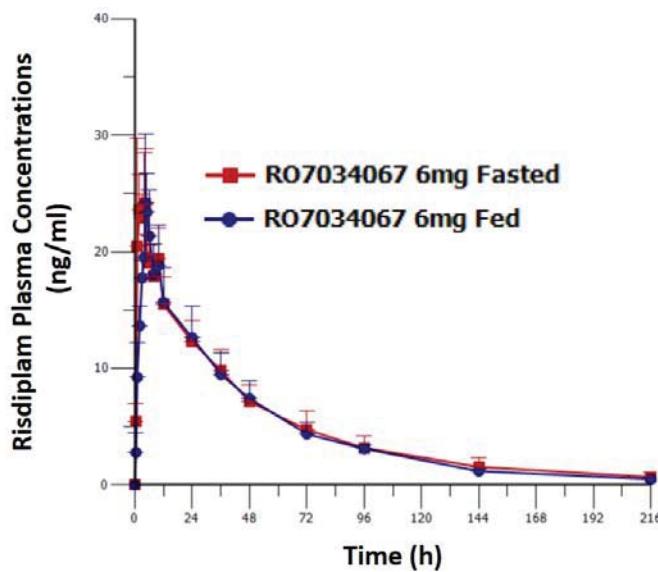
**Table 4. PK parameters of risdiplam in healthy subjects**

Dose (mg)	t <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>0-24h</sub> (h·ng/ml)	AUC <sub>inf</sub> (h·ng/ml)	t <sub>1/2</sub> (h)
<b>0.6 (n=3)</b>	3.00 (2.00–4.50)	2.82 (26.9%)	41.5 (15.5%)	86.7 (14.0%)	24.8 (34.3%)
<b>2 (n=3)</b>	3.00 (1.00–4.00)	8.33 (9.2%)	117 (24.9%)	294 (30.0%)	40.1 (2.3%)
<b>6 (n=3)</b>	2.00 (1.00–3.00)	24.5 (19.9%)	391 (14.0%)	1080 (26.1%)	47.7 (19.3%)
<b>18 (n=6) <sup>a</sup></b>	2.00 (1.00–4.00)	93.2 (14.7%)	1290 (8.0%)	3290 (7.4%)	68.7 (9.0%)

Values indicate geometric mean (geometric CV%) except for t<sub>max</sub>, median (range); <sup>a</sup> indicates one of the subjects was withdrawn from 18 mg dose group. Therefore, n=5 for PK parameters, AUC<sub>0-24h</sub>, AUC<sub>inf</sub> and t<sub>1/2</sub>. Source: Study report BP29840; Module 5.3.3.1

As part of Study BP29840, an exploratory evaluation of the effect of food on the PK of risdiplam was conducted in three healthy subjects. Subjects received 6 mg risdiplam on Day 1 after a high-fat and high-calorie breakfast. Followed by, blood samples were collected over 216 h for PK assessment under fed condition. Subsequently, the PK of risdiplam under fed condition was compared to those obtained after administration of 6 mg risdiplam under fasted state in 3 subjects in the SAD part. The results indicate that food did not appear to influence the exposures (C<sub>max</sub>, AUC<sub>0-24h</sub> and AUC<sub>inf</sub>) to risdiplam. However, food delayed the median T<sub>max</sub> from 2 h to 4.5 h (Figure 5; Table 5).

**Figure 5. Average plasma concentration-time profile of risdiplam following single oral administration under fasted and fed condition in healthy subjects. Error bars indicate standard deviation (SD).**



**Table 5. PK parameters of risdiplam under fasted and fed condition in healthy subjects**

Treatment	T <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>0-24h</sub> (h.ng/mL)	AUC <sub>inf</sub> (h.ng/mL)	HL (h)
<b>Fasted (n=3)</b>	2.00 (1.00 – 3.00)	24.5 (19.9%)	391 (14.0%)	1080 (26.1%)	47.7 (19.3%)
<b>Fed (n=3)</b>	4.50 (4.50 – 5.00)	24.8 (18.3%)	370 (17.9%)	1010 (17.5%)	43.2 (8.5%)

Values indicate geometric mean (Geometric CV%) except those for Tmax, median (range). Source: Study report BP29840; Module 5.3.3.1

*Reviewer's comments: Typically, the food effect is evaluated in a dedicated study in approximately 20 healthy subjects or greater. The Sponsor conducted a food effect assessment for risdiplam as part of a phase 1 study (BP29840) in a small number of healthy subjects (N=3). High fat and high calorie diet did not appear to affect the exposures to risdiplam. Because of the smaller sample size, the food effect assessment for risdiplam is considered exploratory. In the clinical efficacy/safety studies, risdiplam was mostly administered with a morning meal or after breastfeeding in breastfed infants. Therefore, the labeling should reflect the similar language.*

Following multiple oral administration of risdiplam 5 mg once daily for 14 days in healthy subjects (Study BP41361), approximately 3-fold accumulation of C<sub>max</sub> and AUC<sub>0-24h</sub> was observed. In patients with SMA (Study BP39055), approximately 2.3-fold accumulation of AUC<sub>0-24h</sub> was observed. The median (range) steady state plasma exposures (AUC<sub>0-24h</sub>) to risdiplam after 5 mg once daily dosing in healthy subjects (Study BP41361) was 1140 (943-1870) ng/ml\*h and those in patients with SMA (Study BP39055) was 1862 (987-3700) ng/ml\*h. Although approximately 1.6-fold higher median AUC<sub>0-24h</sub> at steady state was observed in patients with SMA compared to those in healthy subjects, due to a large variability in systemic exposures to risdiplam, a large degree of overlap in systemic exposures were seen between healthy subjects and patients with SMA. Therefore, it was considered that the PK of risdiplam is not different between healthy subjects and patients with SMA. The exposures to major metabolite, N-hydroxy risdiplam (M1) is approximately 30% as that of the parent drug exposure in plasma at steady state in patients with SMA. The metabolite, M1 is pharmacologically inactive.

A mass balance study (Study BP39122) was conducted using a single dose of 18 mg [<sup>14</sup>C/<sup>12</sup>C]-risdiplam in healthy subjects. Approximately 53% of administered radioactive dose was recovered in feces [14% of unchanged risdiplam, ≤4% of each of piperazine metabolites (M5, M7), carboxylic acid metabolite (M10) and ≤1.5% of each of other low-level metabolites] and 28% of the dose administered was recovered in urine [8% of unchanged risdiplam, 1.8% piperazine metabolite (M7) and ≤1% of each of other low-level metabolites]. The overall recovery ranges from 60% to 89.6% (one subject had a low recovery of 60%, and exclusion of this subject results in the average total recovery of approximately 86%). The major circulating

component in plasma was risdiplam (83% of AUC<sub>0-48h</sub>). The major metabolite, N-hydroxy risdiplam (M1) contributes approximately 14% of circulating component in plasma. The mass balance study suggests that risdiplam is mainly excreted via feces.

### ***In vitro metabolism***

Risdiplam is primarily metabolized by FMO 1 and 3 to N-hydroxy risdiplam (M1). CYP3A4 and CYP2J2 enzymes are also involved in the metabolism of risdiplam (Study 1092235). To a minor extent, CYP1A1, CYP2C8 and CYP2C9 enzymes are also capable of metabolizing risdiplam to M1. N-hydroxy risdiplam (M1) is also mainly metabolized by FMO 1 and 3, CYP3A4 and CYP2J2 enzymes to M5 and M14.

### ***In vitro transport***

The efflux ratio of risdiplam is 2.9 in LLC-PK1 cells expressing human MDR1 and 3.1 in MDCKII cells expressing human BCRP. This suggests that risdiplam is a substrate of P-gp and BCRP transporters. However, the passive permeability of risdiplam is high in both LLC-PK1 cells (350 nm/s) and MDCKII cells (>300 nm/s). Furthermore, based on the mass balance study, the oral bioavailability of risdiplam is greater than 80%. Therefore, P-gp and BCRP inhibitors are not expected to cause clinically significant increase in the exposures to risdiplam.

### **CYP inhibition/induction**

The direct and time-dependent inhibitory potential of risdiplam and N-hydroxy risdiplam (M1) against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 were evaluated in human liver microsomes *in vitro* (Studies 1090549 and 1077033). The results suggest that both risdiplam and N-hydroxy risdiplam (M1) are not either a direct or time dependent inhibitors for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6 enzymes at clinically relevant concentrations. Risdiplam and its metabolite (M1) showed a time dependent inhibition of CYP3A *in vitro* at concentrations higher than the clinically relevant concentrations (*in vitro* KI for CYP3A is greater than 10 times of Cmax). Additionally, a clinical drug interaction study suggests that risdiplam did not significantly alter the exposures to CYP3A substrate, midazolam in healthy subjects.

The induction potential of risdiplam and N-hydroxy risdiplam (M1) were evaluated against CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 in human hepatocytes (Study 1090966). Both risdiplam and N-hydroxy risdiplam are not inducers of any of the CYP enzymes tested in this study at clinically relevant concentrations.

Based on CYP inhibition/CYP induction studies, the drug interaction risks with risdiplam is anticipated to be low.

### **Transporter inhibition**

The inhibitory potential of risdiplam and N-hydroxy risdiplam (M1) against human MDR1, BCRP, OATP1B1, OATP1B3, OAT1, OAT3, MATE1, MATE2K transporters were evaluated *in vitro* (Studies 1067280, 1087637, 1081903 and 1074124). Risdiplam and N-hydroxy risdiplam

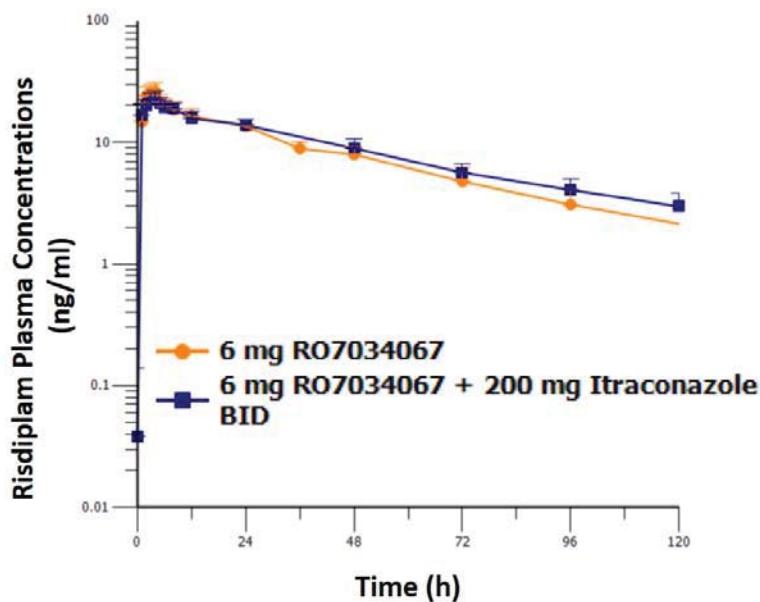
are not inhibitors for human MDR1, BCRP, OATP1B1, OATP1B3, OAT1, OAT3 at clinically relevant plasma concentrations. However, risdiplam but not N-hydroxy risdiplam inhibits MATE1 and MATE2K transporters (the concentration at which 50% inhibition ( $IC_{50}$ ) occurs at: 0.15  $\mu$ M and 0.09  $\mu$ M, respectively) at clinically relevant concentrations. The unbound  $C_{max}/IC_{50}$  for MATE1 and MATE2K transporters is  $\geq 0.1$ . This suggests that risdiplam may increase the systemic exposures to MATE1 and MATE2K substrates. Please refer to section 3.3.4 for additional information.

#### **Clinical drug interaction: Effect of strong CYP3A inhibitor, itraconazole on the PK of risdiplam in healthy subjects**

In addition to FMOs 1 and 3, CYP3A4 enzyme also contributes for the metabolism of risdiplam. Therefore, the effect of strong CYP3A inhibitor, itraconazole on the PK of risdiplam was evaluated as part of Study BP29840. A single-center, open-label, one-sequence, two-period crossover drug interaction study was conducted in 8 healthy subjects. In Period 1, PK samples were collected over 120 h following administration of a single oral dose of 6 mg risdiplam (30 minutes after a standardized light breakfast) on Day 1. After 14 days washout period, in Period 2, 200 mg itraconazole capsule was administered twice daily from Day 1 to Day 8. A single oral dose of 6 mg risdiplam was concomitantly administered in the fed state on Day 4 and PK samples were collected over 120 h.

The average plasma concentration-time profile and PK parameters are shown in Figure 6; Table 6, respectively.

**Figure 6. Average plasma concentration-time profile of risdiplam following single oral administration in the presence and absence of steady state itraconazole in healthy subjects. Error bars indicate standard deviation (SD).**



**Table 6. PK parameters of risdiplam in the presence and absence of itraconazole in healthy subjects**

Treatment Period	T <sub>max</sub> (h)	C <sub>max</sub> (ng/mL)	AUC <sub>0–120h</sub> (h.ng/mL)
<b>Period 1: 6 mg RO7034067 alone (n=8)<sup>a</sup></b>	3.50 (2.00–4.00)	26.8 (15.7%)	925 (16.4%)
<b>Period 2: 6 mg RO7034067 + 200 mg Itraconazole BID (n=7)</b>	4.00 (1.00–4.00)	23.5 (12.4%)	1020 (14.1%)
Parameter	Geometric Mean Ratio	Lower 90% CI	Upper 90% CI
AUC <sub>0–120h</sub>	1.11	1.03	1.19
C <sub>max</sub>	0.906	0.841	0.976

Values in the upper level table indicate geometric mean (Geometric CV%) except those for T<sub>max</sub>, median (range).  
Source: Study report BP29840; Module 5.3.3.1

The results indicate that itraconazole did not appreciably increase the systemic exposures (11% increase in AUC<sub>0–120h</sub>) to risdiplam. This suggests that co-administration of strong CYP3A inhibitors are unlikely to affect the systemic exposures to risdiplam.

#### **Clinical drug interaction: Evaluate the effect of risdiplam on the PK of CYP3A substrate, midazolam in healthy subjects**

Risdiplam appears to show a time-dependent inhibition of CYP3A in human liver microsomes at concentrations higher than those of clinically relevant exposures *in vitro*. Therefore, the Applicant conducted this clinical drug interaction study to evaluate the effect of risdiplam on the PK of CYP3A substrate, midazolam in healthy subjects. An open-label, non-randomized, two-part, safety, tolerability and PK evaluation following multiple oral administration of risdiplam was conducted in healthy subjects (Study BP41361). In part 1, eight subjects received risdiplam 5 mg once daily for 14 days. The PK of risdiplam was evaluated following single dose administration (Day 1) and at steady state (Day 14). The part 1 of this study was aimed to evaluate whether risdiplam 5 mg multiple dose administration achieves steady state mean AUC<sub>0–24h</sub> of 2000 ng/ml\*h. If not, based on the PK observations from part 1, the dose of risdiplam that achieves target AUC<sub>0–24h</sub> (2000 ng/ml\*h at steady state) will be selected for part 2 of the study to evaluate the effect of risdiplam on the PK of CYP3A substrate, midazolam. In Part 2, twenty-seven subjects enrolled but twenty-six subjects completed the study and one subject was withdrawn from the study. Subjects received single oral dose of 2 mg midazolam on Day 1 and Day 15. Risdiplam 8 mg once daily was administered from Day 3 to Day 16. The PK of midazolam was evaluated on Day 1 and Day 15 and the PK of risdiplam was evaluated on Day 3 and Day 16. Between Day 3 and Day 16, pre-dose PK of risdiplam was also evaluated.

The results from Part 1 indicate that risdiplam 5 mg once daily dosing over 14 days achieved the steady state AUC<sub>0–24h</sub> of 1250 ng/ml\*h (Table 7). Approximately, 3-fold accumulation of AUC<sub>0–24h</sub> and C<sub>max</sub> was seen at steady state compared to single dose administration in healthy subjects.

Because risdiplam 5 mg once daily dosing achieved exposures lower than the target exposure, the dose was increased to 8 mg in part 2 of the study.

**Table 7. PK parameters of risdiplam following administration of 5 mg once daily for 14 days in healthy subjects**

Parameter	5 mg risdiplam QD	
	Profile Day 1 (N = 8)	Profile Day 14 (N = 8)
AUC <sub>tau</sub> (h*ng/mL)	404 (15.8) [8]	1250 (24.6) [7]
AUC <sub>last</sub> (h*ng/mL)	399 (16.2) [8]	3160 (33.3) [7]
C <sub>max</sub> (ng/mL)	25.9 (13.2) [8]	78.6 (23.7) [7]

Values indicate geometric mean (CV%) [number of subjects]. One subject was excluded from analysis on Day 14 due to missed risdiplam dosing. AUC<sub>tau</sub> represents AUC<sub>0-24h</sub>. Source: Study report BP41361; Module 5.3.3.4

The results from part 2 suggest that risdiplam 8 mg once daily achieved a geometric mean steady state AUC<sub>0-24h</sub> of 1730 ng/ml\*h (Table 8). Although this exposure is slightly lower than the mean target AUC<sub>0-24h</sub> (2000 ng/ml\*h), the exposures are relatively similar to the median steady state AUC<sub>0-24h</sub> (1862 ng/ml\*h) observed in patients with SMA treated with risdiplam 5 mg once daily (Study BP39055). Therefore, the clinical drug interaction study with risdiplam 8 mg dose was deemed to be reasonable.

**Table 8. PK parameters of risdiplam following administration of 8 mg once daily for 14 days (Day 3 to Day 16) in healthy subjects**

Parameter	Day 1: 2 mg midazolam; Days 3 to 14: 8 mg risdiplam QD; Day 15: 2 mg midazolam and 8 mg risdiplam QD; Day 16: 8 mg risdiplam QD	
	Profile Day 3 (N = 27)	Profile Day 16 (N = 27)
AUC <sub>tau</sub> (h*ng/mL)	613 (24.5) [27]	1730 (21.3) [26]
AUC <sub>last</sub> (h*ng/mL)	597 (24.6) [27]	4280 (26.5) [26]
C <sub>max</sub> (ng/mL)	42.6 (30.8) [27]	113 (21.5) [26]

Values indicate geometric mean (CV%) [number of subjects]. One subject was excluded from analysis on Day 14 due to missed risdiplam dosing and missed midazolam dosing. AUC<sub>tau</sub> represents AUC from time 0 to 24 h. AUC<sub>last</sub> is the AUC from time 0 to the last quantifiable concentrations. Source: Study report BP41361; Module 5.3.3.4

Risdiplam showed 11% increase in AUC<sub>last</sub>, 8% increase in AUC<sub>0-inf</sub> and 16% increase in C<sub>max</sub> of midazolam (Table 9). The observed magnitude of increase in exposures to midazolam was considered to be clinically not significant. This suggests that risdiplam is a weak inhibitor of CYP3A, and the drug interaction risk is anticipated to be minimal when risdiplam is concomitantly used with drugs that are substrates of CYP3A. Furthermore, dose adjustment of CYP3A substrates is not necessary when risdiplam is concomitantly administered.

Risdiplam treatment showed 20% increase in AUC<sub>last</sub>, 12% increase in AUC<sub>0-inf</sub> and 27% increase in C<sub>max</sub> of 1-hydroxy midazolam (Table 10). Risdiplam mediated increase in exposures to 1-hydroxy midazolam may be due to the inhibition of enzymes involved for the

glucuronidation (Uridine diphosphate glucuronyl transferases – UGT1A4, UGT2B4 and UGT2B7) of 1-hydroxy midazolam.

**Table 9. PK parameters of midazolam following administration of a single dose of midazolam either alone or in combination with risdiplam in healthy subjects**

Parameter	Profile		n	GLSM	Test versus Reference Ratio of GLSMs (90% CI)
	Day	Treatment			
AUC <sub>inf</sub> (h*ng/mL)	1	2 mg midazolam (Reference)	12	23.2	
	15	2 mg midazolam and 8 mg risdiplam QD (Test)	11	25.1	1.08 (0.93, 1.26)
AUC <sub>last</sub> (h*ng/mL)	1	2 mg midazolam (Reference)	27	19.9	
	15	2 mg midazolam and 8 mg risdiplam QD (Test)	26	22.0	1.11 (1.02, 1.20)
C <sub>max</sub> (ng/mL)	1	2 mg midazolam (Reference)	27	7.65	
	15	2 mg midazolam and 8 mg risdiplam QD (Test)	26	8.91	1.16 (1.06, 1.28)

**Table 10. PK parameters of 1-hydroxy midazolam following administration of a single dose of midazolam either alone or in combination with risdiplam in healthy subjects**

Parameter	Profile		n	GLSM	Test versus Reference Ratio of GLSMs (90% CI)
	Day	Treatment			
AUC <sub>inf</sub> (h*ng/mL)	1	2 mg midazolam (Reference)	17	8.42	
	15	2 mg midazolam and 8 mg risdiplam QD (Test)	15	9.43	1.12 (0.99, 1.27)
AUC <sub>last</sub> (h*ng/mL)	1	2 mg midazolam (Reference)	27	7.75	
	15	2 mg midazolam and 8 mg risdiplam QD (Test)	26	9.32	1.20 (1.11, 1.30)
C <sub>max</sub> (ng/mL)	1	2 mg midazolam (Reference)	27	3.18	
	15	2 mg midazolam and 8 mg risdiplam QD (Test)	26	4.02	1.27 (1.14, 1.41)

GLSM- Geometric least square mean; AUC<sub>inf</sub> represents AUC from time 0 to infinitive. AUC<sub>last</sub> is the AUC from time 0 to the last quantifiable concentrations. Source: Study report BP41361; Module 5.3.3.4

### 4.3 Population PK Analyses

Population PK analysis of risdiplam was conducted using PK data from a study in healthy volunteers (BP29840, N=26), a study in infants with Type 1 SMA (FIREFISH, BP39056, N=62;

Part 1: 21 and Part 2: 41), a study in pediatric and adult patients with Type 2/3 SMA (SUNFISH, BP39055, N=227; Part 1: 51 and Part 2: 176), and a study in children and adult patients with Type 1, 2, or 3 SMA who were under the background therapies targeting SMN2 splicing (JEWELFISH, BP39054, N=12). A brief summary of four studies included in the population PK analysis is shown in Table 11.

**Table 11. Summary of study design used in Studies BP29840, BP39056, BP39055 and BP39054**

Study No.	Objectives	Study Design	Population	No. Subjects	Dose, Route, Regimen
<b>BP29840</b> (completed)	Entry-into-Human study Part 1: Safety, tolerability, PK and PD of single ascending doses of risdiplam Part 2: Food effect Part 3: Itraconazole interaction	Part 1: Single-center, randomized, double-blind, placebo-controlled, single ascending dose study Part 2: Food effect (not conducted; food effect investigated in Part 1) Part 3: Single-center, open-label, one-sequence, two-period crossover study	Healthy male subjects, age 18-45 years	Part 1: 25 (18 active, 7 placebo) Part 3: 8	Part 1: single oral doses of 0.6, 2, 6, 18 mg risdiplam or placebo Part 3: single oral doses of 6 mg risdiplam alone or in combination with 200 mg bid itraconazole (Day 1 to Day 8)
<b>BP39056</b> <b>FIREFISH</b> (ongoing) pivotal Phase 2/3 study	Part 1: Safety, tolerability, PK, PD, dose selection for Part 2 Part 2: Efficacy, safety and tolerability, PK, PD	Seamless <sup>1</sup> , multicenter, two-part study Part 1: Open-label dose-escalation phase with a 24 month treatment period, followed by an open-label extension (OLE) for up to 2 years Part 2: Open-label single-arm study with a 24-month treatment period, followed by an OLE for up to 2 years	Infants with Type 1 SMA; age 1-7 months at enrollment	Part 1: 21 patients Part 2: 41 patients	Once daily oral administration Part 1: 0.00106 mg/kg single dose; 0.0106, 0.04, 0.08, 0.2, 0.25 mg/kg once daily. Part 2 starting dose at enrollment: infants >1 - <3 months: 0.04 mg/kg, infants ≥3 - <5 months: 0.08 mg/kg, infants ≥5 months: 0.2 mg/kg. The dose for all infants <2 years has been adjusted to 0.2 mg/kg. Infants ≥2 years: 0.25 mg/kg.
<b>BP39055</b> <b>SUNFISH</b> (ongoing) pivotal Phase 2/3 study	Part 1: Safety, tolerability, PK, PD, dose selection for Part 2 Part 2: Efficacy, safety and tolerability, PK, PD	Seamless <sup>1</sup> , two-part randomized, multicenter, placebo-controlled, double-blind study Part 1: double-blind, randomized (2:1), placebo controlled, exploratory dose finding phase, followed by open label phase up to 24 months, and an OLE for up to 3 years thereafter Part 2: double-blind, randomized (2:1), placebo controlled, parallel group treatment period, followed by an OLE for up to 3 years	Part 1: Type 2 and Type 3 SMA (ambulant and non-ambulant) Part 2: Type 2 and non-ambulant Type 3 SMA patients; age 2-25 years	Part 1: 51 patients in 2 age groups, 2-11 years (n = 31) Part 2: (n = 20) Part 2: 180 patients age 2-25 years	Once daily oral administration Part 1: placebo; 3 and 5 mg; 0.02, 0.05, 0.15 and 0.25 mg/kg; Part 2: 0.25 mg/kg for patients with BW <20 kg, 5 mg for patients with BW ≥ 20 kg; placebo
<b>BP39054</b> <b>JEWELFISH</b> , (ongoing)	Safety, tolerability, PK, PD	Multicenter, open-label, non-comparative; patients, previously enrolled in BP29420 or treated with nusinersen, AVXS-101 or olesoxime	Type 1, 2 or 3 SMA patients age 6 months to 60 years	Up to 180 patients N=12 at CCOD	Once daily oral administration age 2-60 years: 5 mg for patients with BW ≥20 kg and 0.25 mg/kg for patients with BW <20 kg; age 6 months to <2 years: 0.2 mg/kg

Source: Population PK Reports; Module 5.3.3.5, ALNY-CSC-122PKPD

The PK sampling collection from these studies are described as below.

In Study BP29840 (healthy volunteers study), plasma PK samples were collected at: pre-dose, 0.5, 1, 2, 3, 4, 4.5, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 144 and 216 h post dose and at follow-up visit between 14 and 21 days after the risdiplam administration.

In Study BP39056 (FIREFISH), plasma PK samples were collected from 62 Type 1 SMA patients (Part 1 and Part 2). For Part 1, plasma PK samples were collected at: 2, 4, 6 hr post-dose on Day 1, pre-dose, 2, 4, 6 hr post-dose on Weeks 4,12, 52, 78 and 104, while pre-dose samples were drawn on Day 2, pre-dose and 4h post-dose samples were collected on Weeks: 1 (Day 7), 2, 8, 17, 26, 35, 43, 61, 70, 87 and 96. For Part 2, plasma PK samples were collected at: 2, 4, 6 hr

post-dose on Day 1, pre-dose, 2, 4, 6 hr post-dose on Weeks 4, 8, 26, 43, 78 and 96, while pre-dose samples were drawn on Weeks: 1 (Day 2), 2, 17, 35, 52, 61, 70, 87 and 104. Data from PK samples collected until 24th April 2019 from all patients enrolled in Part 1 and Part 2 of this study has been included in the PK analysis.

In Study BP39055 (SUNFISH), plasma PK samples were collected from Part 1 at: 1, 2, 4, 6 hr post-dose on Day 1, pre-dose, 1, 2, 4, 6 hr post-dose on Weeks 4, 8, 52 and 87, while pre-dose samples were drawn on Weeks 1 (Day 7), 2, 17, 35, 70 and 104. From Part 2 at: 1, 2, 4, 6 h post-dose on Day 1, pre-dose, 1, 2, 4, 6 h post-dose on Weeks 4, 52 and 87, while pre-dose samples were drawn on Weeks 1 (Day 7), 2, 8, 17, 35, 70 and 104. Data from PK samples collected until 6th of September 2019 from all Part 1 and Part 2 patients has been included in the PK analysis.

In Study BP39054 (JEWELFISH), plasma PK samples were collected from 12 Type 2 or 3 SMA patients who have previously received treatment with therapies targeting SMN2 splicing at: 1, 2, 4, 6 h post-dose on Day 1, pre-dose, 1, 2, 4, 6 hr post-dose on Weeks 4, 8, 52 and 87 while pre-dose samples were drawn on Weeks 1 (Day 7), 2, 17, 26, 35, 43, 70 and 104 according to protocol version 1 (2017). The study protocol versions 2 (2018) and 3 (2019) have the following PK sampling points: 1, 2, 4, 6 hr post-dose on Day 1, pre-dose, 1, 2, 4, 6 hr post-dose on Weeks 4, 13, 52 and 91, and pre-dose samples on Weeks 2, 26, 39, 65 and 104 for patients aged 2 - 60 years. Data from PK samples collected until 1st of December 2018 has been included in the PK analysis.

The objectives of this analysis were, 1) to develop population PK models for risdiplam using PK data from healthy subjects and patients with SMA, 2) to identify covariates that explain variability in PK and quantify intra- and inter-subject variability of risdiplam.

### **Applicant's Analysis:**

#### **Population PK Analysis:**

A total of 429 plasma concentrations from 26 healthy volunteers and 5720 plasma concentrations from 301 patients with SMA were included in the pooled population PK analysis dataset. Of 5906 venous blood samples and 243 capillary blood samples were collected.

**Data Exclusions:** Ninety-two samples (<1.5%) with risdiplam concentrations below the limit of quantitation were excluded from the analysis. Furthermore, five samples were suspected for patient non-compliance and five samples with conditional weighted residuals (CWRES) greater than 5 were also excluded.

**Modeling Strategy:** Population PK modeling and model validation were performed using NONMEM software (ICON Development solution). Modeling strategy includes, 1) development of structural PK model 2) development of random effects model including between-subject (BSV) variability and residual unexplained variability, 3) evaluation of

covariates that explain BSV, 4) development of final model, 5) evaluation of model adequacy [goodness-of-fit (fitted and observed concentrations, conditional weighted residuals versus time] and 6) validation of final model using bootstrapping and visual predictive check methods.

One, two and three compartment models with first order absorption and elimination were evaluated. The relationship between plasma concentration and time was described in the model using,

$$C_{ij} = f(X_i, P_i, \eta_i, t_{ij}, \varrho_{ij})$$

$X_i$ ,  $P_i$ , and  $\eta_i$  are the vectors of patient covariates, individual typical parameter estimates, and inter-individual random effects for subject  $i$ , respectively;  $t_{ij}$  is the time of the  $j$ th observation for subject  $i$  and  $\varrho_{ij}$  is the unexplained, random residual error for observation  $ij$ .

The between-subject variability (BSV) was evaluated with the assumption that data follows a log-normal distribution.

$$P_i = P_{TV} e^{\eta_i}$$

$P_i$  is the estimate of the individual parameter value,  $P_{TV}$  is the parameter estimate for the population typical value and  $\eta_i$  is the proportional deviation of the  $i$ th individual from that mean. The random effects for the parameters were modeled using a multivariate normal distribution (MVN) with mean value 0.

$$(\eta_1, \dots, \eta_n) \sim MVN(0, \Omega)$$

where  $\Omega$  is the variance-covariance matrix of the random effects components  $\eta$ .

The residual variability (or within-subject variability) was assumed to be a function of normally distributed random effects with mean 0. Additive, proportional and combined additive and proportional models for residual error listed below were evaluated.

$$C_{ij} = F_{ij} + \mathcal{E}_{1, ij}$$

$$C_{ij} = F_{ij} \cdot (1 + \mathcal{E}_{2, ij})$$

$$C_{ij} = F_{ij} \cdot (1 + \mathcal{E}_{2ij}) + \mathcal{E}_{Iij}$$

Where  $F_{ij}$  represents the model prediction for the  $j$ th observation for subject  $i$ . The intra-subject random effects ( $\mathcal{E}_1$  and  $\mathcal{E}_2$ ) were assumed to be normally distributed with mean value 0 and variance  $\sigma^2$

$$\mathcal{E} \sim N(0, \sigma^2)$$

**Covariate analysis:** Given the analysis dataset include infants to adults (age: 2.2 months to 52 years) with body weight ranges from 4.1 kg to 95.3 kg, the time-varying covariates, age and

body weight were included in structural model using maturation function with sigmoidal model and allometry with power model, respectively. The time varying covariates, weight was included in clearance (CL/F), apparent intercompartmental clearance (Q/F), central volume of distribution (V1/F) and apparent peripheral volume of distribution (V2/F), and age (maturation function) was included in CL/F and V1/F.

The baseline covariates evaluated in this analysis include gender, race, SMA type, alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) and Hammersmith Infant Neurological Examination (HINE).

The effect of continuous covariates  $X_i$ , on a model parameter,  $P_i$ , were evaluated using a power model,

$$P_i = P_{TV} \left( \frac{X_i}{\tilde{X}} \right)^{\theta_X}$$

where  $\theta_X$  is the power estimate for the covariate effect.

The effect of categorical covariates with M categories ( $X_m$ ) on a model parameter,  $P_i$ , were evaluated using a proportional model,

$$P_i = P_{TV} (1 + \theta_{Xm})$$

where  $\theta_{Xm}$  represents the fractional change in P for category m of covariate X;  $P_{TV}$  is the parameter estimate of the population typical value.

The relationship between post-hoc parameter estimates and individual covariate values was evaluated with regression analysis using generalized additive model (GAM). The statistically significant covariates based on Akaike Information Criterion (AIC) were retained in the model. Subsequently, an automated step-wise covariate modeling (SCM) such as step-wise forward inclusion ( $p < 0.05$ ) and step-wise backward elimination ( $p < 0.01$ ) procedures were carried out using Perl speaks NONMEM (PsN). The covariate is considered clinically important if 90% CI of the posterior distribution of 10,000 estimates of the covariate effect lies outside  $\pm 20\%$  of the median value of the parameter estimates normalized to the median. To obtain non-parametric 95% confidence intervals of the parameter estimates, 200 stratified bootstrap simulations were performed. The stratification factors for bootstrap include study and SMA type.

## Results:

A two compartment PK model with three transit absorption compartments and first order elimination was adequately described the PK of risdiplam. The model included between subject variability on  $K_{tr}$ , CL/F and V1/F as fixed random effects and proportional residual variability for venous blood samples and capillary blood samples. Given the dataset include infants, adolescents and adults with wide age range and body weight, the time varying covariates, age and body weight were included in the model, and were not considered for covariate analysis.

The influential covariates identified by GAM analysis include SMA type, bilirubin and ALT on CL/F, and sex on V1/F. Subsequently, SCM analysis was carried out. This analysis identified SMA type as an influential covariate on CL/F and sex on V1/F. Because the sex effect on V1/F was <20% of the median value of the parameter estimates normalized to the median, the covariate, sex was considered clinically not relevant. Given that SMA type showed high condition number ( $>1000$ ) and RSE (75%) on CL/F, SMA type was not included in the final model. Therefore, covariates other than age and body weight were not included in the final model.

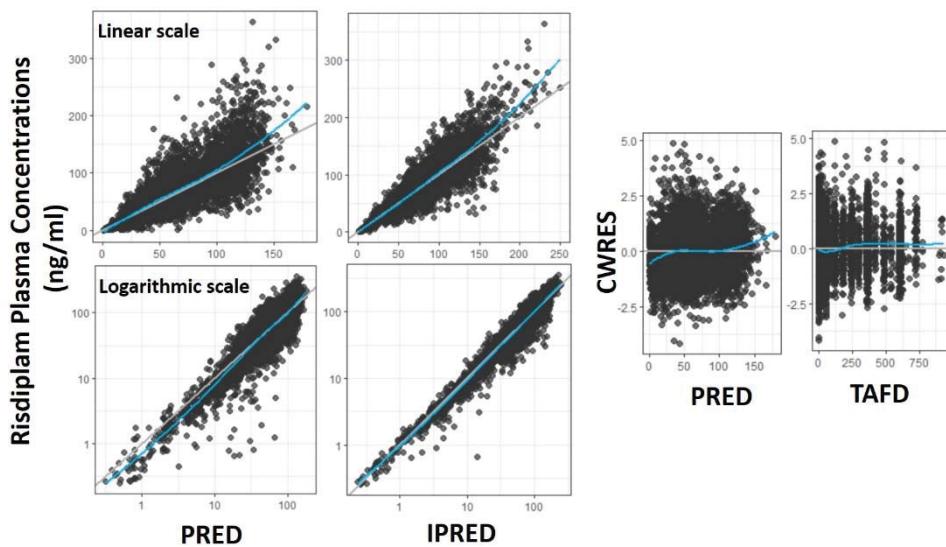
The parameter estimates and bootstrap estimates from the final PK model for risdiplam are shown in Table 12. The precision of PK parameter estimates for fixed effects are <15% (RSE) except for Age50, CL and Age50, V1. The final model parameter estimates, and 95% CI are reflecting the 95% CI for bootstrap parameter estimates. This suggests that the performance and stability of the final model is acceptable. The BSV on K<sub>tr</sub>, CL/F and V1/F was 55%, 26%, and 26%, respectively. The residual variability for venous blood samples and capillary blood samples was 24% and 34%, respectively. The ETA shrinkage for K<sub>tr</sub>, CL/F and V1/F is 27%, 10% and 10%, respectively.

**Table 12. Parameter estimates from the final population PK model**

Parameter	Estimate	RSE (%)	95% CI	Bootstrap Median (95% CI)
<b>Fixed Effects</b>				
CL/F (L/hr)	2.18	8.99	(1.8 – 2.57)	2.17 (1.94 – 2.52)
k <sub>tr</sub> (/hr)	5.12	1.46	(4.97 – 5.26)	5.07 (4.53 – 5.60)
V <sub>c</sub> /F (L)	60.8	7.37	(52 – 69.6)	60.7 (52.6 – 71.9)
Q/F (L/hr)	0.553	11.0	(0.434 – 0.672)	0.556 (0.434 – 0.771)
V <sub>p</sub> /F (L)	33.0	11.7	(25.5 – 40.6)	32.5 (26.4 – 43.5)
<b>Covariate Effects</b>				
Effect of WT on CL/F and Q/F	0.493	12.8	(0.37 – 0.617)	0.494 (0.393 – 0.582)
Effect of WT on V <sub>c</sub> /F and V <sub>p</sub> /F	0.799	7.38	(0.684 – 0.915)	0.807 (0.665 – 0.916)
Age <sub>50</sub> – CL/F (yr)	0.821	26.9	(0.388 – 1.26)	0.805 (0.534 – 1.22)
Age <sub>50</sub> – V <sub>c</sub> /F (yr)	0.541	24.6	(0.281 – 0.801)	0.539 (0.318 – 0.866)
<b>Random Effects</b>				
IIV-CL/F (CV)	0.271	6.18	(0.236 – 0.302)	0.270 (0.223 – 0.311)
IIV-k <sub>tr</sub> (CV)	0.482	2.91	(0.453 – 0.508)	0.488 (0.400 – 0.577)
IIV-V <sub>c</sub> /F (CV)	0.230	9.77	(0.180 – 0.270)	0.229 (0.173 – 0.279)
<b>Error Model</b>				
$\sigma_1$ proportional - venous	0.0644	2.82	(0.0573 – 0.0715)	0.0637 (0.06 – 0.071)
$\sigma_2$ proportional – capillary	0.112	7.14	(0.0809 – 0.143)	0.109 (0.08 – 0.151)

RSE- Relative standard error; Age50 – age to reach 50% of the maximum. Source: Population PK report; Module 5.3.3.5

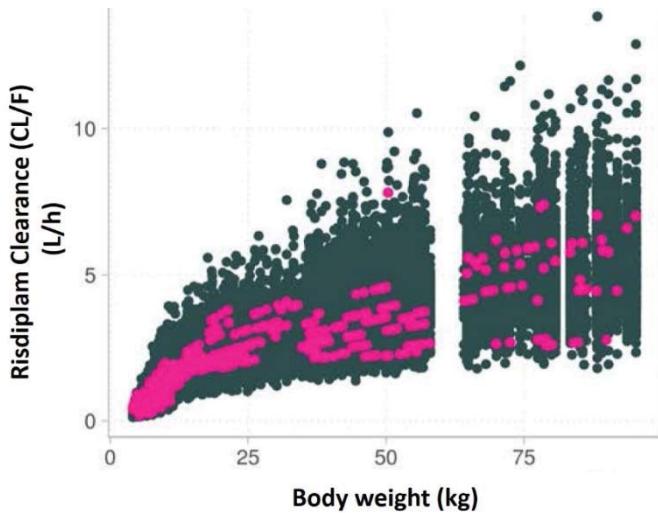
**Figure 7. Goodness-of-fit of the final PK model for risdiplam**



PRED: Population predicted plasma concentrations (ng/ml); IPRED: Individual predicted plasma concentrations (ng/ml); CWRES: Conditional weighted residuals; TAFD: Time after the first dose. Source: Population PK Report; Module 5.3.3.5

The goodness-of-fit plots suggest that the model describes the data reasonably well (Figure 7). As the clearance of risdiplam increases with body weight up to 20 kg, and thereafter the clearance reaches plateau (Figure 8). Therefore, weight-based dosing was studied in subjects who are  $\leq$  2 years and subjects who are  $>$  2 years but  $\leq$  20 kg. Subjects who were  $>$  2 years and  $>$  20 kg were studied with the fixed dose, 5 mg. The model predicted PK parameters for risdiplam are shown in (Table 13).

**Figure 8. Relationship between body weight and risdiplam clearance**



Source: Population PK/PD report; Module 5.3.3.5

**Table 13. Model predicted PK parameters for risdiplam at steady state in patients with SMA**

Study	Dose	N	Age (years)	AUC <sub>0-24h</sub> (ng/ml*h)	C <sub>max</sub> (ng/ml)
<b>BP39054 (JEWELFISH)</b>	5 mg	12	21 [14-53]	1440 [1800-2170]	73.3 [42.4-111]
<b>BP39055 (SUNFISH)</b>	0.25 mg/kg	28	4.8 [3.2-11]	2286 [1660-3100]	178 [122-258]
	5 mg	89	12.8 [4.9-26.4]	1943 [830-3700]	134 [65-290]
<b>BP39056 (FIREFISH)</b>	0.08 mg/kg	4	0.54 [0.45-1.4]	1060 [646-1540]	60 [37.6-81.6]
	0.2 mg/kg	53	1.1 [0.37-2.1]	1930 [1100-3700]	117 [77.8-200]
	0.25 mg/kg	5	2.6 [2.1-2.7]	1770 [1280-2140]	114 [87.8-133]

Values in Age indicate median (range) and those in PK parameters indicate mean (range). Steady state values were estimated using data from subjects who received risdiplam treatment over at least 4 weeks or greater.

Source: Population PK/PD report; Module 5.3.3.5

*Reviewer's comments:* The reviewer was able to verify the Applicant's analyses and replicate the results. The results suggest that the two compartment PK model with three absorption compartments and first order elimination adequately describes the PK of risdiplam. Because the dataset contains infants, adolescents and adults with varying age and body weights, the time varying covariates, age and body weight were included in the model. No other covariates were included in the model either due to lack of their effects on the PK of risdiplam or high conditional number ( $>1000$ ) and variability (75%). The proposed doses, 0.2 mg/kg once daily for subjects who are  $\leq 2$  years, 0.25 mg/kg once daily for subjects who are  $> 2$  years but  $< 20$  kg and 5 mg once daily for subjects who are  $> 2$  years and  $> 20$  kg achieved an average AUC<sub>0-24h</sub>  $\leq 2000$  ng/ml\*h in patients with SMA and are acceptable.

#### 4.4 Physiologically-based Pharmacokinetic Analysis

##### Executive Summary

The aim of this review is to evaluate the adequacy of physiologically-based pharmacokinetic (PBPK) modeling to predict the drug-drug interaction (DDI) potential of risdiplam as a CYP3A4 perpetrator in pediatric populations (aged 2 months to 18 years-old).

The Division of Pharmacometrics has reviewed the PBPK report, supporting modeling files, and response to information request to conclude the following:

- PBPK simulations showed a comparable DDI effect of risdiplam on the sensitive CYP3A substrate midazolam in pediatrics as observed in adults.
- There is low potential for a clinically relevant interaction (assumed as > 2-fold increase in AUC) between risdiplam and a sensitive CYP3A4 substrate, in any of the age groups of SMA patients.

## **Background**

Risdiplam PK was approximately linear following single dose administration of oral solution (0.6-18 mg) in healthy subjects [Study BP29840], and multiple dose (0.02 - 0.25 mg/kg and 3-5 mg) in SMA patients. Body weight and age have significant effect on risdiplam PK. Food did not appear to affect the PK of risdiplam oral solution. [BP29840-part 2, Report 1073057].

Risdiplam is a substrate for both CYP3A4 and FMO clearance pathways, based on *in vitro* assay using human liver, kidney and intestinal microsomes and recombinantly expressed CYP and FMO enzymes [Report 1066973]. Clinically, the strong CYP3A inhibitor itraconazole (200 mg BID) did not significantly change the PK of risdiplam (6 mg SD). The geometric mean ratios (90%CI) of risdiplam in the presence of itraconazole were 1.11 (1.03, 1.19) and 0.91 (0.84, 0.98) for AUC<sub>0-120h</sub> and Cmax, respectively [BP29840-part 3].

*In vitro*, risdiplam and its major circulating metabolite M1 (RO7112063, corresponding to approximately 30% of parent plasma exposure) are time-dependent inhibitors (TDI) of CYP3A4. The CYP3A4 interactions parameters for risdiplam, Ki (concentration causing half- maximal inhibition; competitive inhibition), KI (concentration causing half- maximal inactivation) and Kinact (maximum rate of enzyme inactivation) were 6.2 µM (predicted fumic=0.95), 13 µM (predicted fumic=0.82) and 3.9 h-1, respectively [Report 1090549]. For M1, the KI and Kinact values were 13.7 µM (predicted fumic=0.95) and 3.8 h-1, respectively [Report 1077033]. *In vitro* risdiplam and M1 did not show induction potential towards CYP enzymes, including CYP3A4 [Report 1090966].

Clinically, a Phase 1 study [BP41361] was conducted in a healthy adult population to evaluate the effect of multiple doses of risdiplam (8 mg QD for 14 days) on the PK of midazolam (2 mg SD on Day 13). The geometric mean ratios (90%CI) of midazolam in the presence of risdiplam were 1.08 (0.93, 1.26), 1.11 (1.02, 1.20), and 1.16 (1.06, 1.28) for AUCinf, AUClast and Cmax, respectively.

The Applicant's proposed label stated "*EVRYSDI is a weak inhibitor of CYP3A. In healthy adult subjects, administration of EVRYSDI once daily for 2 weeks slightly increased the exposure of midazolam, a sensitive CYP3A substrate (AUC 11%; Cmax 16%). Based on physiologically*

based pharmacokinetic (PBPK) modelling a similar [REDACTED] (b) (4) is expected in children and infants as young as 2 months [REDACTED] (b) (4) (Section 12.3, Drug Interaction).

The aim of this review is to assess the adequacy of the Applicant's PBPK analysis to support risdiplam drug interaction potential in pediatrics.

## Methods

The PBPK analyses were performed using the population-based PBPK [REDACTED] (b) (4) Predictions of plasma concentration-time profiles and drug-drug interactions were conducted using the software's default [REDACTED] (b) (4) Simulator' was used for prediction in pediatric subjects aged 2 months to 18 years-old.

The PBPK model of risdiplam was developed based on physicochemical properties, *in vitro*, and clinical PK data. Key model parameters are described as follows. The absorption of risdiplam following oral solution was described using the ADAM (Advanced Dissolution Absorption and Metabolism) model and *in vitro* permeability data ( $LLC\text{-}PK_1=20.4 \times 10^{-6}$  cm/s) [Report 1065753]. The fraction absorbed ( $fa$ ) was predicted to be 0.94. The unbound fraction in enterocytes ( $f_{\text{gut}}$ ) was assumed to be 1. A full PBPK model with an adjusted  $K_p$  scalar of 2.8-fold (based on tissue distribution in cynomolgus monkey [Report 1065261] and Rodgers equation) was used to estimate the volume of distribution at steady-state ( $V_{\text{ss}}=4.1$  L/kg). The predicted low  $V_{\text{ss}}$  agrees with the apparent volume of distribution value ( $V_z/F$ ) of 5.5 L/kg observed in healthy adults and the  $V_1/F$  of 42 L for a 14.9 kg SMA patient, estimated from population PK (PPK) analysis. The unbound fraction of risdiplam in plasma ( $f_{\text{up}}$ ) is 0.89, and albumin is the main plasma binding protein [Report 1066030]. There was no age-dependency of risdiplam plasma protein binding [Report 1077760]. The blood-plasma partitioning ratio of risdiplam is 1.3 [Report 1066030].

The renal clearance (Cl<sub>r</sub>) of 0.33 L/h, which corresponds to 5% of total oral clearance was assigned based on the observed value following risdiplam SAD study BP29840 [Report 1073057]. Following 18 mg SD, 7.7% unchanged risdiplam was eliminated in urine [Study BP39122, Report 1078092]. The contribution of hepatic CYP3A4 metabolism (fmCYP3A4) was assigned to be 0.2 based on the clinical DDI with itraconazole [BP29840-part 3]. Sensitivity analysis of the fmCYP3A4 value (range 0.2-0.95) was performed to verify the assumption. The remaining of risdiplam metabolic clearance was assigned to hepatic metabolism via FMO3 enzyme. The intrinsic clearance (Cl<sub>int</sub>) values for CYP3A4 and FMO3 were calculated using the retrograde method. The CL/F value of 5.5 L/h, observed with risdiplam SAD PK in healthy adults, was used. The calculated Cl<sub>int</sub> values for CYP3A4 and FMO3 were 0.018 μl/min/pmol and 0.364 μl/min/pmol, respectively (The Applicant assigned FMO intrinsic clearance under CYP2J2 in the software (V18) while incorporating FMO abundance of 27 pmol/mg protein in the

liver). Refer to section Q3 (Reviewer's comment) for discussion of the relevance of enzyme-based clearance in the current PBPK analysis.

#### *Pediatric PBPK model*

The PBPK model of risdiplam in healthy adults was used to predict PK in adult and pediatric SMA populations. The apparent oral clearance (CL/F), based on empirical Bayesian estimates (EBE) in adolescent and adult SMA patients, was approximately 30-35% lower than in healthy subjects. In order to recover the lower CL/F in the SMA population, the Applicant used a 35% lower total clearance of risdiplam. This was achieved by reducing the CYP3A4 and FMO3 intrinsic clearances, and the renal clearance by 35%. The CLint values for CYP3A4 and FMO3 were 0.0133  $\mu\text{l}/\text{min}/\text{pmol}$  and 0.27  $\mu\text{l}/\text{min}/\text{pmol}$ , respectively, in the SMA population. The renal clearance was assumed to be 0.244 L/h. The median CL/F in SMA patients aged 12 to 18 years-old was predicted to 3 L/h compared to the EBE estimate of 2.9 L/h.

Subsequently, the PBPK model of risdiplam was extended to pediatric SMA patients younger than 12 years-old. Scaling relationship between age, height and body weight were refined in default population to capture the demographic of pediatric SMA patients in the clinical trials. Different CYP3A4 and FMO3 ontogenies were also explored to describe the relationship between CL/F and age. The default ontogenies<sup>4,5</sup> for those hepatic enzymes overestimated risdiplam exposure in pediatrics. In the other hand, the maturation function for CYP3A according to Upreti and Wahlstrom<sup>6</sup> showed overall good agreement with the observed CL/F of risdiplam in pediatrics. Based on this observation, the Applicant chose to use this maturation function for hepatic CYP3A4 in the risdiplam PBPK model in pediatrics. For intestinal CYP3A, the software's default ontogeny, according to Johnson et al<sup>7</sup>, was used.

Figure 9 illustrates the different maturation functions for CYP3A4 evaluated in the current PBPK analysis: "Upreti function"<sup>6</sup> and "Salem function"<sup>4</sup> (default Simcyp V18) for hepatic CYP3A4; and "Johnson function"<sup>4</sup> (default Simcyp V18) for intestinal CYP3A4.

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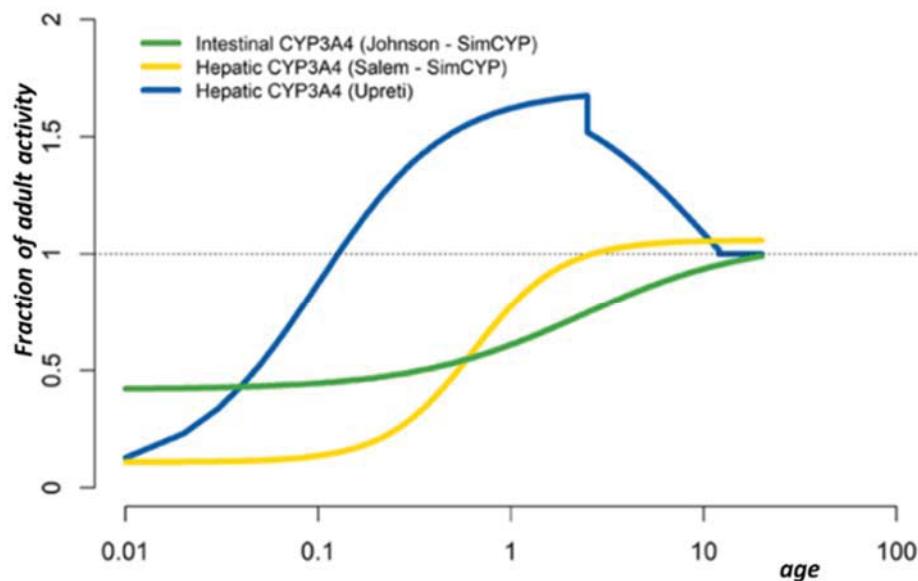
<sup>4</sup> Salem F, Johnson TN, Abduljalil K, et al. A re-evaluation and validation of ontogeny functions for cytochrome P450 1A2 and 3A4 based on in vivo data. Clin Pharmacokinet 2014; 53:625-636.

<sup>5</sup> Xu, M et al. Genetic and nongenetic factors associated with protein abundance of flavin-containing monooxygenase 3 in human liver. J Pharmacol Exp Ther 2017; 363: 265-274.

<sup>6</sup> Upreti VV and Wahlstrom JL. Meta-analysis of hepatic cytochrome P450 ontogeny to underwrite the prediction of pediatric pharmacokinetics using physiologically based pharmacokinetic modeling. J Clin Pharmacol 2016; 56:266-283.

<sup>7</sup> Johnson TN, Tanner MS, Taylor CJ, et al. Enterocytic CYP3A4 in a paediatric population: developmental changes and the effect of coeliac disease and cystic fibrosis. Br J Clin Pharmacol 2001; 51:451-460.

**Figure 9. Comparison of ontogeny models for CYP3A4 enzyme**



(Source: Report 1101345, Figure 1)

Sensitivity analysis (SA) was performed on the maturation functions for hepatic and intestinal CYP3A4 concerning CYP3A-mediated DDI risk assessment in pediatrics (refer to Q4 section). Pediatric PBPK model for risdiplam were verified by comparing the predicted and observed PK data of risdiplam in patients from 2 months to 18 years-old, as reported in Studies BP39055 and BP39056.

*Reviewer's comment: The reviewer notes the aim of the current PBPK analysis was to extend the CYP3A-mediated DDI risk observed in adults to pediatrics, rather than to address the information gap about ontogeny of CYP3A. Nonetheless, the SA proposed by the Applicant will consider the multiple ontogeny functions, based on current knowledge, to cover possible scenarios while focusing on DDI risk in pediatrics.*

#### CYP3A4 DDI parameters

The *in vitro* CYP3A4 TDI parameters of risdiplam ( $\text{kinact} = 3.9 \text{ h}^{-1}$ ,  $\text{KI} = 13 \mu\text{M}$ ,  $\text{fumic} = 0.82$ ) were optimized based on the clinical DDI effect on midazolam (Study BP41361). Using SA, the  $\text{kinact}$  value was reduced 18-fold from the *in vitro* value ( $1/18^{\text{th}}$  of  $3.9 = 0.217 \text{ h}^{-1}$ ) to recover the observed midazolam AUC ratio (refer to Q2 section). In the current DDI risk assessment, CYP3A4 TDI parameters of the metabolite M1 were not included in the PBPK model. It is assumed that the effect of M1 on CYP3A inactivation was accounted for in the optimization of the  $\text{kinact}$  value. Further SA on the  $\text{kinact}$  value was conducted as part of the DDI risk assessment in pediatrics (refer to section Q4).

*Reviewer's comment: The Applicant assumed that the clinical CYP3A inhibition observed in adults is a combined effect of both parent and M1 metabolite. This assumption would be reasonable for DDI risk in pediatrics if the relative exposure of M1 metabolite to parent (MP ratio) in plasma is similar between adults and pediatrics. Indeed, the median MP ratio in SMA patients (aged 2 months to 25 years-old from Studies BP39055 and BP39056) was approximately 30% with no apparent age dependency (Investigator Brochure, V6). The median MP ratio in neonates (2m -<7m) was around 26% (Reviewer's analysis). These values are in line with the M1 to parent data reported in the ADME study (Report 1076764).*

### **Model application**

The pediatric PBPK model of risdiplam was applied to predict the CYP3A4 inhibitory effect of risdiplam on midazolam in pediatrics. The default midazolam PBPK model ("Sim-Midazolam", V18) from the software's library was used for simulations. A virtual population of 1806 subjects aged between 2 months to 18 years was simulated. The youngest patients of the risdiplam PK data set available was 2 months-old.

The following study design was implemented in the DDI simulations:

- Midazolam: 0.1 mg/kg before and 13 days after initiation of the risdiplam treatment. On Day 13, midazolam was given 1h after administration of risdiplam.
- Risdiplam: the following dosing algorithm according to Part 2 of Studies BP39055 and BP39056 was applied for 14 days.
  - (1) 0.2 mg/kg QD for infants younger than 2 years old;
  - (2) 0.25 mg/kg QD for children 2 years or older and body weight of 20 kg or less;
  - (3) 5 mg for children older than 2 years old and body weight of more than 20 kg.

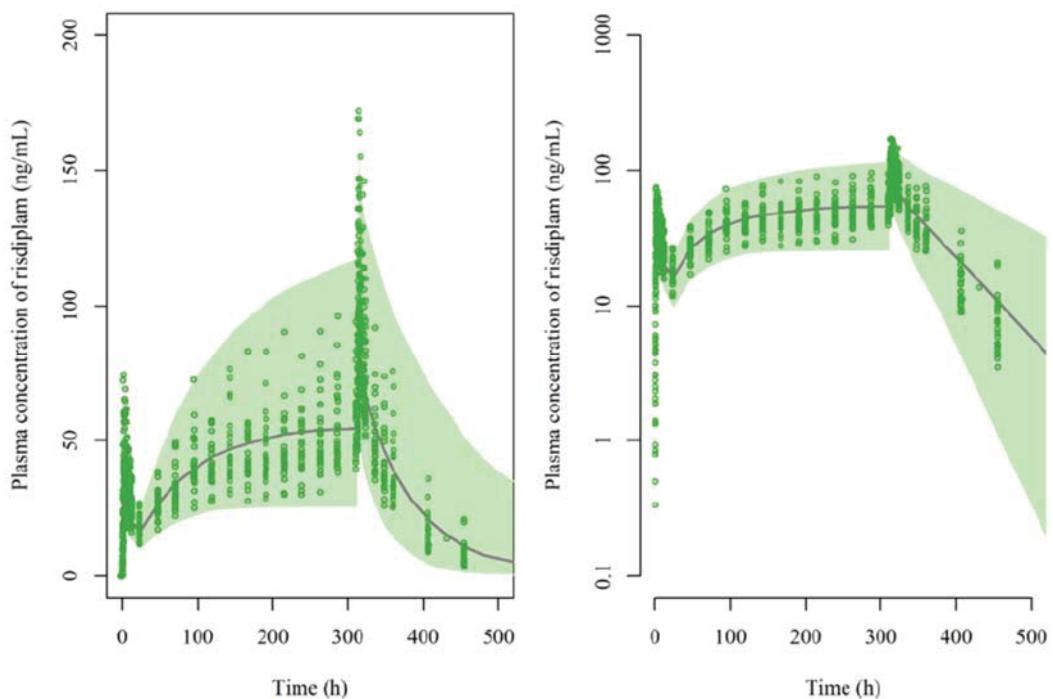
Simulations were performed for 400 individuals for treatment groups (1) or (2); and 1000 individuals for treatment group (3), to produce an even distribution of number of individuals for each age group.

### **Results**

#### **Q1. Can PBPK analysis provide a reasonable description of the PK of risdiplam in adult healthy population?**

There was a reasonable agreement between PBPK predicted and observed PK profile of risdiplam 8 mg QD for 14 days in healthy adults [Study BP41361], as shown in Figure 10 and Table 14.

**Figure 10. PBPK Predicted and observed PK profiles of risdiplam in healthy adults**



PBPK predicted median (solid lines), observed (circles-individual data- Study BP41361) and 90% prediction interval (shaded area) of plasma concentration-time profiles of risdiplam following 8 mg QD for 14 days. (Source: Report 1101345, Figure 2).

**Table 14. PBPK predicted and observed Cmax and AUC values of risdiplam in healthy adults**

PK Parameter	Observed	Predicted
Cmax (ng/mL)	113 (21.5%)	102 (36%)
AUCTau (ng.h/mL)	1730 (21.3%)	1790 (45%)

PK data are geometric means (%CV). Observed: Study BP41361. (Source: Report 1101345, Table 2).

## Q2. Can PBPK analysis predict the effect of risdiplam CYP3A4 inhibition on a sensitive CYP3A4 substrate in adults?

The Applicant's risdiplam PBPK model can predict the interaction effect of risdiplam on a sensitive CYP3A4 substrate such as midazolam.

Prospective PBPK simulations using *in vitro* CYP3A4 TDI parameters overestimated the *in vivo* inhibition potency of risdiplam on a sensitive CYP3A4 substrate in the adult population. The predicted increase in the AUC and Cmax of midazolam in the presence of risdiplam were 2.2- and 1.5-fold respectively, higher than those observed in the clinical DDI study BP41361 (Table 15, *in vitro* kinact).

**Table 15. PBPK predicted and observed PK of midazolam in the absence and presence of risdiplam in healthy adults**

Risdiplam model	Treatment	Cmax (ng/mL)		AUClast (ng.h/mL)		Cmax ratio		AUC ratio	
		Pred	Obs	Pred	Obs	Pred	Obs	Pred	Obs
<i>in vitro</i> kinact	Control	7.51	7.65	22.8	19.9	1.76	1.16	2.12	1.11
	+risdiplam	13.2	8.96	48.4	22.0				
<i>in vivo</i> kinact	Control	7.51	7.65	22.8	19.9	1.11	1.16	1.12	1.11
	+risdiplam	8.32	8.96	25.6	22.0				

PK data are geometric means. Observed: Study BP41361. Pred ratio: geometric mean of predicted PK ratios of midazolam (2m g SD) in the presence of risdiplam (8 mg QD, 14 days) in healthy adults, using risdiplam PBPK model in adults. (Source: Report 1101345, Tables 3 and 5).

Optimization of the CYP3A4 *in vitro* kinact value was performed by incrementally reducing it from 6- to 18-fold until predictions recovered the observed inhibitory effect of risdiplam on the PK of midazolam (Table 16).

**Table 16. Sensitivity analysis of CYP3A4 kinact value for prediction of midazolam Cmax and AUC ratios**

Scenario	MDZ Cmax Ratio*	MDZ AUC Ratio*
Observed	1.16	1.11
Predicted with <i>in vitro</i> kinact ( $3.9 \text{ h}^{-1}$ )	1.76	2.12
Predicted with 1/6 kinact ( $0.650 \text{ h}^{-1}$ )	1.22	1.26
Predicted with 1/8 kinact ( $0.488 \text{ h}^{-1}$ )	1.19	1.22
Predicted with 1/10 kinact ( $0.390 \text{ h}^{-1}$ )	1.16	1.19
Predicted with 1/12 kinact ( $0.325 \text{ h}^{-1}$ )	1.14	1.16
Predicted with 1/15 kinact ( $0.260 \text{ h}^{-1}$ )	1.12	1.14
Predicted with 1/18 kinact ( $0.217 \text{ h}^{-1}$ )	1.11	1.12

Data are presented as geometric mean of predicted midazolam ratios in the presence of risdiplam (8 mg QD, 14 days) in healthy adults, using risdiplam PBPK model in adults. (Source: Report 1101345, Table 4).

Using the optimized kinact value (*in vivo* kinact= 1/18 of the *in vitro* value), the predicted effect of risdiplam on the PK of midazolam are consistent with the observed values in adults (Table 15, *in vivo* kinact).

### Q3. Can PBPK analysis provide a reasonable description of risdiplam PK in adult and pediatric patient population?

The simulated risdiplam demographics and PK in pediatrics between 2 months and 18 years-old were comparable with reported data from Studies BP39055 and BP39056. A virtual population of subjects aged between 2 months to 18 years-old were simulated for evaluation of risdiplam PBPK model performance in pediatrics. The distribution of body weight and height showed good agreement between the virtual pediatric population and the pediatric SMA patients enrolled in the clinical trials (data not shown).

The PBPK predictions of risdiplam AUC<sub>tau</sub> after multiple dosing were consistent with the estimates derived from the PPK model, stratified by risdiplam dose (Table 17) or age (Table 18).

**Table 17. PBPK predicted and observed (PPK estimates) risdiplam AUC<sub>tau</sub> in SMA patients per dose groups**

Risdiplam Dose	AUC <sub>tau</sub> (ng.h/mL)	
	Observed	Predicted
0.2 mg/kg (SMA patients aged 2 months-2 years)	1850 [1270-3460]	2190 [1040 -4560]
0.25 mg/kg ( $\geq$ 2 years, body weight < 20 kg) or 5 mg ( $\geq$ 2 years, body weight $\geq$ 20 kg)	2080 [1200-3010]	2150 [832-5090]

Data are median [2.5<sup>th</sup>-97.5<sup>th</sup> percentiles]. Observed: Reports 1096622 and Population pharmacokinetic analyses report for risdiplam, 6th December 2019. (Source: Report 1101345, Table 6).

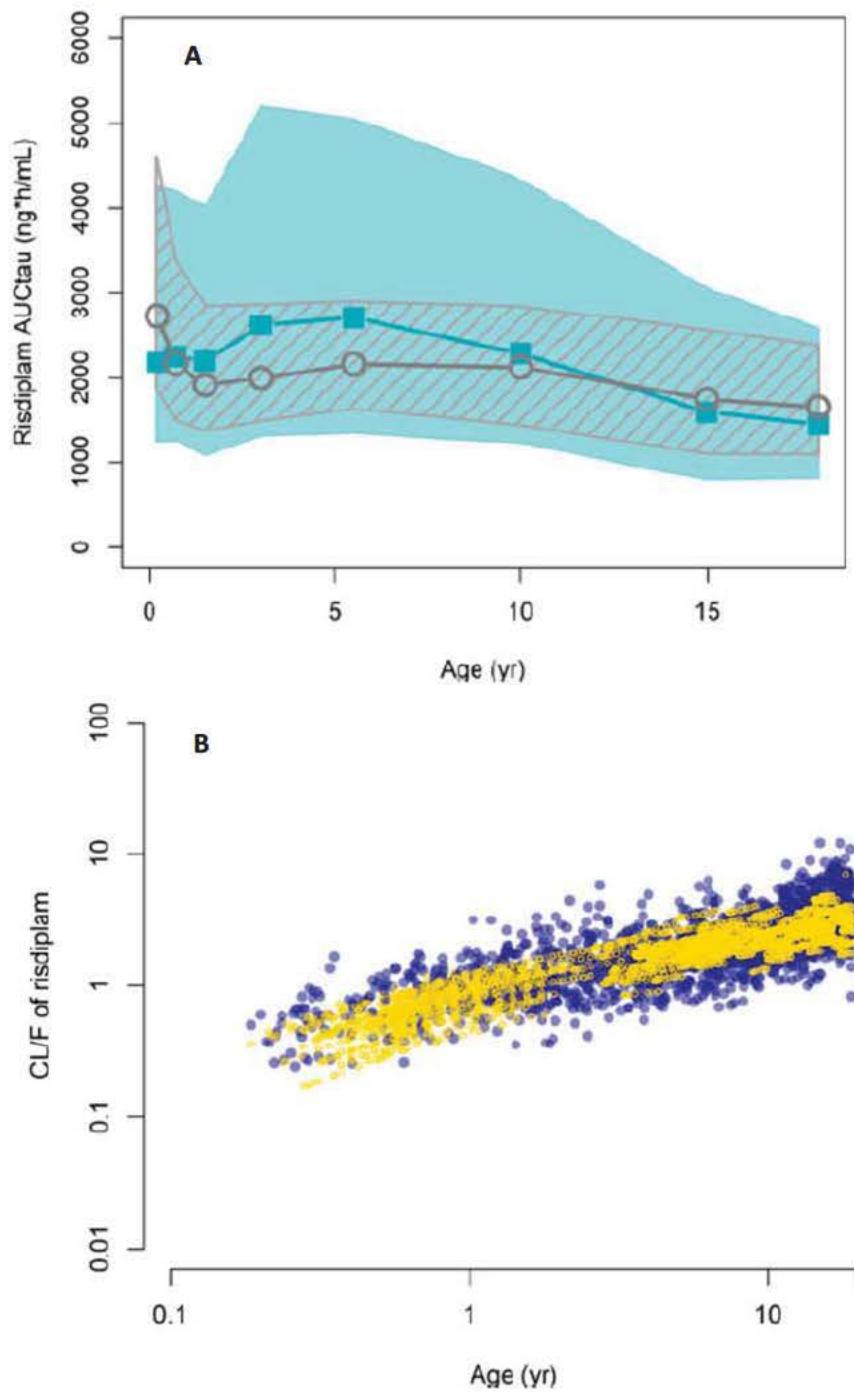
**Table 18. PBPK predicted and observed (PPK estimates) risdiplam AUC<sub>tau</sub> in SMA patients per age groups**

Age	Model	Body weight (kg) <sup>1</sup>	AUC <sub>tau</sub> (ng•h/mL) <sup>2</sup>
2m to <7m	PBPK (n=82)	6.47 [4.29 – 10.2]	2180 [1240 - 4280]
	PPK (n=34, 34 simulated values)	6.64 [4.53 – 9.1]	2730 [1870 - 4600]
7m to <1y	PBPK (n=103)	9.10 [6.49 – 13.0]	2250 [1250 - 4200]
	PPK (n=35, 35 simulated values)	7.56 [6.16 – 11.4]	2170 [1490 - 3380]
1y to <2y	PBPK (n=215)	11.7 [7.56 – 18.9]	2200 [1070 - 4020]
	PPK (n=37, 54 simulated values)	9.19 [7.72 – 12.1]	1910 [1380 - 2840]
2y to <4y	PBPK (n=252)	14.3 [10.2 – 19.8]	2620 [1310 - 5190]
	PPK (n=23, 45 simulated values)	12.3 [10.1 – 20.9]	1990 [1490 - 2860]
4y to <7y	PBPK (n=287)	18.4 [12.1 – 30.3]	2700 [1340 - 5050]
	PPK (n=58, 133 simulated values)	17.5 [10.6 – 34.0]	2160 [1630 - 2890]
7y to <12y	PBPK (n=361)	28.6 [16.1 – 52.6]	2280 [1220 - 4340]
	PPK (n=50, 123 simulated values)	28.0 [13.3 – 48.5]	2120 [1440 - 2840]
12y to <18y	PBPK (n=426)	54.1 [24.2 - 120]	1590 [791 - 3050]
	PPK (n=57, 147 simulated values)	43.7 [21.0 - 90.0]	1740 [1100 - 2560]
>18y	PBPK (n=80)	60.1 [37.0 - 123]	1440 [805 - 2590]
	PPK (n=34, 88 simulated values)	53.0 [21.9 - 102]	1650 [1090 - 2380]

<sup>1</sup>Data are observed and respectively predicted median body weight and range. <sup>2</sup>Geometric means [5<sup>th</sup>-95<sup>th</sup> percentiles] are presented. (Source: Response to PBPK IR dated 4/1/20, Table 1).

Figure 11A illustrates the comparison of the predicted AUC<sub>tau</sub> by PBPK model to the PPK estimates in the adult and pediatric SMA population, across the age groups. The PBPK predictions mostly covered the 95<sup>th</sup> percentile of the estimated AUC<sub>tau</sub> by the PPK model. The Applicant noted that the variability of PBPK predictions for AUC<sub>tau</sub> was larger compared to the PPK estimates (Figure 11A). This observation reflected the larger variability in PBPK predicted CL/F compared to PPK post-hoc estimates (Figure 11B). Nonetheless, the PBPK predictions of risdiplam CL/F in pediatrics were consistent with the post-hoc estimates of CL/F derived from the PPK model, across the age groups.

**Figure 11. PBPK predicted and observed (PPK estimates) AUCtau and CL/F of risdiplam in SMA patients by age**



(A) Data presented as geometric mean of the risdiplam AUCtau for each age category predicted by the PBPK (blue closed squares) and PPK (grey open circles). The shaded areas represent 5<sup>th</sup>-95<sup>th</sup> percentiles (Source: Response to PBPK IR dated 4/1/20, Figure 1). (B) PBPK predictions of risdiplam CL/F using the pediatric risdiplam PBPK model (blue circles) and post-hoc estimate of the PPK model (yellow circles). (Source: Report 1101345, Figure 2).

PBPK predictions of risdiplam Cmax were also compared to observed Cmax values following the final selected risdiplam dosing regimen (n=249 SMA patients). The Cmax values were stratified by the age at the corresponding time of the Cmax observation, or dose. The geometric means of predicted Cmax values was consistent with the observed values across the age groups. Also, the 5<sup>th</sup>-95<sup>th</sup> percentiles (or respectively range for the categories with n<20) of the predicted Cmax values covered most of the range of the observed values (Table 19).

**Table 19. PBPK predicted and observed risdiplam Cmax in SMA patients per age groups**

Age	Model	Body weight (kg) <sup>1</sup>	C <sub>max</sub> (ng/mL) <sup>2</sup>
2m to <7m	PBPK (n=82)	6.47 [4.29 – 10.2]	155 [107 - 246]
	Observed (n=12)	6.78 [5.16 – 8.8]	180 [37.5 - 364]*
7m to <1y	PBPK (n=103)	9.10 [6.49 – 13.0]	155 [104 - 229]
	Observed (n=34)	7.53 [6.31 – 10.8]	164 [99.1 - 256]
1y to <2y	PBPK (n=215)	11.7 [7.56 – 18.9]	149 [100 - 222]
	Observed (n=8)	8.91 [7.20 – 12.7]	176 [125 - 267]*
2y to <4y	PBPK (n=252)	14.3 [10.2 – 19.8]	172 [110 - 285]
	Observed (n=17)	12.0 [10.1 – 20.9]	166 [116-222]*
4y to <7y	PBPK (n=287)	18.4 [12.1 – 30.3]	164 [97.5 - 260]
	Observed (n=46)	18.9 [11.7 – 34.0]	167 [124 - 229]
7y to <12y	PBPK (n=361)	28.6 [16.1 – 52.6]	128 [76.8 - 211]
	Observed (n=45)	29.0 [13.3 – 45.4]	142 [79.4 - 234]
12y to <18y	PBPK (n=426)	54.1 [24.2 - 120]	84.0 [48.3 - 148]
	Observed (n=49)	43.5 [22.6 – 83.1]	110 [75.3 - 170]
>18y	PBPK (n=80)	60.1 [37.0 - 123]	75.4 [44.6 - 124]
	Observed (n=38)	52.3 [21.9 - 102]	102 [45.8 - 172]

<sup>1</sup>Data are observed and respectively predicted median body weight and range. <sup>2</sup>Geometric mean [5<sup>th</sup>-95<sup>th</sup> percentiles] are presented, except for the observations of 2m-7m, 1y-2y and 2y-4y where n<20. \* Geometric mean and observed range due to small sample size. (Source: Response to PBPK IR dated 4/1/20, Table 2).

Likewise, the geometric means of predicted Cmax values were consistent with the observed values across the risdiplam dose groups (0.2 mg/kg, 0.25 mg/kg, and 5 mg) with PE ranging from -16% to 2.4% (Table 20).

**Table 20. Cmax between PBPK predicted and observed in SMA patients per dose groups**

Risdiplam Dose	Cmax (ng/mL)	
	Observed	Predicted
0.2 mg/kg (patients aged 2 months-2 years)	169 [89.7 - 304]	152 [101 - 230]
0.25 mg/kg ( $\geq$ 2 years, body weight < 20 kg)	167 [121 - 207]	171 [108 - 273]
5 mg ( $\geq$ 2 years, body weight $\geq$ 20 kg)	120 [67.6 - 208]	101 [51.0 - 196]

Data are geometric means [5<sup>th</sup>- 95<sup>th</sup> percentiles]. Observed: Reports 1096622 and Population PK Analyses Report 6th December 2019. (Source: Response to PBPK IR dated 4/1/20, Table 3).

Overall, the pediatric PBPK model of risdiplam was able to predict risdiplam exposure (AUC<sub>tau</sub> and Cmax) in SMA patients across all age groups, at the therapeutic dose levels. The pediatric PBPK model could fairly predict risdiplam exposure in infants (2m-7m and 7m-<1y) and

toddlers (1y-<2y) compared to observed values (or PPK estimates); even though the PK data in such population was limited.

*Reviewer's comments: The PBPK model of risdiplam for the adult and pediatric populations considered the enzyme kinetics for CYP3A4 and FMO3. The assumption of the relative contribution of each pathway ( $f_m$ ) to the total clearance of risdiplam in adults and pediatrics was not the focus of this review. Given that the current PBPK analysis aimed to address risdiplam as a perpetrator of CYP3A-mediated interaction in pediatrics, the ability of the pediatric PBPK model to predict risdiplam total clearance and exposure, across the age groups at the therapeutic dose levels, was the goal.*

#### **Q4. Can PBPK analysis predict the effect of risdiplam CYP3A4 inhibition on a sensitive CYP3A4 substrate in pediatrics?**

The pediatric PBPK model of risdiplam can be used to simulate the effect of risdiplam on the PK of a sensitive CYP3A4 substrate in pediatrics (down to 2 months-old). The CYP3A inhibitory effect of risdiplam on midazolam PK was simulated using an optimized CYP3A4 inhibition parameter (*in vivo*  $k_{inact}$ = 1/18 of the *in vitro* value, refer to section Q2).

The changes in midazolam AUC and Cmax predicted by PBPK simulations, stratified by age and risdiplam dose are listed in Table 21 and Table 22 , respectively.

The geometric mean AUC and Cmax ratios of midazolam remained constant across the age groups (2 months – 18 years), ranging between 1.09 to 1.18 and 1.08 to 1.16, respectively. The 95<sup>th</sup> percentiles of the AUC ratio were below 1.4 across the age groups. (Table 21). The geometric mean AUC and Cmax ratios of midazolam for each dose according to the proposed label ranged from 1.12 to 1.18, and 1.10 to 1.15, respectively (Table 22).

**Table 21. Predicted midazolam AUC and Cmax ratios in the presence of risdiplam per age groups**

Age	AUC ratio	C <sub>max</sub> ratio
2m to <7m (n=82)	1.16 [1.07 – 1.29]	1.14 [1.05 – 1.26]
7m to <1y (n=103)	1.15 [1.08 – 1.26]	1.13 [1.06 – 1.22]
1y to <2y (n=215)	1.15 [1.06 – 1.26]	1.13 [1.06 – 1.24]
2y to <4y (n=252)	1.18 [1.08 – 1.35]	1.16 [1.07 – 1.30]
4y to <7y (n=287)	1.17 [1.07 – 1.33]	1.15 [1.06 – 1.28]
7y to <12y (n=361)	1.14 [1.06 – 1.28]	1.12 [1.05 – 1.24]
12y to <18y (n=426)	1.10 [1.04 – 1.20]	1.09 [1.04 – 1.17]
>18y (n=80)	1.09 [1.04 – 1.17]	1.08 [1.03 – 1.15]

Data are geometric means [5<sup>th</sup>-95<sup>th</sup> percentiles]. (Source: Response to PBPK IR dated 4/1/20, Table 4).

**Table 22. Predicted midazolam AUC and Cmax ratios in the presence of risdiplam per dose groups**

Risdiplam dose	n	MDZ AUC ratio	MDZ Cmax ratio
0.2 mg/kg (patients aged 2 months-2 years)	400	1.15 [1.07 – 1.28]	1.13 [1.06 – 1.24]
0.25 mg/kg ( $\geq$ 2 years, body weight < 20 kg)	485	1.18 [1.08 – 1.35]	1.15 [1.07 – 1.29]
5 mg ( $\geq$ 2 years, body weight $\geq$ 20 kg)	921	1.12 [1.05 – 1.25]	1.10 [1.04 – 1.21]

Data are geometric means [5<sup>th</sup>-95<sup>th</sup> percentiles]. (Source: Response to PBPK IR dated 4/1/20, Table 5).

The predicted increase in midazolam AUC in pediatrics, aged 2 months to 18 years, was comparable to the effect observed in healthy adults (midazolam AUC increased by 11% following risdiplam 8 mg QD [Study BP41361]).

Applicant's PBPK analysis predicted a reduction of CYP3A4 activity by 3% and 20% in the liver and small intestine, respectively, following risdiplam dosing in the pediatric population. The results suggest that the hepatic CYP3A clearance for midazolam will be less impacted, and the inhibition effect of risdiplam would be on intestinal CYP3A clearance rather than hepatic clearance.

#### *Sensitivity Analysis*

The Applicant conducted a comprehensive sensitivity analysis to investigate the impact of the uncertainties related to CYP3A TDI parameters and ontogeny profile on the assessment of DDI risk in pediatrics.

For the CYP3A TDI parameter, a range of kinact value, which were tried against the observed AUC and Cmax ratios of midazolam following risdiplam dosing in adults (refer to section Q2), were examined. For ontogeny of CYP3A, combinations of maturation functions for CYP3A4 were examined as aged-related changes in fractional metabolic elimination pathways may affect metabolic DDIs. The summary results of the sensitivity analyses of different maturation functions for hepatic and intestinal CYP3A and kinact values are presented in Table 23.

For hepatic CYP3A ontogeny, the Applicant applied the Upreti function in the pediatric model of risdiplam. This function predicts a higher CYP3A activity in children than Salem function (see Figure 9 in Methods section), leading to a higher susceptibility to hepatic CYP3A4 inhibition. SA results showed that the predicted increase in midazolam AUC using the Salem function for the hepatic CYP3A ontogeny was identical to the prediction using the Upreti function (see results of simulations #1 vs. #2, and #3 vs. #4). This observation is in line with the minimal inhibition effect on CYP3A predicted for the liver.

For intestinal CYP3A ontogeny, the Johnson function (used in the Applicant's pediatric model) resulted in a consistent Fg (=0.6) of midazolam between pediatrics and adults (see Figure 12). The Applicant explored the assumption of full maturity of CYP3A activity from birth. This function would result in higher intestinal CYP3A metabolism and higher intestinal extraction

(lower Fg) of midazolam in pediatrics (especially in children younger than 5 years) than predicted by the Johnson function. Thus, it would represent a more conservative assessment of intestinal CYP3A inhibitory risk. Although this scenario had higher susceptibility to intestinal CYP3A inhibition, the predicted increase in midazolam AUC was comparable with the prediction using the Johnson function (see results of simulations #1 vs. #5, and #4 vs. #6). Of note, the risdiplam PBPK model assumed unbound fraction in enterocytes (fugut) to be 1, which would lead to a conservative estimation for intestinal inhibition by risdiplam.

Lastly, simulations considering a combination of the more conservative scenarios: a CYP3A kinact value of 1/10 of the *in vitro* data (recovered the observed Cmax ratio of midazolam but overpredicted AUC ratio, refer to section Q2) and full maturity from birth for intestinal CYP3A activity (simulation #6), predicted an increase in midazolam AUC up to 1.32-fold, with a 95<sup>th</sup> percentile below 1.7-fold, across the pediatric age groups.

Overall, the PBPK analysis suggested a clinically relevant interaction (assumed as > 2-fold increase in exposure) between risdiplam and a sensitive CYP3A substrate is unlikely in any of the age groups of SMA patients.

**Table 23. Summary of the sensitivity analysis results**

Simulation	Hepatic CYP3A ontogeny	Intestinal CYP3A ontogeny	<i>In vivo</i> kinact	Outcome
				*Predicted MDZ AUC ratio
1	Upreti <sup>#</sup>	Johnson <sup>#</sup>	1/18	1.08 – 1.18 across the age groups 95 <sup>th</sup> percentile is < 1.4 <sup>#</sup>
2	Salem <sup>&amp;</sup>	Johnson	1/18	1.08 – 1.19 across the age groups 95 <sup>th</sup> percentile is < 1.4
3	Salem <sup>&amp;</sup>	Johnson	1/10	1.13 – 1.28 across the age groups 95 <sup>th</sup> percentile is < 1.6
4	Upreti	Johnson	1/10	1.13 – 1.28 across the age groups 95 <sup>th</sup> percentile is < 1.6
5	Upreti	full maturity from birth	1/18	1.08 – 1.21 across the age groups 95 <sup>th</sup> percentile is < 1.4
6	Upreti	full maturity from birth	1/10	1.13 – 1.32 across the age groups 95 <sup>th</sup> percentile is < 1.7

\*Geometric means. <sup>#</sup>Simulations using the pediatric PBPK model of risdiplam (results on Tables 8 and 9). <sup>&</sup>To maintain risdiplam exposure, the hepatic metabolism of risdiplam (CYP3A4 and FMO3) were all assigned to FMO3 enzyme (which is modeled with Upreti function). (Source: Report 1101345, Table 7).

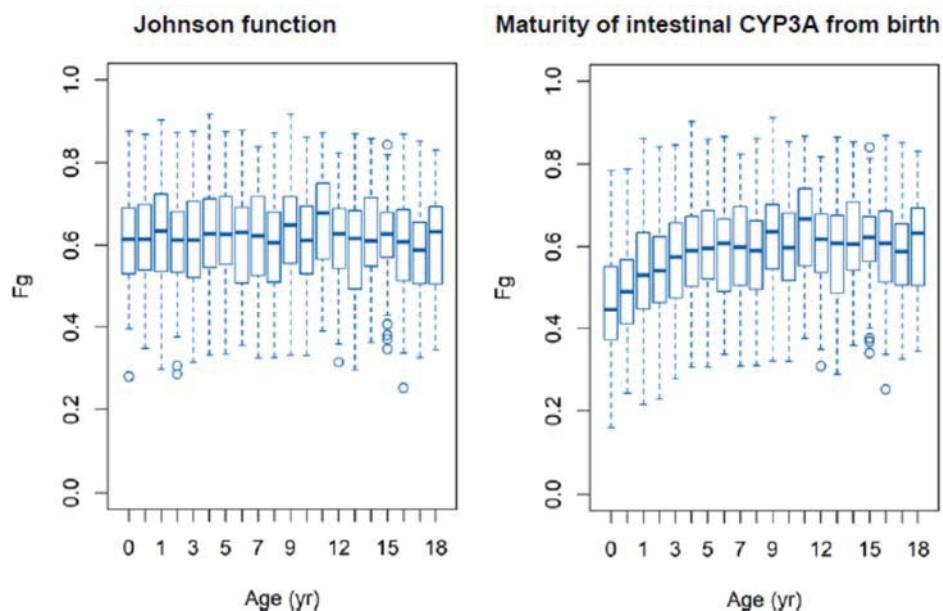
Of note, the Applicant acknowledges literature data<sup>8,9</sup> showing higher estimates of midazolam Fg in pediatrics than reported for adults and predicted by the Johnson function (Fg= 0.6). This observation suggested a reduced intestinal CYP3A activity in pediatrics than this function

<sup>8</sup> Brussee JM, Yu H, Krekels EHJ, et al. First-pass CYP3A-mediated metabolism of midazolam in the gut wall and liver in preterm neonates. CPT Pharmacometrics Syst Pharmacol. 2018; 7:374-383.

<sup>9</sup> Brussee JM, Yu H, Krekels EHJ, et al. Characterization of intestinal and hepatic cyp3a-mediated metabolism of midazolam in children using a physiological population pharmacokinetic modelling approach. Pharm Res. 2018; 35:182.

estimates. The Applicant noted the assumption of full maturity at birth would represent a highly conservative scenario based on the current knowledge of intestinal CYP3A ontogeny.

**Figure 12. Midazolam intestinal extraction (Fg) by age, using different maturation functions for intestinal CYP3A**



PBPK predicted individual Fg of midazolam using Johnson function or assumption of maturity from birth, summarized by age, are shown. (Source: Report 1101345, Appendix 5- Figure 1).

*Reviewer's comments:* The Reviewer acknowledges the existence of knowledge gaps, such as enzymes maturation, which may limit the characterization of ADME properties and applications of PBPK in pediatrics<sup>10</sup>. In the case of risdiplam, the pediatric PBPK model provided reasonable estimates of risdiplam exposures (AU<sub>Ctau</sub> and Cmax) compared to those observed (or PPK estimates) in SMA patients across all age groups. The sensitivity analysis and midazolam fg scenarios described above addressed some degree of uncertainties while focusing on DDI risk evaluation. Thus, this PBPK analysis can be used to evaluate CYP3A mediated DDI potential of risdiplam in pediatrics in conjunction with other clinical evidences. Given the PBPK simulations showed a comparable DDI effect on midazolam in pediatrics and adults, the review team did not include the language proposed by the applicant related to DDI between risdiplam and the CYP3A substrate midazolam in the pediatric population in Section 12.3 of the label.

<sup>10</sup> Verschaeijden LFM., Koenderink JB, Johnson TN, et al., Physiologically-based pharmacokinetic models for children: Starting to reach maturation? *Pharmacology & Therapeutics*.2020. <https://doi.org/10.1016/j.pharmthera.2020.107541>.

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