20 July 2023
EMA/CHMP/391797/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Evrysdi

International non-proprietary name: risdiplam

Procedure No. EMEA/H/C/005145/II/0005/G

Note

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

Table of contents

List of abbreviations

AAV	Adeno-Associated Virus
ADR	Adverse Drug Reaction
AE	Adverse Events
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area Under the concentration-time Curve
$AUC_{0\text{-}24h}$	Area Under the concentration-time Curve from time 0 to 24 hours.
BSID III	Bayley Scales of Infant and Toddler Development – Third Edition
C_{av}	average concentration over observation period
CCOD	Clinical Cutoff Date
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI(s)	Confidence Interval(s)
CL/F	Apparent Clearance
C_{max}	maximum serum concentration
CMAP	Compound Muscle Action Potential
CNS	Central Nervous System
CSR	Clinical Study Report
E_0	Fraction of risdiplam clearance at birth [$Frac_{birth}$]
ECG	Electrocardiogram
E_{max}	Maximum Effect
ERA	Environmental Risk Assessment
ETA	Individual Deviations
Fracbirth	A fraction of CL/F at birth to the maturation function of CL/F
FMO	Flavin Monooxygenase
GOF	Goodness-Of-Fit
HINE-2	Hammersmith Infant Neurological Examination, Module 2
IIV	inter-individual variability
k_{tr}	transfer constant rate
LC-MS/MS	Liquid Chromatography tandem Mass Spectrometry
MAH	Marketing Authorisation Holder
mRNA	pre-messenger ribonucleic acid
OFV	Objective Function
OLE	Open Label Extension
PAES	Post-authorisation Efficacy Study
PAM	Post Authorization Measure

PBT	Persistent and Bioaccumulative
pc-VPC	Prediction-Corrected Visual Predictive Check
PD	Pharmacodynamic(s)
PET	Preservative Efficacy Test
PK	Pharmacokinetic(s)
PIP	Paediatric Investigational Plan
PL	Packet Leaflet
popPK	Population PK
(I)PRED	(Individual) Predicted plasma concentrations
RSE	Relative Standard Error
SAE	Serious Adverse Events
SD-OCT	Spectral Domain Optical Coherence Tomography
SMA	Spinal Muscular Atrophy
SMN	Survival Motor Neuron
SmPC	Summary of Product Characteristics
SOC	System Organ Class
ULN	Upper Limit of Normal
Vc/F	apparent central volume of distribution
Vp/F	apparent peripheral volume of distribution

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 16 December 2021 an application for a group of variations.

The following variations were requested in the group:

Variations requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
B.IV.1.b	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	Type IAin	I, IIIA and IIIB
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	I, IIIA and IIIB

Grouping of three variations as follows:

Extension of indication to include treatment of patients below 2 months of age based on interim results from study BN40703 (RAINBOWFISH). The pivotal study RAINBOWFISH is an ongoing phase II multicentre, open-label, and single-arm study designed to evaluate the efficacy, safety, tolerability, and pharmacokinetics (PK)/ pharmacodynamics (PD) of risdiplam in pre-symptomatic infants below 2 months of age, who were genetically diagnosed with Spinal Muscular Atrophy (SMA). As a consequence, SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated in accordance. In addition, the MAH took the opportunity to make some editorial improvements in the product information. A revised RMP version 1.1 was also submitted as part of the application.

Type IAIN, B.IV.1.a.1 variation to update Evrysdi pack configuration with the addition of anew 1 mL oral syringe into the product carton allowing precise dosing of infants below 2 months of age. The 1 mL oral syringe is a CE-marked product provided by the same legal manufacturer as the current ones (6 mL and 12 mL syringes). As a consequence, section 6.5 of the SmPC has been updated and the labelling and Package Leaflet have been updated in accordance.

Type IAIN, B.IV.1.b variation to remove the spare unit of 12 mL oral syringe out of the two units currently provided in the product carton. As a consequence, section 6.5 of the SmPC has been updated and the labelling and Package Leaflet have been updated in accordance.

Information relating to orphan designation

Evrysdi, was designated as an orphan medicinal product EU/3/19/2145 on 26-02-2019. Evrysdi was designated as an orphan medicinal product in the following indication: Treatment of spinal muscular atrophy

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0470/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0470/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Protocol assistance

The MAH did not seek Protocol Assistance at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Bruno Sepodes Co-Rapporteur: Armando Genazzani

Timetable	Actual dates
Submission date	16 December 2021
Start of procedure:	23 January 2022
CHMP Rapporteur Assessment Report	21 March 2022
PRAC Rapporteur Assessment Report	25 March 2022
PRAC members comments	28 March 2022
CHMP Co-Rapporteur Critique	30 March 2022
Updated PRAC Rapporteur Assessment Report	31 March 2022
PRAC Outcome	7 April 2022
CHMP members comments	8 April 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 April 2022
Request for supplementary information (RSI)	22 April 2022
MAH's responses submitted to the CHMP on:	20 May 2022
CHMP Rapporteur Assessment Report	27 June 2022
PRAC Rapporteur Assessment Report	24 June 2022
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	30 June 2022
PRAC Outcome	7 July 2022
CHMP members comments	11 July 2022
Updated CHMP Rapporteur Assessment Report	15 July 2022
Request for supplementary information (RSI)	21 July 2022
MAH's responses submitted to the CHMP on:	12 August 2022
CHMP Rapporteur Assessment Report	13 September 2022
PRAC Rapporteur Assessment Report	16 September 2022
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	22 September 2022

Timetable	Actual dates
PRAC Outcome	29 September 2022
CHMP members comments	26 September 2022
Updated CHMP Rapporteur Assessment Report	07 October 2022
Request for supplementary information (RSI)	13 October 2022
MAH's responses submitted to the CHMP on:	16 May 2023
CHMP Rapporteur Assessment Report	26 June 2023
PRAC Rapporteur Assessment Report	26 June 2023
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	29 June 2023
PRAC Outcome	06 July 2023
CHMP members comments	11 July 2023
Updated CHMP Rapporteur Assessment Report	14 July 2023
CHMP opinion:	20 July 2023
The CHMP adopted a report on similarity of Evrysdi with Spinraza and Zolgensma on date (Appendix 1)	20 July 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Given the unmet medical need for alternative treatment options for this very young patient population (as described below) and the rapidly progressive nature of the disease in some patients, particularly those with two survival motor neuron 2 (SMN2) copies, the marketing authorisation holder (MAH) considers the need for an update in the indication to support the treatment of infants with SMA under 2 months of age. The MAH regards this to be a matter of urgency for patients and their families and proposes the extension of the indication to those children below 2 months of age.

Disease or condition

SMA is a monogenic neuromuscular disorder resulting in severe weakness of the limbs, trunk, bulbar and respiratory muscles secondary to the dysfunction of alpha motor neurons. SMA spectrum is highly variable; patients may experience failure to gain motor milestones and motor function, recurrent respiratory infections, swallowing difficulties, contractures, scoliosis, and reduced life expectancy.

State the claimed the therapeutic indication

This variation application provides interim results from Study BN40703 (RAINBOWFISH) in order to support the risdiplam dose determination for patients below 2 months of age.

Epidemiology

When not treated, SMA is the leading genetic cause of mortality in infants and young children with an estimated incidence of 1 in 6,000 to 1 in 10,000 live births and carrier frequency of 1 in 40□60 individuals.

Aetiology and pathogenesis

SMA is an autosomal recessive disorder secondary to loss-of-function mutations in both alleles of the SMN1 gene with subsequent loss of SMN protein expression. In humans, there are two SMN genes, the SMN1 gene and its paralog SMN2. The SMN2 pre-messenger ribonucleic acid (mRNA) undergoes alternative splicing that excludes exon 7 from 85%-90% of mature SMN2 transcripts, which produces an unstable SMNdelta7 protein that is rapidly degraded. Therefore, full length SMN2 mRNA is generated in only 10%-15% of splicing events.

SMA is characterized by the dysfunction of alpha motor neurons within the anterior horn of the spinal cord, leading to skeletal muscle weakness and atrophy.

Clinical presentation

Clinically, SMA ranges in disease severity. For classification purposes, patients are usually categorized into four main subtypes (Types 1-4) based on clinical criteria, including achieving (or failing to achieve) motor milestones, age at onset, and life span. As evidenced in a worldwide cohort report, in SMA patients with 2 *SMN2* copies, the phenotype identified corresponded to Type 1 (79% of patients), Type 2 (16%), and Type 3 (5%), while in SMA patients with 3 *SMN2* copies, the phenotype identified corresponded to Type 1 (15% of patients), Type 2 (54%), and Type 3 (31%). In SMA patients with 4 SMN2 copies, the phenotype identified corresponds to Type 3 (88%), Type 2 (11%) and Type 1 (1%). Most patients reported as Type IV presented four gene copies (21/26; 81%), 2 had five copies (8%), and one individual showed 6 SMN2 copies (4%).

Management

There is evidence to support early administration of therapy with minimal delay after diagnosis is critical to prevent motor neuron loss, ensuring better clinical outcomes such as prevention of long-term disease complications. International consensus is to offer immediate treatment for infants diagnosed with SMA via newborn screening.

For patients with SMA below 2 months of age, there are currently two approved therapies: Spinraza® (nusinersen) and Zolgensma® (onasemnogene abeparvovec). Spinraza is an SMN2-directed antisense oligonucleotide administered intrathecally, thus largely limiting the effects to the central nervous system (CNS) only. The first 3 loading doses of Spinraza are administered at 14-day intervals, followed by a 4th loading dose after 30 days and maintenance dose every 4 months thereafter. Zolgensma is a one-time intravenously administered gene-replacement therapy that uses a nonreplicating adeno-associated virus (AAV) capsid to deliver a functional copy of the SMN1 gene. High-dose, systemic corticosteroid treatment is required prior to and following Zolgensma administration.

Despite the availability of these therapies, there remains an unmet medical need for additional treatment options for patients below 2 months of age, especially when considering prompt treatment initiation. Specific factors contributing to the current unmet medical need are described below:

Required hospital setting for Zolgensma and Spinraza administration presents challenges for patients: both Zolgensma and Spinraza therapies require an in-hospital setting for treatment administration and short-term monitoring. Exposure to a hospital setting can introduce an infection risk to newborn babies. In addition, situations where external factors may prevent patients visiting health care facilities can limit therapy administration (for both therapies) and the consistent use of Spinraza. An example of an external factor is the COVID-19 pandemic and the global measures applied to ensure social isolation and changes in hospital priorities, thereby forcing physicians to postpone elective procedures such as repeat nusinersen intrathecal administration. These situations pose extra challenges for affected patients, which could be addressed by availability of risdiplam as an orally administered medication for home use.
Other logistical restrictions can arise, such as the distance to specialized centers, which may reduce the patients' ability to access Zolgensma and Spinraza. A survey of patients and caregivers in the United States found that 39 of 77 respondents (50%) had to drive more than 1 hour to receive Spinraza at their treatment center. This may pose extra challenges when travelling with a fragile newborn baby.

Zolgensma administration may be delayed in patients with elevated anti-AAV9 antibody titers or infections: In Zolgensma clinical trials, patients were required to have baseline anti-AAV9 antibody titers of δ1:50. As the safety and efficacy of Zolgensma in patients with titers above 1:50 have not been

evaluated, the Zolgensma E.U. Summary of Product Characteristics (SmPC) describes the need to perform baseline testing for the presence of anti-AAV9 antibodies prior to treatment infusion and that re-testing may be performed if titers are >1:50. The presence of anti-AAV9 IgG could limit Zolgensma' s therapeutic benefit, as it can potentially reduce transduction capacity. Data indicate that even low levels of neutralizing antibodies (1:5–1:10) can completely abrogate transduction even with high titers of vectors. An IgG to AAV9 seropositive rate of 47% has been reported in healthy volunteers. IgG antibodies cross the placental barrier and, in a small proportion, may be detected in breastmilk. Both processes are mechanisms of acquired immunity in newborn infants. Considering the half-life of passively acquired IgG antibodies (35 to 40 days), in SMA patients < 2 months of age with elevated anti-AAV9 antibody titers, repeating the test prior to Zolgensma treatment administration could considerably delay the initiation of treatment due to the time period required for the decay of this passive immunity and to re-test antibodies. In Zolgensma clinical trials, screen failures due to antibody elevations (> 1:50 of anti-AAV9 IgG) have been reported. In the SPR1NT trial, in patients aged δ6 weeks, this accounted for 2 of 14 (14.3%) patients who were tested at screening. In the event of an infection (e.g., rhinovirus infection common in infants), it is recommended that patients should wait at least 2 weeks after the illness resolves before initiating treatment with Zolgensma, because infection before or after infusion could lead to more serious complications (Zolgensma SmPC). A delay of at least 2 weeks before treatment can be started is significant for a disease where time is critical to prevent motor neuron loss.

Safety risks are associated with Zolgensma therapy and concomitant corticosteroid treatment: the Zolgensma SmPC includes special warnings and precautions for use for acute serious liver injury, acute liver failure, and elevated aminotransferases requiring intensive liver function monitoring prior to, and for at least 3 months after the infusion. In the SPR1NT study, which investigated Zolgensma use in 30 presymptomatic SMA patients aged δ6 weeks, adverse events (AEs) related to hepatotoxicity were reported for 8 of 30 (26.7%) infants (Novartis Gene Therapies website). In addition, of the 29 patients with 2 and 3 *SMN2* copies, transaminase elevations□though not reported as AEs□occurred in 10 of 14 (71%) and 9 of 15 (60%) patients, respectively.
The high-dose, systemic corticosteroid regimen required in association with Zolgensma administration can be of variable duration depending on any observed clinical or laboratory findings and may also require adjustment to the vaccination schedule. Corticosteroids may increase the risks related to infections with any pathogen (Prednisolone SmPC), and this risk may be greater for neonates who have more immature immune systems compared to older children and adults and, thus, are more vulnerable to infections. Other known risks associated with prolonged systemic corticosteroid treatment are hypertension, gastrointestinal effects, and hyperglycemia, and the risk of adrenal insufficiency may be greater in newborns.

Safety risks are associated with intrathecal route of administration of Spinraza: the intrathecal injection route of administration is relevant to the Spinraza safety profile and has been associated with AEs. In the NURTURE trial, investigating Spinraza in 25 pre-symptomatic SMA patients aged δ6 weeks, 17 AEs in 8 patients were reported to be possibly related or definitely related to the lumbar puncture procedure. This included 1 serious event of post-lumbar puncture syndrome. Five hemorrhages near the thecal space in 4 participants occurred in the setting of multiple lumbar puncture attempts; all events occurred when participants were <6 weeks old. In addition, patients who have low platelets or who have an abnormal coagulation profile may be prevented from receiving Spinraza due to risks of hemorrhage during administration and medical contraindication to lumbar puncture procedures. This example illustrates that contraindications to lumbar puncture procedures may prevent patients from receiving Spinraza, supporting the need for SMA therapies with an alternative route of administration in neonates.

In conclusion, although there are two therapies (Zolgensma and Spinraza) approved for the treatment of infants aged <2 months diagnosed with SMA, there remains an unmet medical need. The option of an oral therapy with an easy and sustainable at-home administration schedule and a favorable safety profile should be available to physicians and parents as soon as possible, to support an early treatment plan for a life-long disease. For the reasons described above, and given the crucial and narrow window of opportunity for optimal efficacy of any SMA treatment in neonates and young infants up to 2 months of age who are expected to present with a severe phenotype, risdiplam provides a valuable treatment option for infants aged <2 months diagnosed with SMA.

2.1.2. About the product

Risdiplam (Evrysdi→), also known as RO7034067, is the first orally administered small molecule *SMN2* (survival of motor neuron 2) splicing modifier developed for the treatment of SMA. It directly targets the underlying molecular deficiency of the disease, promoting the inclusion of exon 7 to generate full length *SMN2* mRNA and thereby increasing the production of functional SMN protein.

Risdiplam was approved in August 2020 in the United States and March 2021 in the European Union, followed by additional marketing authorizations in over 90 international markets as of the date of this report.

This variation application provides interim results from Study BN40703 (RAINBOWFISH) in order to support the risdiplam dose determination for patients below 2 months of age. Due to the challenges of recruiting such young infants with a rare disease, Study BN40703 was still open for enrollment at the time of the start of this procedure.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

This submission is based on data from an interim analysis, with 18 patients included in the efficacy and safety data set (clinical cutoff date [CCOD] 1 July 2021). A later cut-off for PK data (31 August 2021) enabled inclusion of further PK data (including 1 additional new patient), in order to maximize the PK data available for dose selection. Although the primary objectives of Study BN40703 are safety and efficacy, tt must be highlighted that PK and PK-PD are the main objectives in this application.

As discussed upon Marketing Authorization (please refer to risdiplam EPAR) "*it may be acknowledged that the overall findings of the risdiplam studies and the literature support the early initiation of treatment with risdiplam. The benefit/risk balance is therefore considered favorable also in patients with up to 4 SMN2 copies that have received a genetic diagnosis, considering the unmet need and extrapolating the observed beneficial effects from the symptomatic patients. The uncertainties of such extrapolation of the data from symptomatic patients to pre- or pauci-symptomatic patients that have not yet reached the criteria for clinical diagnosis are also expected to be clarified by the data, generated in the agreed post-authorization measures*".

As detailed in Annex II, the MAH shall complete by 2030 the following Post-authorisation Efficacy Study (PAES): a long-term prospective, observational study to further evaluate disease progression in SMA patients (both pre-symptomatic and symptomatic) with 1 to 4 SMN2 copies treated with risdiplam, in comparison to natural history data in untreated patients.

As discussed by PDCO Rapporteur at the time of the EMA/PDCO Modification report, the minimum required number of patients submitted in this interim analysis is no longer based, at this step, on primary endpoint and statistical power but on a sufficient number of patients (not especially meeting the criteria for the primary efficacy population) required for an appropriate PK dose finding.

2.1.4. General comments on compliance with GCP

The clinical trial BN40703 is being conducted in accordance with GCP as claimed by the MAH.

2.2. *Quality aspects*

Risdiplam is a co-packaged drug-device combination product. It includes the drug product powder for oral solution and a delivery kit, which contains a press-in bottle adapter and oral/enteral ENFit syringes of 6 mL and 12 mL.

This application proposes to ensure accurate dosing for patients under 2 months of age, which will need a lower volume of reconstituted solution, by using a 1 mL oral/enteral ENFit syringe. The proposed additional 1 mL oral/enteral ENFit syringe will be part of the new co-packaged delivery kit (Table 1).

Table 1: Current and proposed oral/enteral syringes

Current Co-Packaged Delivery Kit	Proposed Co-Packaged Delivery Kit

2 x 6 mL oral/enteral ENFit syringes (0.1 mL syringe increments) 2 x 12 mL oral/enteral ENFit syringes (0.2 mL syringe increments) 1 x press-in bottle adapter (PIBA)	2 x 6 mL oral/enteral ENFit syringes (0.1 mL syringe increments) 1 x 12 mL oral/enteral ENFit syringe (0.2 mL syringe increments) 1 x press-in bottle adaptor (PIBA) 2 x 1 mL oral/enteral ENFit syringes (0.01 mL syringe increments)

The 1 mL syringe is from the same manufacturer and made of the same material as the currently registered and supplied 6 mL and 12 mL oral/enteral ENFit syringes, and covered by the same 510(k) and CE mark. All syringes provided in the new co-packaged delivery kit are reusable.

One of the 12 mL oral/enteral ENFit syringes will be removed from the new co-packaged delivery kit. Indeed, a spare unit of the different syringe sizes is currently included in the new co-packaged delivery kit for the user's convenience, to mitigate potential risk of ink fading with the multi-use of the syringes. However, considering the high volume withdrawn with a 12 mL syringe, fewer use cycles are required until all drug product solution is withdrawn from the bottle and therefore there is no risk of ink fading for this syringe size, and the spare unit will be withdrawn.

The use of the 1 mL oral/enteral ENFit syringe is supported by the information included in the updated CTD sections of Module 3, as well as Module 1. It has been assessed by the MAH for quality, safety, and efficacy. The assessment studies included the following parameters:

USABILITY

The usability risk assessment for the intended quality of 1 mL oral/enteral syringe was based on intended use, instruction for constitution, and user interface.

Intended use: the reconstituted solution is to be orally or enterally administered with the current 6 or 12 mL oral/enteral syringes or with the proposed 1 mL oral/enteral syringe. There is no change in the intended use with the new syringe size.

Instructions for constitution: almost similar instructions for constitution are provided with the addition of a new size of syringe. The new syringe enables users to perform the same tasks to administer a dose of reconstituted solution. Only minor updates have been introduced in the Instructions for constitution: Full information is provided in this application.

User interface: The design features of the new 1 mL oral/enteral syringe are comparable with the currently registered and used 6 mL and 12 mL oral/enteral syringes. The potential impact of the change in graduation units is related to dosing rather than patient use.

COMPATIBILITY ASSESSMENT

Compatibility studies have been carried out with the proposed 1 mL syringes during product development, supporting compatibility with the drug and with the feeding tubes using ENTFit connectors.

DOSING ACCURACY

The proposed 1 mL syringe will have graduation units of 0.01 mL, whereas the current 6 and 12 mL syringes have graduation units of 0.1 mL and 0.2 mL, respectively. Due to this change, updates have been made to the *Instructions for Constitution* and *Instructions for Use*. Dosing accuracy testing was conducted according to ISO 7886-3 using risdiplam oral solution clinical formulation at 0.25 mg/mL and for higher dose with the commercial formulation at 0.75 mg/mL. For each solution strength, a minimum dose volume was withdrawn with the smaller oral syringe size (1 mL) and the maximum volume with the larger oral syringe size (6 mL and 12 mL). Due to the low and comparable viscosities of the two risdiplam oral solution strengths, the dosing accuracy of the 1mL oral syringes is also confirmed for the 0.75 mg/mL risdiplam oral solution based on the testing results from the 0.25 mg/mL risdiplam oral solution.

The formulation proposed is unchanged compared to the already authorized formulation intended for a patient population of 2 months or older. The procedure of first authorization was accompanied by a post authorization measure since the data on the adequacy of the proposed amount of sodium benzoate (0.375

mg/mL) in the formulation were uncertain. The MAH was requested to perform a new preservative efficacy test (PET) study according to Ph. Eur. 5.1.3 in order to re-evaluate the antimicrobial efficacy of sodium benzoate in the range of 0 to 0.30 mg/mL and provide results by the end of Q2 2021.

Subsequently, the MAH presented a PET study, according to the Ph. Eur. 5.1.3 requirements, including formulations with three different concentrations of sodium benzoate (0.0 mg/mL, 0.15 mg/mL and 0.30 mg/mL). Results obtained with the preservative-free formulation (0.0 mg/mL,) did not comply with the Ph. Eur. specifications, particularly for *Aspergillus brasiliensis*. Therefore, this formulation did not provide a preservative effect and confirmed the need for preservative inclusion in the formulation. The sodium benzoate concentrations of 0.15 mg/mL and 0.3 mg/mL resulted to be the most efficacious concentrations since they met all Ph. 5.1.3. requirements, thus providing preservative effect. In the light of these results, the MAH proposed to modify the commercial formulation containing the lowest feasible level of sodium benzoate, using as a starting point a 0.15 mg/mL sodium benzoate concentration. This proposal was considered acceptable, yet still to be evaluated.

However, in the proposed line extension the formulation maintains the same amount of sodium benzoate and no discussion in this regard was present. According to the guideline EMEA/CHMP/QWP/396951/2006 '*Guideline on excipients in the dossier for application for marketing authorization of a medicinal product*' the concentration of antimicrobial preservatives used should be at the lowest feasible level. This aspect is especially relevant since in the extension of indication the target patient population concerns infants below 2 months of age.

Sodium benzoate is of particular concern in pre-term and full-term neonates where immaturity of metabolic enzymes until 8 weeks of age may result in an accumulation of benzoic acid. Neonatal unconjugated hyperbilirubinemia and resultant clinical jaundice affect up to 85% of newborns, usually this condition is benign. However, the displacement of bilirubin from albumin leads to hyperbilirubinaemia which may cause a serious concern of brain injury in some neonates with jaundice (please refer to EMA/CHMP/508189/2013).

In this context, the CHMP concluded that a lower concentration could have been feasible based on the results of the conducted PET study. However, studies conducted to decrease the sodium benzoate concentration to the lowest feasible level showed a significant test-to-test variability, although the results from testing Lab 1 appear not variable, while those from Lab 2 are highly variable. PET results for EMA from Lab 2 show similar behaviour to findings from Lab 1. Therefore, variability may be related to Lab 2 and not to the method.

The MAH declared that no significant decrease of the sodium benzoate content until end of shelf life was found for Evrysdi, but preservative efficacy decreased over shelf life, which may, in fact, be due test variability. According to the MAH results also conducted to a minimal efficacious concentration of 0.25 mg/mL, leading to a nominal sodium benzoate concentration of 0.33 mg/mL in the new formulation. Therefore, the MAH proposed to maintain the current market formulation containing 0.375 mg/mL sodium benzoate, however, at this stage doubts remain on the selected amount of preservative.

Additional data from PET test conducted in different laboratories could clarify the reason of the variability of the results among different labs and justify the calculation of minimum amount of sodium benzoate.

It should be noticed that sodium benzoate is used in concentrations of 0.02–0.5% in oral medicines (*Handbook of Pharmaceutical Excipients*, 9th Edition, 2020). A toxicological assessment of the excipients, including sodium benzoate, in the oral drug formulation (report 1077240) for paediatric use was submitted in the first marketing authorisation application. The calculated maximum dose per kg body weight and per day was calculated (1.95 mg for a 6 kg baby), which took into consideration the low dose strength of Ro703-4067/F12 (0.25 mg/mL RO7034067) as a worst-case scenario. The total daily dose is below the threshold for toxic effects (the accepted daily intake is 5 mg/kg/day) and considered not to pose a particular risk relevant for any paediatric age group.

Sodium benzoate is reported to be not mutagenic and shows no evidence of carcinogenicity in mice and rats. Benzoic acid yields no adverse effects at 750 mg/kg/day via dietary administration. Moreover, in developmental and reproductive studies, sodium benzoate had no adverse effects in mice and rabbits up to doses of 175 mg/kg/day and 250 mg/kg/day, respectively. In rats, sodium benzoate showed adverse effects on foetuses and delivered offspring only at very high dietary doses with a no-observed-adverse-effect level established at 1310 mg/kg/day. However, no clear reference was provided by the MAH with regards to sodium benzoate non-clinical toxicity data.

From the totality of available data and previous discussions, it's agreed that the inclusion of an antimicrobial preservative cannot be avoided, but the MAH should continue to develop efforts to demonstrate that the current concentration is the lowest effective level. The weight of evidence approach should be provided in

the follow up Scientific Advice in order to complete the knowledge on the critical issues of this preservative.

According to EMA/CHMP/QWP/805880/2012 Rev. 2, the use of preservatives is normally considered acceptable in multidose preparations, and the need to preserve a paediatric preparation and the choice of the preservative system at the lowest concentration feasible should be justified in terms of benefit-risk balance. Justification in terms of safety and efficacy has been given, based on the positive benefit/risk profile of risdiplam after approval.

Additionally, the inclusion of information in the PI is currently considered adequate and sufficient until further reduction of sodium benzoate concentration is achieved: "*Sodium benzoate may increase jaundice (yellowing of the skin and eyes) in newborn babies (up to 4 weeks old))*."

The CHMP agreed that the selected sodium benzoate levels should be discussed as part of a separate Scientific Advice procedure. The PAM previously agreed continues to apply to the authorisation.

2.3. Non-clinical aspects

No new clinical data have been submitted in this application (besides environmental risk assessment (ERA)), which was considered acceptable by the CHMP.

2.3.1. Ecotoxicity/environmental risk assessment

The ERA provided by the MAH is based on the *guideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00, June 2006) and the *Questions and Answers on 'Guideline on the environmental risk assessment of medicinal products for human use'* (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016).

Based on the low values of $PEC_{surfacewater}$ and log Dow values at 3 environmental relevant pHs, below the action limits established by the guideline, the MAH concludes that no Phase II assessment is required.

The Log Dow values at pH 5, 7 and 9 were below the trigger value of 4.5, risdiplam is not considered to be a persistent and bioaccumulative substance. Then, no formal PBT assessment is required.

$PEC_{surfacewater}$ was determined on the basis of the refined fraction of a population receiving the active substance during a given time which was based on the prevalence of SMA, all types. Although no value was presented in the ERA report,, it was provided upon request.

The precautionary and safety measures taken to reduce any risk to the environment by including the general statement on the SmPC and packet leaflet (PL) have been applied.

2.3.2. Discussion on non-clinical aspects

All issues regarding the ERA were satisfactorily clarified during this procedure, and the updated ERA report is considered acceptable. From the results of ERA studies, no significant environmental safety issues were identified.

2.3.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of risdiplam.

2.4. Clinical aspects

2.4.1. Introduction

This variation application provides PK, PD, safety, and efficacy data from Study BN40703 (RAINBOWFISH) at the time of an interim analysis (CCOD 1 July 2021 for PD, efficacy and safety data, and 31 August 2021 for PK data) in order to support the dose determination for patients below 2 months of age.

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

Table 2: Overview of Clinical Study with Risdiplam in genetically diagnosed SMA patients

Study No.	Objectives	Study Design	Population	No. Subjects	Dose, Route, Regimen
BN40703 RAINBOWFISH (ongoing) Phase II study	Efficacy, safety, PK and PD	Open-label, single-arm, multicenter 24-month treatment period plus extension phase	Presymptomatic infants (age from birth to 6 weeks), genetically diagnosed with SMA	Up to 25 infants planned (18 patients enrolled as of 1 July 2021, including 7 patients treated for at least 12 months; 19 patients with PK data as of 31 August 2021)	Once daily oral administration for 2 years at a dose selected to achieve the target exposure of mean $AUC_{0\text{-}24h,ss}$ ≤2000 ng □ h/mL; all infants had been receiving a dose of 0.2 mg/kg

$AUC_{0\text{-}24h,ss}$ = area under the concentration-time curve from time zero to 24 h at steady state; PD=pharmacodynamics; PK=pharmacokinetics; SMA=spinal muscular atrophy.

2.4.2. Pharmacokinetics

Analytical method

The liquid chromatography tandem mass spectrometry (LC-MS/MS) analytical method SOP_M_1174 used to determine risdiplam and its main metabolite M1 plasma concentration is the same used within the initial marketing authorisation application. Bioanalytical report of RAINBOWFISH study has been submitted and represents the only new data.

Special populations

Pediatric population below 2 months

Population pharmacokinetic (PopPK) modelling was performed to assess risdiplam PK of the SMA patients enrolled in Study BN40703 (RAINBOWFISH), aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA but are not yet presenting with symptoms. All available risdiplam plasma concentrations available by 31 August 2021 from samples collected in Study BN40703 were combined with the PK data included in the previously developed popPK modelling from clinical Studies BP29840, BP39054, BP39055, BP39056 and BP41361. Additional data collected from patients with Type 1 SMA participating in Study BP39056 up to the Month 24 visit (clinical cut-off date [CCOD: 12 November 2020) were also included. The developed model was used to describe risdiplam plasma concentration data of the patients with SMA of Study BN40703.

Study BN40703 (RAINBOWFISH)

Study BN40703 is an ongoing, open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, PK, and PD of risdiplam in patients aged from birth to 6 weeks (at first dose) who have been genetically diagnosed with SMA (SMN1 deletion and any SMN2 copies) but are not yet presenting with SMA symptoms.

Per protocol, the first patient between 4 and 6 weeks (29 to 42 days) of age at first dosing had to receive a once daily oral dose of 0.04 mg/kg of risdiplam to assess safety, tolerability, and PK at this starting dose. According to the protocol, the first patient enrolled aged between 7 days and 28 days at the time of first dose was to receive a once daily oral dose of 0.004 mg/kg. However, the dose could be adjusted based on emerging data from this and other studies with risdiplam, and emerging PK data from the first patients enrolled in this study indicated that the dose of 0.004 mg/kg would not be required.

In the last approved PIP, for the RAINBOWFISH study, it is reported that "*The dose will be selected based on data from BP39056 in infants (Part 1). The dose may be modified to ensure that the target exposure is achieved and the exposure cap of 2000 ng.h/mL is not exceeded*", also in the BD provided for the pre-

submission of the present application is reported "*Study BN40703 / RAINBOWFISH is an open-label, single-arm, multicenter clinical study in presymptomatic SMA patients aged from birth to 6 weeks (at first dose). All patients are receiving risdiplam orally once daily at a dose selected to achieve the targeted exposure of close to a mean area under the concentration-time curve (AUC) 2000 ng.h/mL."* However, in the RAINBOWFISH study, paediatric patients achieved a plasma exposure higher than 2000 ng • h/mL.

An interim clinical study report (CSR) was submitted, presenting results from an interim analysis to support the registration of risdiplam in presymptomatic patients below the age of 2 months.

In Study BN40703, plasma PK samples were collected from neonates and infants <6 weeks old (at first dose) who have been genetically diagnosed with SMA but are not yet presenting with symptoms at: 2, 4, 6 and 24 h post-dose on Day 1, pre-dose, 2, 4, 6 h post-dose on Weeks 4, 8, 28, 52, 78 and 104, while pre-dose samples were drawn on Weeks 2, 16, 40, 64 and 92. All PK data available as of 31 August 2021 were included in the analyses.

PopPK Modelling

A popPK analysis of risdiplam was previously performed for 10,222 observations collected from 525 subjects (61 healthy subjects and 464 patients with SMA) participating in either of the five clinical Studies BP29840 (healthy subjects), BP39054 (JEWELFISH), BP39055 (SUNFISH), BP39056 (FIREFISH) or BP41361 (healthy subjects) (1102699).

The risdiplam PK was adequately described by a structural model comprising a three transit compartment absorption model connected to a systemic linear two-compartmental PK model. The time-varying body weight and age were included with allometric (body weight) and maturation (age) functions in the CL/F (apparent clearance) and Vc/F (apparent central volume of distribution) of the structural model to describe the variability of the heterogeneous population (age and body weight ranges: 2.2 months to 52.1 years and 4.14 to 95.3 kg, respectively). A factor for CL/F of healthy adults was also included as a covariate to account for slightly higher CL/F than patients with SMA.

This model was used as the reference popPK model in the current PK analysis for risdiplam in neonates and infants aged <6 weeks (at first dose) who have been genetically diagnosed with SMA but are not yet presenting with symptoms at enrollment in Study BN40703 (RAINBOWFISH).

The present popPK modelling initiated with evaluation of the reference PopPK model (1102699) against the plasma risdiplam concentration data collected from the SMA patients of Study BN40703 until 31 of August 2021 as well as the patients with Type 1 SMA from Study BP39056 until the Month 24 visit (CCOD: 12 November 2020) which were combined with the data set used for the reference model development. The reference model was fitted to the combined data set without estimation step and goodness-of-fit (GOF) plots were examined. When this was considered not satisfactory, then parameter estimation step and further model modifications were conducted.

Covariate analyses were performed for the reference model development (1102699). In addition to the time-varying age and body weight effect included in the structural model, a factor for CL/F of healthy adults was identified as statistically and clinically relevant covariate for the reference popPK model. Due to the limited sample size of Study BN40703 (371 observations from 19 SMA patients), corresponding to 3.4% of the total risdiplam data, an exploratory analysis on the relationship between *post hoc* PK parameters and covariates was performed instead of formal covariate analyses.

The demographics, risdiplam dosing history and plasma concentrations of risdiplam collected from 544 subjects, consisting of 61 healthy subjects (Studies BP29840 and BP41361) and 483 patients with SMA (Studies BP39054, BP39055, BP39056 and BN40703) were available in the data base as of 31 August 2021 and included in the popPK analysis. The demographics of the patients at the time of the first dose are summarized in Table 3.

Table 3: Summary of Demographic Data at the First Dose

Covariate	All Subjects (n=544)	BP29840 (n=26)	BP39054 (n=173)	BP39055 (n=229)	BP39056 (n=62)	BP41361 (n=35)	BN40703 (n=19)
Age (years)							
Mean	14.2	26.3	17.7	10.8	0.45	42.2	0.077
Median (Min–Max)	12.0 (0.04–61)	24 (18–44)	15.0 (1.1–61)	9.9 (2.2–25.4)	0.47 (0.18–0.58)	40.2 (22.1–56.2)	0.074 (0.04–0.11)
Body Weight (kg)							
Mean	36.6	79.0	41.3	32.3	6.8	80.9	4.0
Median (Min–Max)	31.3 (3.1–109)	79.7 (50.4–95.3)	39.0 (9.2–109)	27.6 (9.8–109)	6.6 (4.1–10.6)	79.7 (52.5–103)	4.0 (3.1–5.8)
Sex							
Male	286	26	95	112	25	20	8
Female	258	0	78	117	37	15	11
SMA Type							
Healthy subjects	61	26	0	0	0	35	0
Type 1	77	0	15	0	62	0	0
Type 2	271	0	107	164	0	0	0
Type 3 non ambulatory	93	0	36	57	0	0	0
Type 3 ambulatory	23	0	15	8	0	0	0
Presymptomatic	19	0	0	0	0	0	19
Race							
White	392	21	142	165	35	14	15
African American	24	2	1	2	0	19	0
Asian	69	2	9	36	18	1	3
Others	59	1	21	26	9	1	1

Max= maximum; min=minimum; SMA=spinal muscular atrophy.

A total of 11,300 plasma samples for measurement of risdiplam concentrations were collected from 544 subjects who participated in Studies BP29840, BP39054, BP39055, BP39056, BN40703 and BP41361. After excluding the following samples, the remaining 10,939 observations including 345 capillary blood samples (3.1%) were available for the analysis. In Table 4, it is presented the number of risdiplam plasma concentrations per study.

Table 4: Number of Risdiplam Plasma Concentrations by Study

Study no.	No. plasma concentration/No. patients
BP29840	426 / 26
BP39054	2361 / 173
BP39055 Part 1	1549 / 51
BP39055 Part 2	2769 / 178
BP39056 Part 1	882 (**65** [a]) / 21
BP39056 Part 2	1271 (**298** [a]) / 41
BP40703	**371** [a] / 19
BP41361	1327 / 35
Total	10956 [b] / 544

a New data combined with the reference PPK modelling data set (1102699).
b After exclusion of 17 observations, a total of 10939 observations were included in the analysis.

The individual plasma concentration time profiles for each study are shown in Figure 1 and Figure 2.

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

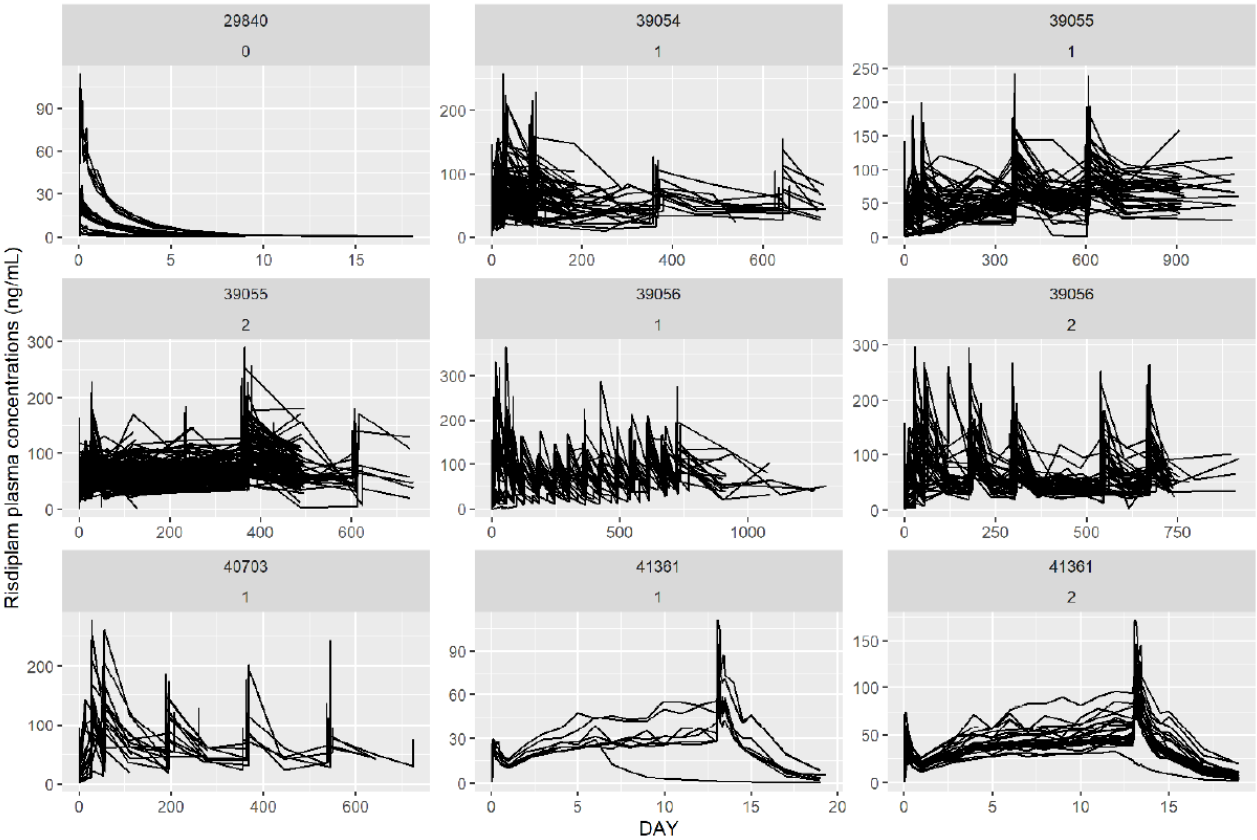
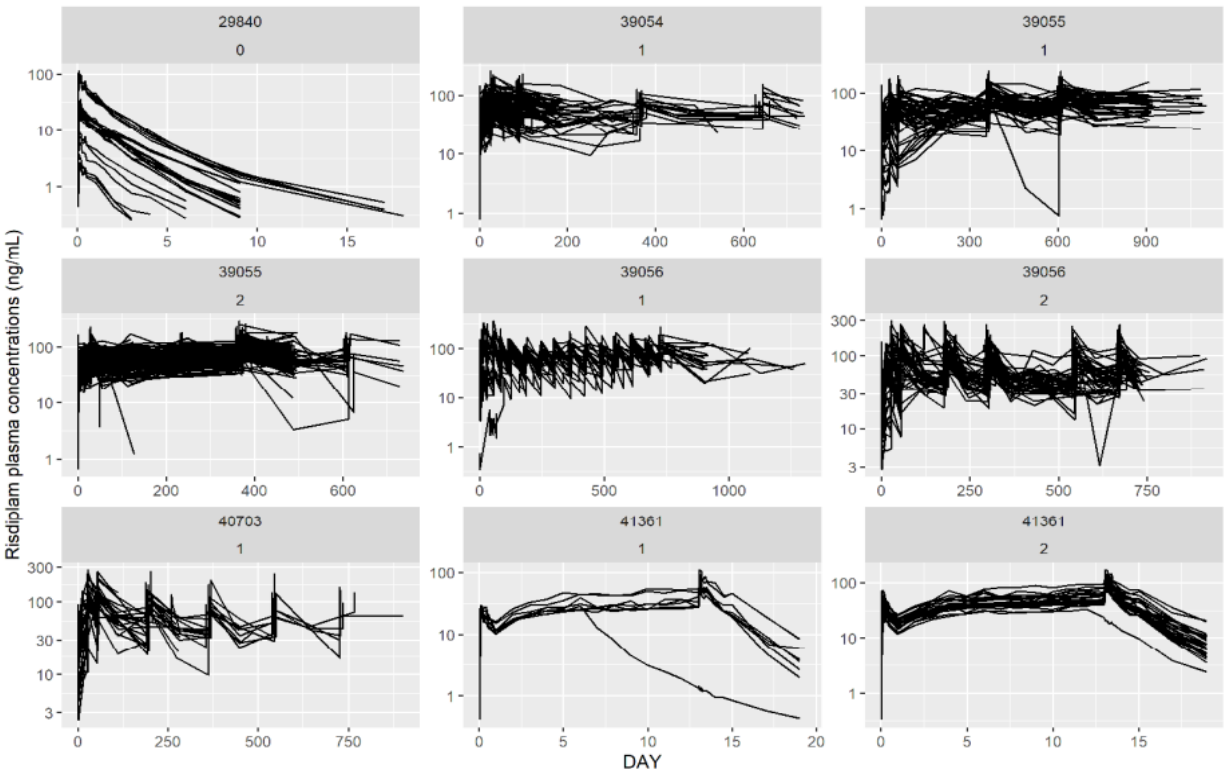


Figure 2: Risdiplam Concentration versus Time since First Dose by Study on Semi-Log Scale



After the reference model (1102699) was fitted to the combined dataset to examine whether the model adequately predict risdiplam PK, focusing on the patients with SMA of Study BN40703, it was decided to modify the reference popPK model of risdiplam to adequately predict risdiplam PK in patients with SMA of Study BN40703 as well as the other populations, with focus on the covariate effects on CL/F and Vc/F.

The plasma risdiplam concentration data collected from the patients with SMA of Study BN40703 as well as the patients with Type 1 SMA from Study BP39056 until the Month 24 visit (CCOD: 12 November 2020) were combined with the data set used for the reference model development (1102699). The reference model (1102699) was fitted to the combined data set to examine whether the model adequately predict risdiplam PK, focusing on the patients with SMA of Study BN40703.

The application of the reference popPK model to the combined risdiplam PK data set without parameter estimation step resulted in biased estimates for the SMA patients of Study BN40703 with tendency to over-predict risdiplam plasma concentrations, particularly for the samples collected while the patients were <6 weeks old.

Subsequently, parameter estimation step was conducted based on the reference popPK model structures with adaptation of the reference body weight in the allometric scaling to the new population (from 33 kg to 31.3 kg) and this was successfully converged. The parameters were generally well estimated with relative standard error (RSE) of <20% except for the maturation function of Vc/F (Age50-Vc/F) which had RSE of 79.3%. Inspection of the GOF plots for all populations shown in Figure 3 did not reveal major unexpected deficiencies. The plots of observed risdiplam plasma concentrations (DV) versus population predicted plasma concentrations (PRED) and the plots of observed risdiplam plasma concentrations (DV) versus individual predicted plasma concentrations (IPRED) mostly displayed a homogeneous distribution of data points around the identity line. However, a subset of the GOFs for the patients with SMA of Study BN40703 shown in Figure 4 indicated tendency of the model to over-predict risdiplam plasma concentrations in the neonates. Distribution of the ETA, inter-individual variability (IIV) of CL/F and Vc/F against age indicated under-prediction of CL/F and Vc/F of these patients (<0.1y). Consistently, the prediction-corrected visual predictive check (pc-VPC) demonstrated bias in predictions of risdiplam concentrations of the patients with SMA of Study BN40703 in the first few months of the treatment whereas the predictions and observations were in a good agreement thereafter where age and body weight overlap with the other population <2 months old.

The parameter estimates, GOFs, and pc-VPCs suggested that the reference popPK model is not suited to predict risdiplam PK of the patients with SMA of Study BN40703 even after adaptation of parameter estimates and therefore, the model modification was considered necessary. The distribution of individual deviations (ETA) against age indicated necessity to adapt covariate effect on CL/F and Vc/F to improve the description of the concentration-time data in the neonates. The steps taken for the model adaptation are summarized in Table 5.

The reference popPK model included a maturation function of CL/F using maximum effect (E_{max}) model. The following additional parameters were included in the maturation function and tested: 1) E_0 (fraction of risdiplam clearance at birth [$Frac_{birth}$]) which is a fraction of CL/F at birth, 2) a decay describing with fraction of CL/F at birth ($Frac_{birth}$) followed by decrease (k_{decay}) with age and 3) fold-factor of CL/F in neonates. The estimated allometric coefficient for Vc/F using the reference model structure was 0.982, so it was fixed to 1.0 and resulting change in objective function (OFV) was inconsequential.

Among the maturation functions, the E_0+E_{max} model for CL/F and fixed allometric coefficient for Vc/F of 1.0 (Model 10) achieved successful parameter estimation with improvement in ETA-CL/F distribution. The maturation function with the E_0+E_{max} model predicts higher risdiplam CL/F in the age range <0.2 years old than that with the E_{max} model of the reference model which predicts CL/F=0 L/h at birth (Figure 3). Furthermore, removal of the maturation function on Vc/F, which was poorly estimated (RSE=79.3%, and indicated little effect (Age_{50} of 0.019 years) in the reference popPK model, resulted in improvement in ETA-Vc/F distribution in neonates (<0.1 year, Model 11).

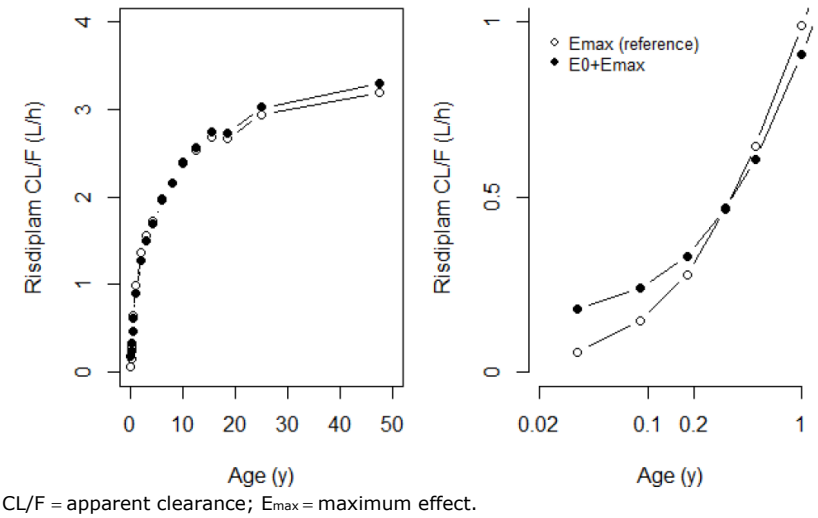
Although the OFV was increased by +12 from Models 10 to 11, improvement in ETA-Vc/F distribution in neonates and numerical stability (condition number: >10,000 versus 88.7, the highest correlation among the parameter estimates: 0.97 versus <0.8, for Models 10 and 11, respectively) were considered to sufficiently justify the selection of Model 11.

Table 5: Summary of Adaptation of the Risdiplam popPK Model for the Combined Data Set with Study BN40703

Model	Description	No. of parameters	OFV	Results
3	The reference PPK model with parameter estimation step	13	70090.9	Bias in prediction for neonates was noted
6	E_0+E_{max} model for maturation function of CL/F $Frac_{birth}$+ [Age /(Age_{50} + Age)]	14	NA	Parameter estimation failed.
7	Decay+E_{max} model for maturation function of CL/F $Frac_{birth}$•$e^{(-kdecay•Age)}$ + [Age /(Age_{50} + Age)]	15	NA	Parameter estimation failed.
8	Factor for CL/F for BN40703 patients and E_{max} model for maturation function of CL/F (1+$F_{neonates}$) + [Age /(Age_{50} + Age)]	14	70076.5	No obvious improvement in GOFs
9	E0+sigmoidal E_{max} model for maturation function of CL/F $Frac_{birth}$ + [Age^{γ} /(Age^{γ}_{50} + Age^{γ})]	15	69918.3	High correlation in CL and E0 estimates (>0.9)
10	The same as model 6 with fixed allometric coefficient on Vc/F and Vp/F to 1.0	13	69973.9	Improvement in numerical stability from Model 6 and ETA-CL/F and IIV-Vc/F distribution
11	The same as model 10 without maturation function for Vc/F	12	69985.8	Further improvement in ETA-Vc/F distributions.

CL/F=apparent clearance; Emax=maximum effect; ETA=individual deviations; Fracbirth=a fraction of CL/F at birth to the maturation function of CL/F; GOF=goodness-of-fit; NA=not applicable; OFV=objective function; PPK=population PK; Vc/F=apparent central volume of distribution; Vp/F=apparent peripheral volume of distribution

Figure 3: Comparisons of the Examined Maturation Functions for Risdiplam CL/F



CL/F = apparent clearance; E_{max} = maximum effect.

Final Model

The parameter estimates of Model 11 summarized in Table 6 show that they were estimated with good precision indicated by RSE<25%. The 95% confidence intervals (CIs) were comparable between the estimates by the covariance matrix and the bootstrap analysis, and the intervals of each parameter estimates were considered reasonable.

Table 6: Parameter Estimates of the Final popPK Model of Risdiplam of the Combined PK Data Set (Model 11)

Parameter	Unit	Estimate	RSE (%)	95%CI	95%CI [a]
Fixed Effects					
CL/F	L/h	2.45	3.49	2.28–2.62	2.28–2.66
ktr	/h	5.21	2.31	4.97–5.44	4.91–5.45
Vc/F	L	87.4	1.36	85.1–89.8	84.5–89.8
Q/F	L/h	0.654	7.41	0.559–0.749	0.571–1.01
Vp/F	L	103.0	18.7	65.1–140	45.6–162
Covariate Effects					
Effect of WT on CL/F and Q/F		0.259	11.7	0.199–0.318	0.177–0.311
Effect of WT on Vc/F and Vp/F		1 FIX	NA	NA	NA
Factor for CL/F of healthy adults		0.476	13.2	0.353–0.599	0.349–0.621
$Frac_{birth}$–CL/F		0.106	23.9	0.0567–0.156	0.0550–0.159
Age_{50}–CL/F (y)		1.39	15.5	0.964–1.81	1.08–1.82
Random Effects					
CL/F (CV)		0.0668 (25.9%)	8.14	0.0562–0.0775	0.0582–0.0761
ktr (CV)		0.2590 (50.9%)	9.46	0.211–0.307	0.216–0.317
Vc/F (CV)		0.0760 (27.6%)	8.35	0.0636–0.0885	0.0667–0.0883
Error Model					
σ_1 proportional–venous (CV)		0.0571 (23.9%)	3.15	0.0536–0.0607	0.0537–0.0606
σ_2 proportional–capillary (CV)		0.0973 (31.2%)	14.90	0.069–0.126	0.0719–0.131
OFV = 69986					

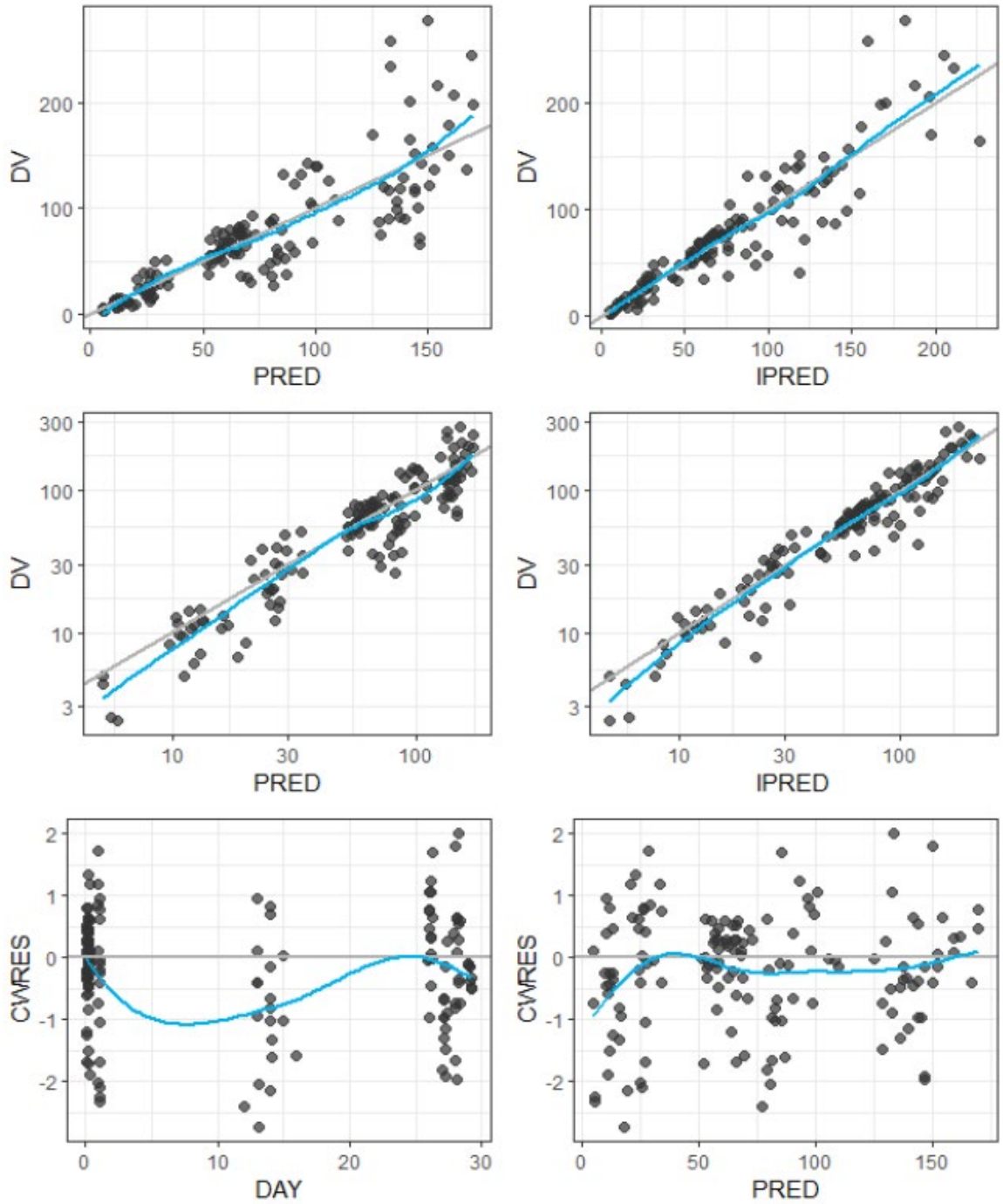
CL/F = apparent clearance; CV = coefficient of variation; Fracbirth = a fraction of CL/F at birth to the maturation function of CL/F; ktr = transfer rate constant; NA = not applicable; OFV =objective function; PK = pharmacokinetic; PPK = population PK; Q/F = apparent inter-compartmental clearance; RSE = relative standard error of estimate; Vc/F = apparent central volume of distribution; Vp/F = apparent peripheral volume of distribution; WT = body weight; y = year.
a bootstrap analyses with 200 replicates (77% were successful).

Degree of η-shrinkage were 5.32, 23.0 and 9.32% for CL/F, transfer constant rate (k_{tr}) and Vc/F, respectively, indicating that the analyses with *post hoc* parameters and estimation of individual secondary PK parameters such as AUC and (average concentration over observation period) C_{av} could be reliably performed. The shrinkage for residual errors were 5.37 and 2.83% for venous and capillary blood samples, respectively. The condition number was low (88.7) and none of the parameters estimated showed high correlations (>0.8) with the others.

The GOFs in Figure 4 show good consistency between DV and PRED, as well as IPRED which mostly displayed a homogenous distribution of data points around the identity line. The distribution of conditional weighted residuals were randomly scattered around the zero line with the majority of data between -2.5 and +2.5 standard deviations against time or population predictions. The IIV (ETA) of CL/F, k_{tr} and Vc/F were generally normally distributed.

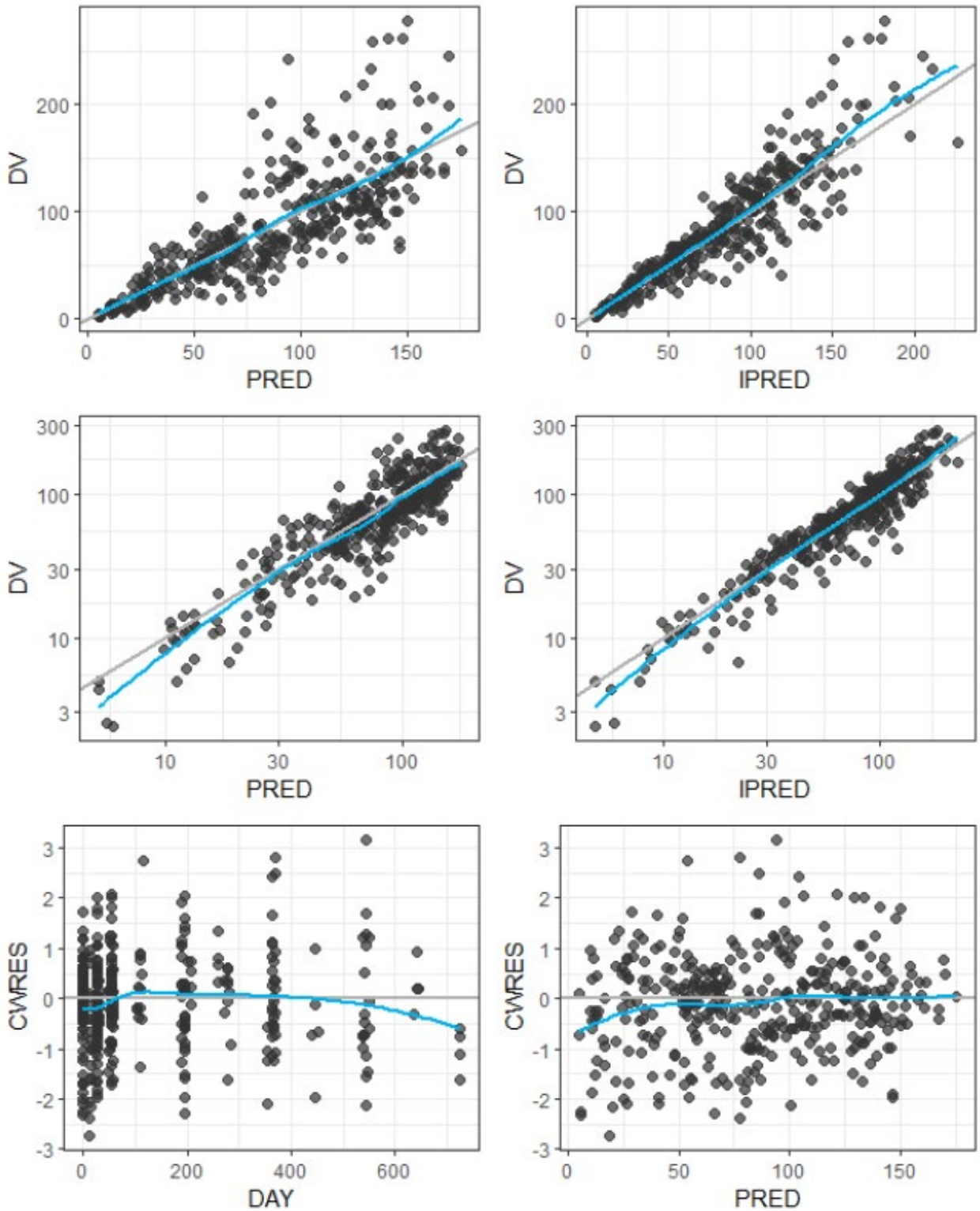
The SMA patients of Study BN40703 were 16-41 days old at the first risdiplam dose and 48 days-2 years old at the last dosing occasion included in this data cut. The GOFs of these patients when they were neonates <6 weeks old (Figure 4) and during the entire observation period (Figure 5) show the ability of the model to predict risdiplam PK along with growth of these neonates.

Figure 4: Goodness-of-Fit Plots for the Final popPK model of Risdiplam (Study BN40703 Population-Neonates <6 Weeks Old)



CWRES = conditional weighted residual; DV = dependent variable; IPRED = individual prediction; Modeling; PPK = population PK; PRED = population predicted value. DV Observed risdiplam concentrations [ng/mL], PRED (IPRED) NONMEM predicted risdiplam concentrations [ng/mL] based on population (individual) PK parameters. Gray and blue lines indicate identity line and smooth, respectively.

Figure 5: Goodness-of-Fit Plots for the Final popPK model of Risdiplam (Study BN40703 Population-Entire Observation Duration)



CWRES = conditional weighted residual; DV = dependent variable; IPRED = individual prediction; Modeling; PPK = population PK; PRED = population predicted value. DV□Observed risdiplam concentrations [ng/mL], PRED (IPRED)□NONMEM predicted risdiplam concentrations [ng/mL] based on population (individual) PK parameters. Gray and blue lines indicate identity line and smooth, respectively

The pc-VPC with time after the first and the last doses of all populations are shown in the Figure 6, Figure 7. Although slight under-prediction of 2.5 percentile was shown, the median and 97.5 percentile were in a good agreement with the observations.

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

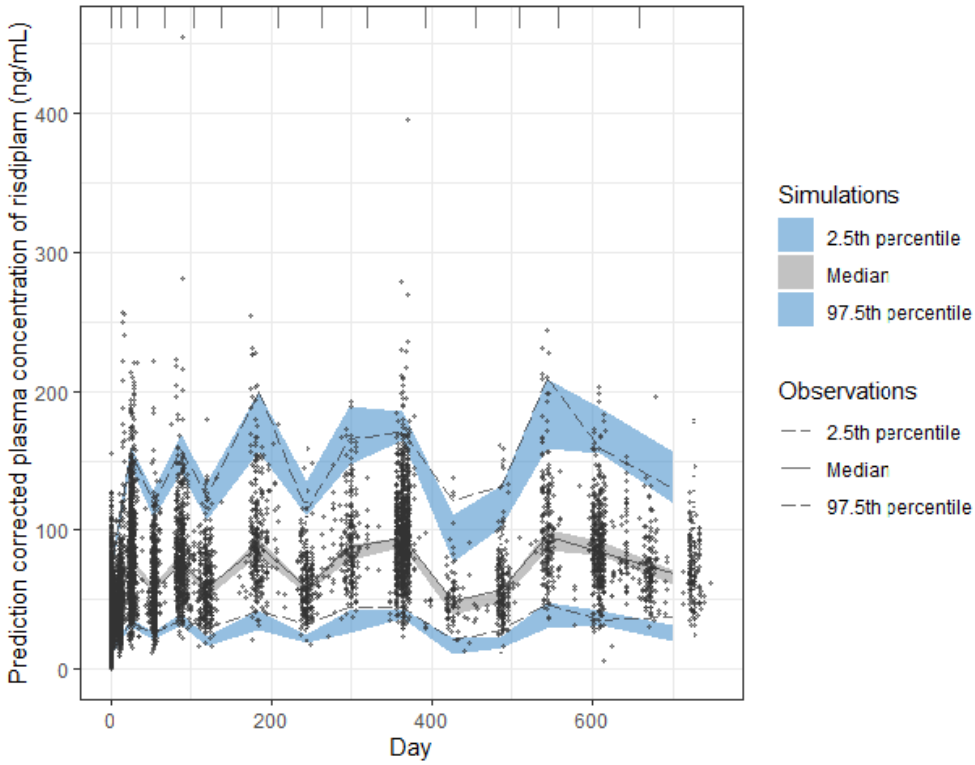
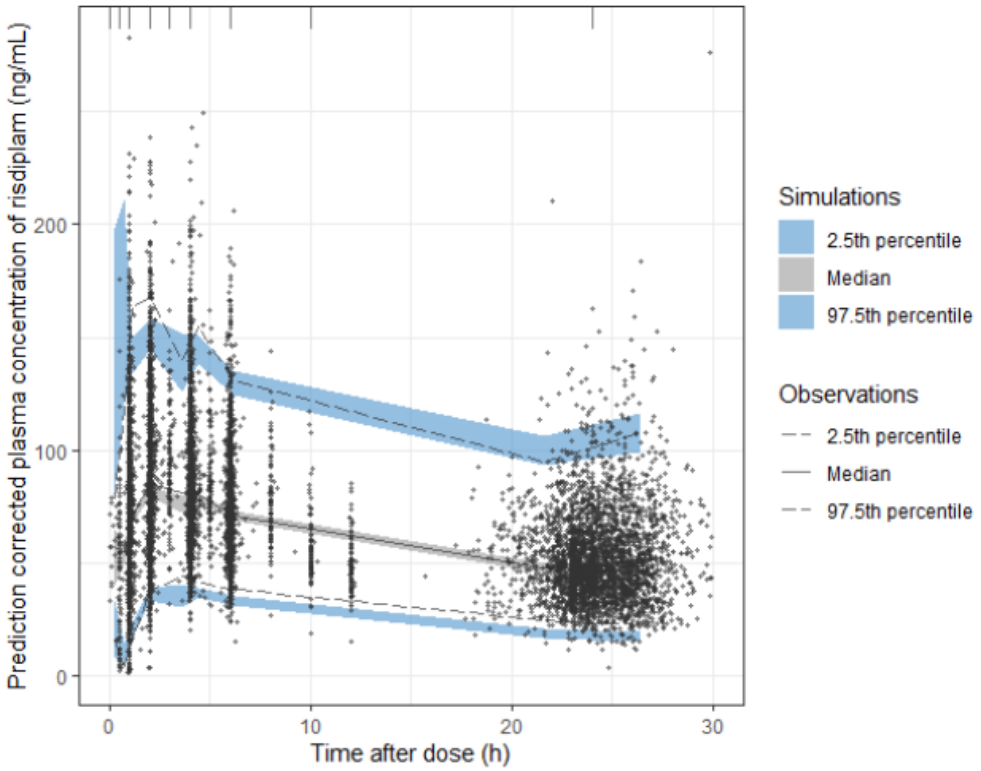
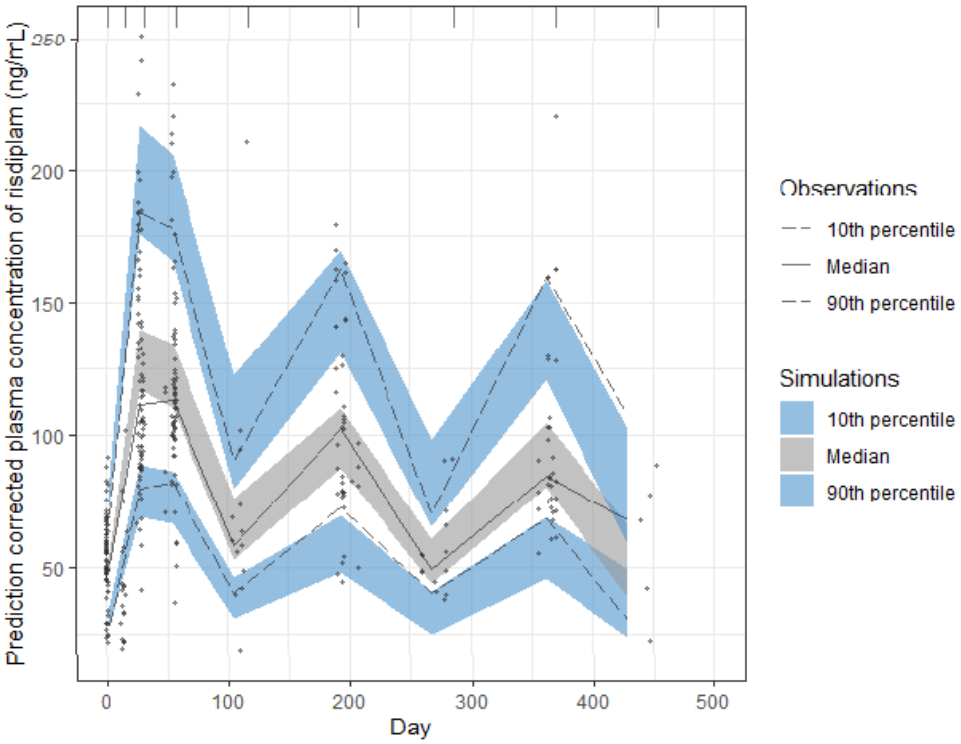


Figure 7: Prediction Corrected Visual Predictive Check (All Population) of the Final popPK Model of Risdiplam with Time After Dose



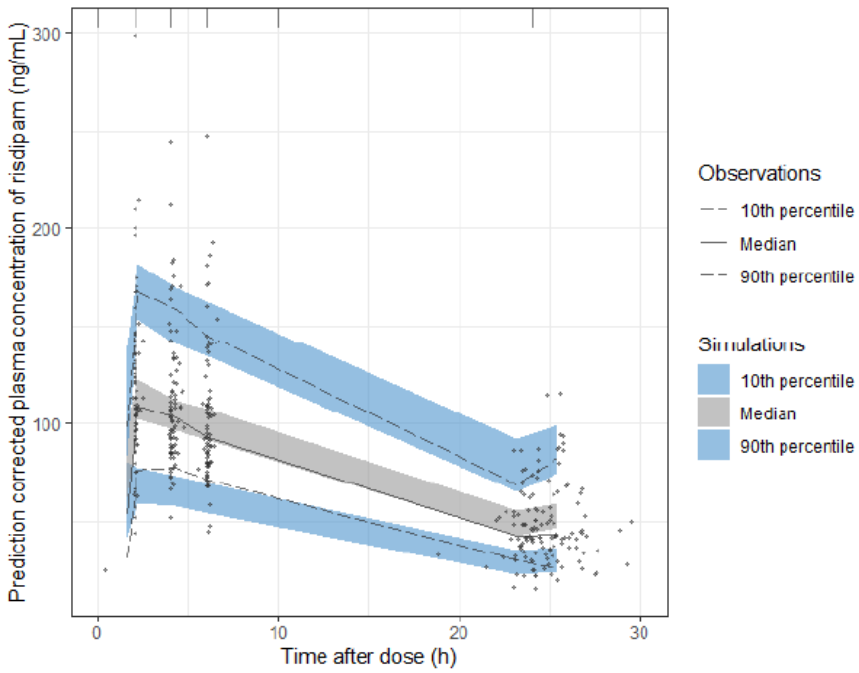
The median, 10th and 90th percentiles of the observations of Study BN40703 population were mostly within the corresponding CI in the pc-VPC except for the median of the first 1-2 months of the observation period (Figure 8).

Figure 8: Prediction Corrected Visual Predictive Check (Study BN40703 Population) of the Final popPK Model of Risdiplam



The pc-VPC with time after the last dose showed good agreement between the observations and the corresponding confidence interval of the patients with SMA of Study BN40703 (Figure 9).

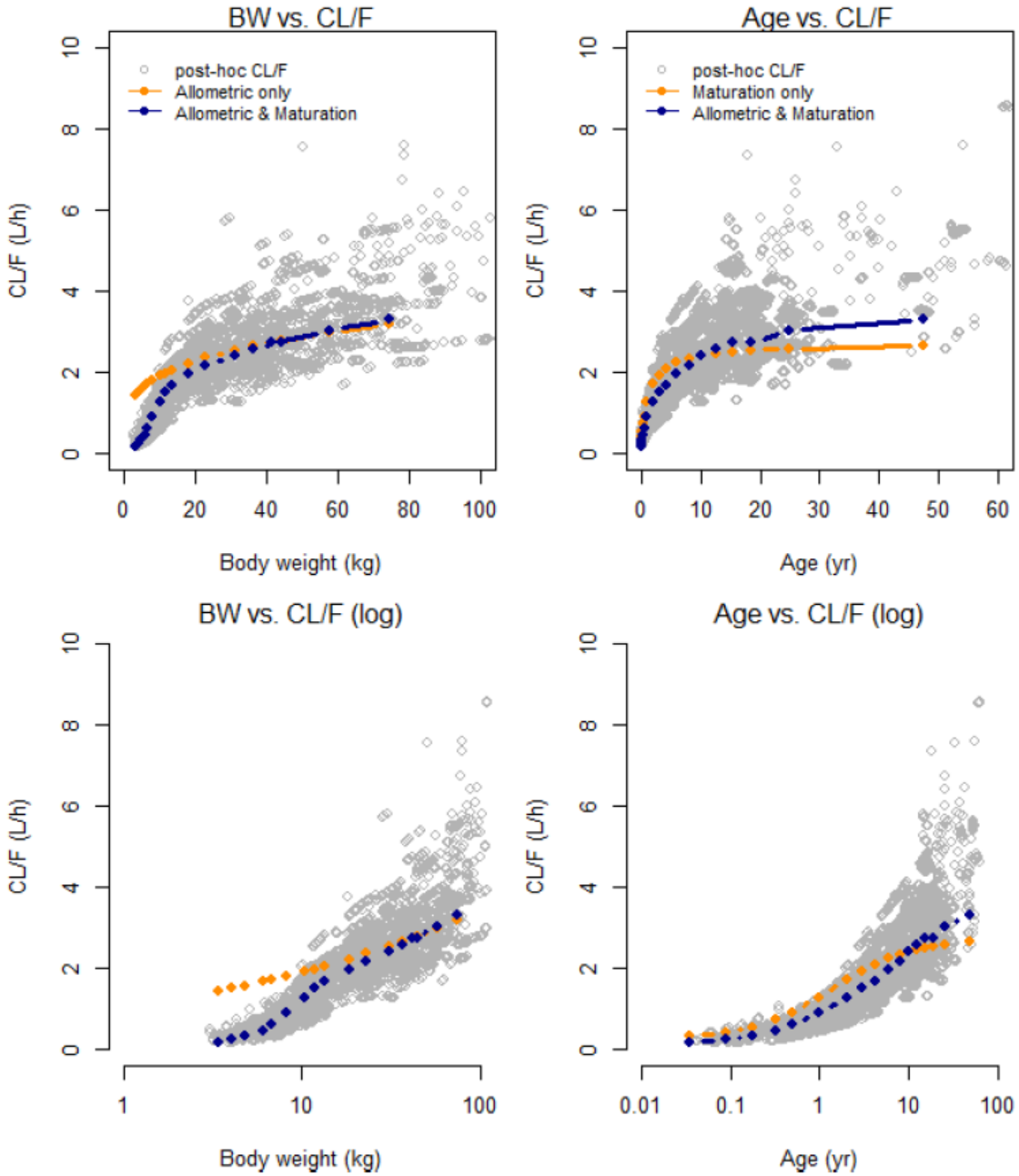
Figure 9: Prediction Corrected Visual Predictive Check (Study BN40703 Population) of the Final popPK Model of Risdiplam with Time After Dose



These pc-VPC demonstrated ability of the model to adequately predict central tendency and inter-individual variability for all populations as well as the SMA patients of Study BN40703, and therefore, the predictive performance of the model was considered satisfactory.

The role of allometric and maturation functions in description of risdiplam CL/F of the final model is illustrated in Figure 10.

Figure 10: The Role of Time-Varying Age (Maturation Function) and Body Weight (Allometric Function) as Covariate on Description of Risdiplam CL/F



BW = body weight; CL/F = apparent clearance

Allometric function alone would lead to significant bias in CL/F in young children, particularly with body weight <10 kg. While the allometric exponent (0.259) describes shallow relationship between body weight and CL/F, the maturation function alone would lead to biased estimates in the risdiplam CL/F across the population. Therefore, both allometric and maturation functions are retained in the final popPK model to capture risdiplam CL/F across the age and body weight range. The final model successfully achieved to describe risdiplam PK in the population ≥16 days old while maintaining continuum to the populations ≥2 months old which have been analyzed in the reference popPK modelling.

Based on the numerical stability, GOFs and pc-VPC, Model 11 was selected as the final popPK model of risdiplam for the combined data set including the SMA patients of Study BN40703.

Covariates

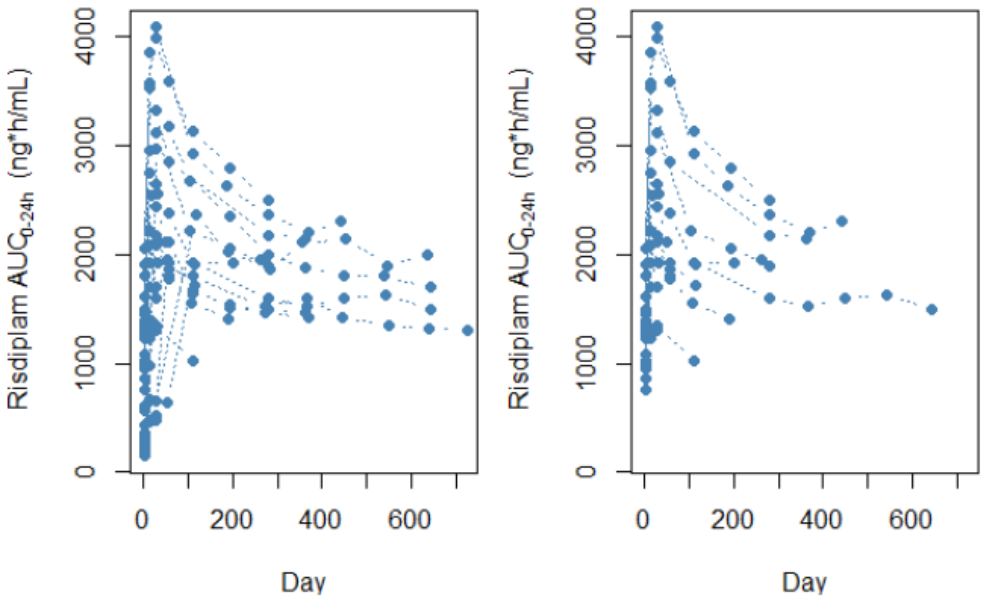
The Empirical Bayes Estimates of ETAs of CL/F, k_{tr} and Vc/F of the patients with SMA of Study BN40703 were graphically analyzed on relationship with continuous and categorical variables. The distribution of ETAs of CL/F, k_{tr} and Vc/F against liver function markers alanine aminotransferase (ALT) and aspartate aminotransferase (AST) and bilirubin were generally homogenous and scattering around ETA=0. There was no obvious difference in these ETAs by sex or race. None of the variables examined in the graphical analyses indicated potential covariate effects on CL/F, k_{tr} or Vc/F of risdiplam in these 19 patients with SMA of Study BN40703.

PK Parameters

Individual secondary PK parameters $AUC_{0\text{-}24h}$ and average concentration from the first dose to the specified time points (C_{av}) were derived using the *post hoc* PK parameters of the final popPK model, patients' actual demographics and risdiplam dosing records. There were 13 patients who initiated risdiplam treatment at 0.2 mg/kg. Two and 4 patients initially received 0.08 or 0.04 mg/kg, respectively, and their dose was then increased to 0.2 mg/kg.

The individual $AUC_{0\text{-}24h}$ vs time course of the patients with SMA of Study BN40703 between Days 14 and the last risdiplam dosing recorded until 31 August 2021 are shown in Figure 11.

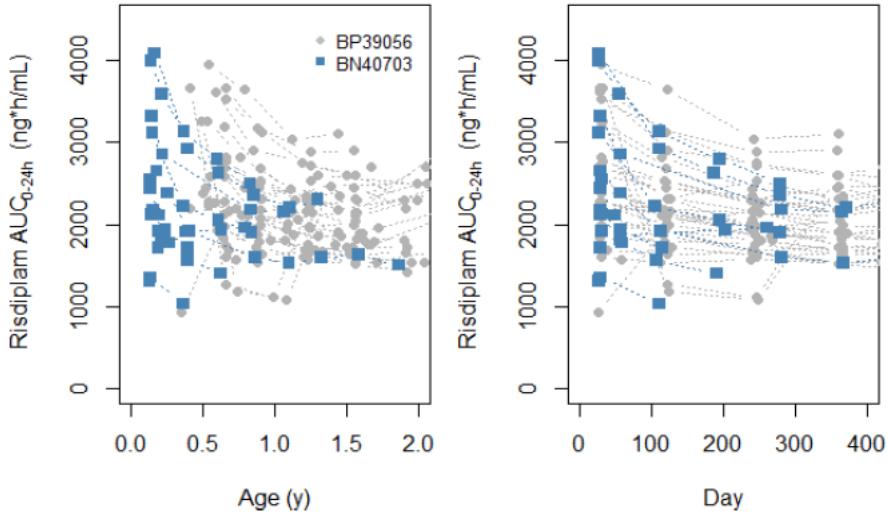
Figure 11: Individual Risdiplam $AUC_{0\text{-}24h}$ of SMA Patients of Study BN40703 between Day 14 and the Last Dose until 31 August 2021



$AUC_{0\text{-}24h}$=area under the plasma concentration time curve from time 0 to 24 hours; SMA = spinal muscular atrophy.
The $AUC_{0\text{-}24h}$ time course of all patients with SMA of Study BN40703 (left) and patients starting with 0.2 mg/kg (right) are shown.

The range and distribution of $AUC_{0\text{-}24h}$ were comparable to that observed in the patients with Type 1 SMA (Figure 12), although the patients with SMA of Study BN40703 were approximately 140 days younger than the patients of Type 1 SMA of Study BP39056 at the first risdiplam dose (median: 28 days [0.074 years] versus 172 days [0.47 years] old).

Figure 12: Risdiplam $AUC_{0\text{-}24h}$ After 0.2 mg/kg in Studies BN40703 and BP39056



$AUC_{0\text{-}24h}$=area under the plasma concentration time curve from time 0 to 24 hours; SMA = spinal muscular atrophy.
$AUC_{0\text{-}24h}$ after risdiplam 0.2 mg/kg for 28 days or longer are compared.

A summary of risdiplam $AUC_{0\text{-}24h}$ and C_{av} on Days 14, 28 and 56 after treatment start is shown in the Table 7. The individual results derived from the popPK model are also presented on the end of this section.

Table 7: Summary of Estimated Individual Secondary PK Parameters for the SMA Patients of Study BN40703

Parameters	Day 14	Day 28	Day 56
Risdiplam 0.2 mg/kg	n=12 [a]	n=13	n=9 [b]
Age (days)			
mean	43.2	56.7	79.7
median [range]	42.0 [35.0–55]	54.0 [49.0–69.0]	80.0 [48.0–96.0]
Body weight (kg)			
mean	4.66	5.11	5.86
median [range]	4.58 [3.79–6.12]	5.0 [4.30–6.56]	5.84 [3.79–7.20]
$AUC_{0\text{-}24h}$ (ng•h/mL)			
mean	2510	2580	2180
median [range]	2380 [1230–3860]	2440 [1350–4080]	1930 [1310–3590]
C_{av} (ng/mL)			
mean	93.4	102	97.8
median [range]	88.8 [50.1–144]	97.5 [52.1–156]	87.9 [52.1–161]
Dose normalized to 0.2 mg/kg	n=18 [a]	n=19	n=14 [b,c]
Age (days)			
mean	43.2	56.5	80.4
median [range]	42.0 [29.0–55.0]	54.0 [43.0–69.0]	79.5 [48.0–96.0]
Body weight (kg)			
mean	4.6	5.03	5.72
median [range]	4.49 [3.63–6.44]	4.97 [3.63–6.77]	5.81 [3.79–7.20]
$AUC_{0\text{-}24h}$ (ng•h/mL)			
mean	2520	2550	2280
median [range]	2420 [1230–3860]	2440 [1350–4080]	2040 [1310–3590]

$AUC_{0\text{-}24h}$=area under the plasma concentration time curve from time 0 to 24 hours; C_{av} = average concentration from the first dose to the specified time points; PK = pharmacokinetic; SMA = spinal muscular atrophy. $AUC_{0\text{-}24h}$ and C_{av} were calculated using simulated plasma concentration of risdiplam at each visit reflecting actual individual age, body weight and dosing information of each patient.
a One patient did not have Day 14 visit. b Two patients had observations up to Day 28; 2 patients had observations longer than 56 days but did not have Day 56 visit. c One patient did not have Day 56 visit.

The median risdiplam $AUC_{0\text{-}24h}$ of the 13 patients initiated with 0.2 mg/kg on Days 14 and 28 was 2380 and 2440 ng.h/mL respectively and decreased to 1930 ng.h/mL on Day 56. Similar values are reported when the dose normalized risdiplam $AUC_{0\text{-}24h}$ values for the 6 patients who started with 0.04 or 0.08 mg/kg were included.

PK parameter $AUC_{0\text{-}24h}$ summarized by age (infants 1 to 2 months old, and infants 2 to 3 months old) is provided in Table 8.

Table 8: Summary of Risdiplam $AUC_{0\text{-}24h}$ of the SMA Patients of Study BN40703 by Age

	Infants 1 month to 2 months	Infants 2 month to 3 months
Risdiplam 0.2 mg/kg	n=13	n=10 [b]
Age (days)	49.0 [35.0–56.0]	70.0 [60.0–88.0]
$AUC_{0\text{-}24h}$ (ng•h/mL)[a]		
mean	2500	2420
median [range]	2440 [1230–3990]	2110 [1710–4080]
Dose normalized to 0.2 mg/kg	n=19	n=16 [b]
Age (days)	49.0 [35.0–56.0]	70.0 [60.0–88.0]
$AUC_{0\text{-}24h}$ (ng•h/mL) [a]		
mean	2490	2460
median [range]	2440 [1230–3990]	2120 [1710–4080]

$AUC_{0\text{-}24h}$=area under the plasma concentration time curve from time 0 to 24 hours. Median [range] of age is shown.
a Individual $AUC_{0\text{-}24h}$ estimates on Day 14 or later were included. Multiple estimates per patient were included when they were available in the specified age range. b Three patients did not have $AUC_{0\text{-}24h}$ estimates between 2 months and 3 months of age.

The median risdiplam $AUC_{0\text{-}24h}$ for infants age 1 to 2 months and age 2 to 3 months were 2440 and 2110 ng.h/mL, respectively in the patients initiated with 0.2 mg/kg, and they were 2440 and 2120, respectively, when the dose normalized risdiplam $AUC_{0\text{-}24h}$ values of the 6 patients who started with 0.04 or 0.08 mg/kg were included.

The individual $AUC_{0\text{-}24h}$ results derived from the popPK model are presented in Table 9.

Table 9: Individual Risdiplam $AUC_{0\text{-}24h}$ Estimates of the SMA Patients of Study BN40703

ID	Age (days)[a]	Dose (mg/kg)[a]	Day 14	Day 28	Day 56
[redacted]	37	0.2	2750	2650	2380
	22	0.2	1230	1350	1310
	22	0.2	NA	2440	2110
	20	0.2	2540	2550	NA
	24	0.2	3530	3320	2850
	22	0.08	974	1610	1960
	28	0.2	2950	3110	NA
	25	0.2	3580	3990	3590
	39	0.2	1930	1920	1770
	31	0.2	1710	2120	1930
	40	0.04	483	516	643
	37	0.08	1400	2080	1800
	41	0.2	1700	1710	NA
	37	0.04	654	660	NA
	24	0.04	676	2980	3180
	35	0.2	3860	4080	NA
	16	0.04	459	480	2120
	29	0.2	2080	2180	1860
	24	0.2	2220	2120	1810

[a]Age and risdiplam dose at the first dose. NA: not available.

In response to the major objection raised during the assessment of the procedure regarding the most appropriate dose regimen for infants <2 months old, the MAH has updated the PK analysis with data available as of April 2022 from all 26 patients enrolled into Study BN40703 (RAINBOWFISH), using the final reference popPK model.

The objective of this analysis was to describe risdiplam PK in 26 patients aged < 6 weeks old at first dose who have been genetically diagnosed with SMA but are not yet presenting with symptoms at enrollment of Study BN40703 (RAINBOWFISH). The previously developed popPK model using a dataset with 19 patients from Study BN40703 served as the reference popPK model in the present analysis, which has included the following:

1) Evaluate the previously developed popPK model against the updated data including risdiplam plasma samples collected from all 26 enrolled patients in the study.
2) Derive secondary PK parameters ($AUC_{0\text{-}24h}$ and C_{av}) of all 26 patients to evaluate risdiplam exposure.
3) Conduct simulations to explore different risdiplam doses in patients < 2 months old.

The previously performed popPK model included a total of 10,939 plasma risdiplam concentrations collected from 544 subjects (61 healthy subjects and 483 SMA patients) participating in either of the six clinical studies BP29840, BP39054, BP39055, BP39056, BN40703 or BP41361. Data from study BN40703 as of 31st August 2021 included a total of 371 samples from 19 SMA patients available. In the updated popPK analysis, 7 additional patients and 182 observations available from Study BN40703 were included in the model, and therefore a total of 553 observations from 26 patients from Study BN40703 were included in the present analysis dataset. Table 10 summarizes the number of observations and number of patients used from each study in the revised dataset.

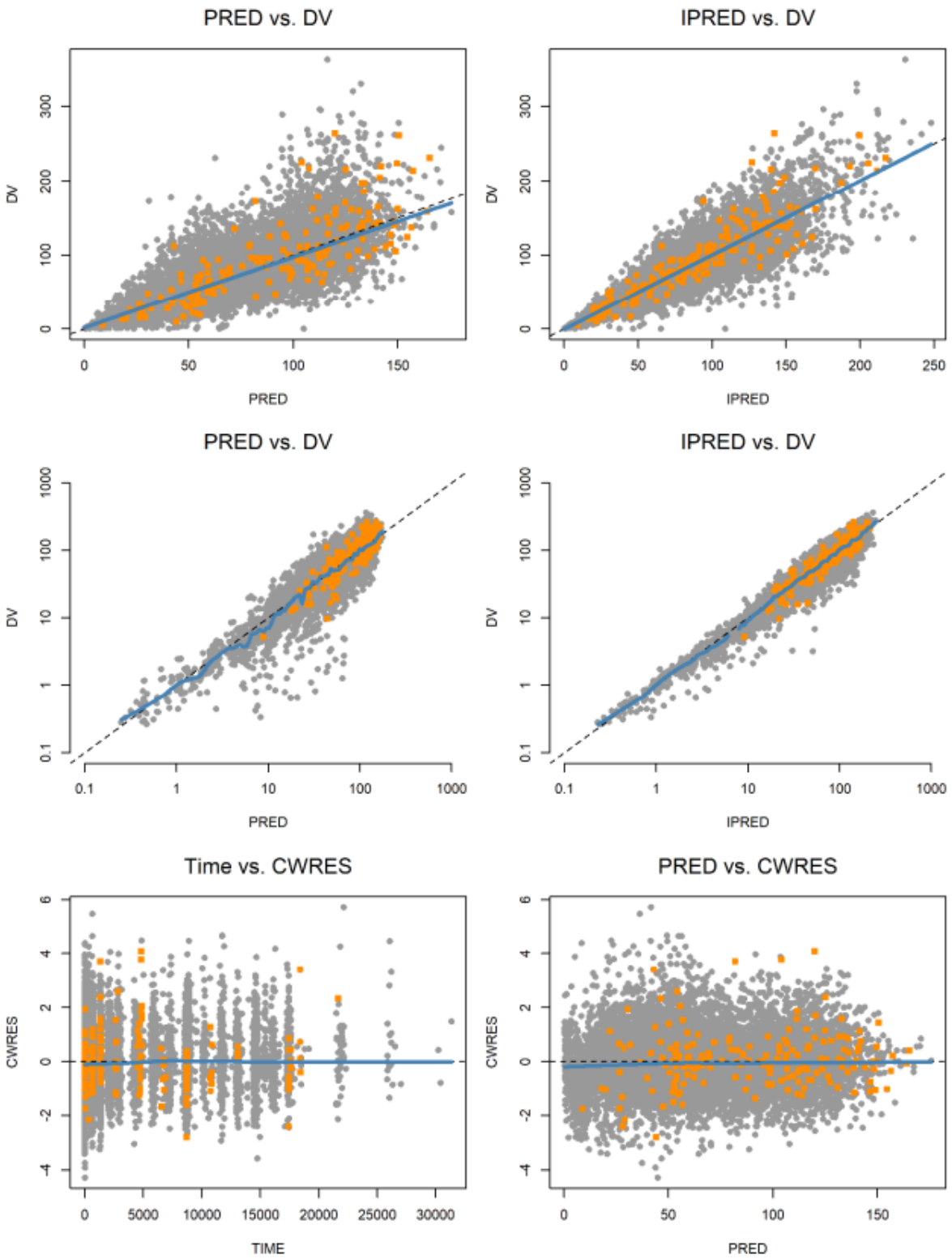
Table 10: Number of Risdiplam Plasma Concentrations by study

Study no.	No. plasma concentration/No. patients
BP29840	426 / 26
BP39054	2361 / 173
BP39055 Part 1	1549 / 51
BP39055 Part 2	2769 / 178
BP39056 Part 1	882 / 21
BP39056 Part 2	1271 / 41
BP40703	**553**[a] / 26
BP41361	1327 / 35
Total	11138[b] / 551

[a] New data combined with the reference PPK modelling data set [1],
[b] After exclusion of 22 observations, total of 11116 observations were included in the analysis.

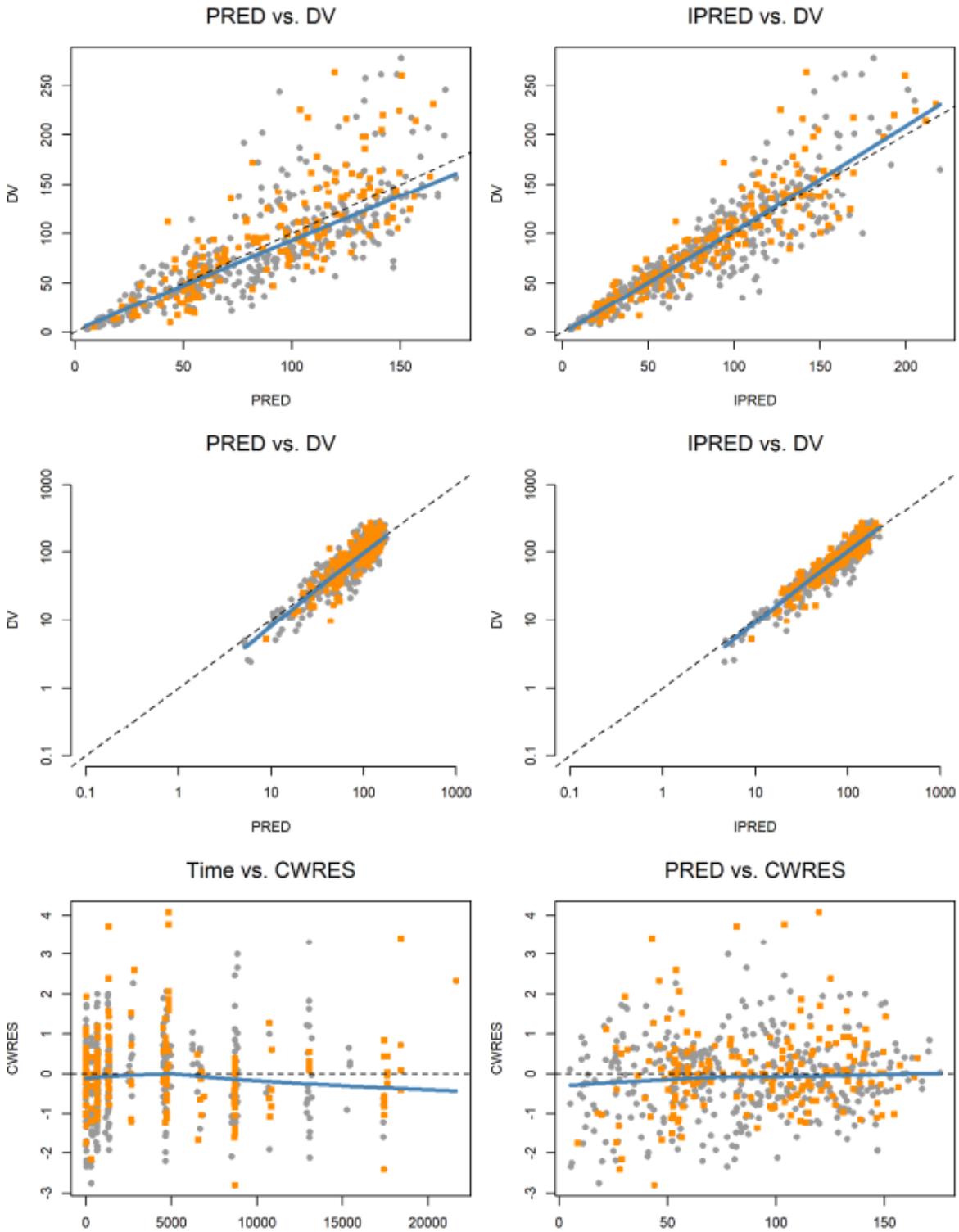
The GOFs by the application of reference popPK model to the combined risdiplam PK dataset without parameter estimation step are shown in Figure 13, Figure 14 and Figure 15 below with indication of these additional data from Study BN40703.

Figure 13: Goodness-of-fit plots for the reference popPK model of risdiplam (all populations)



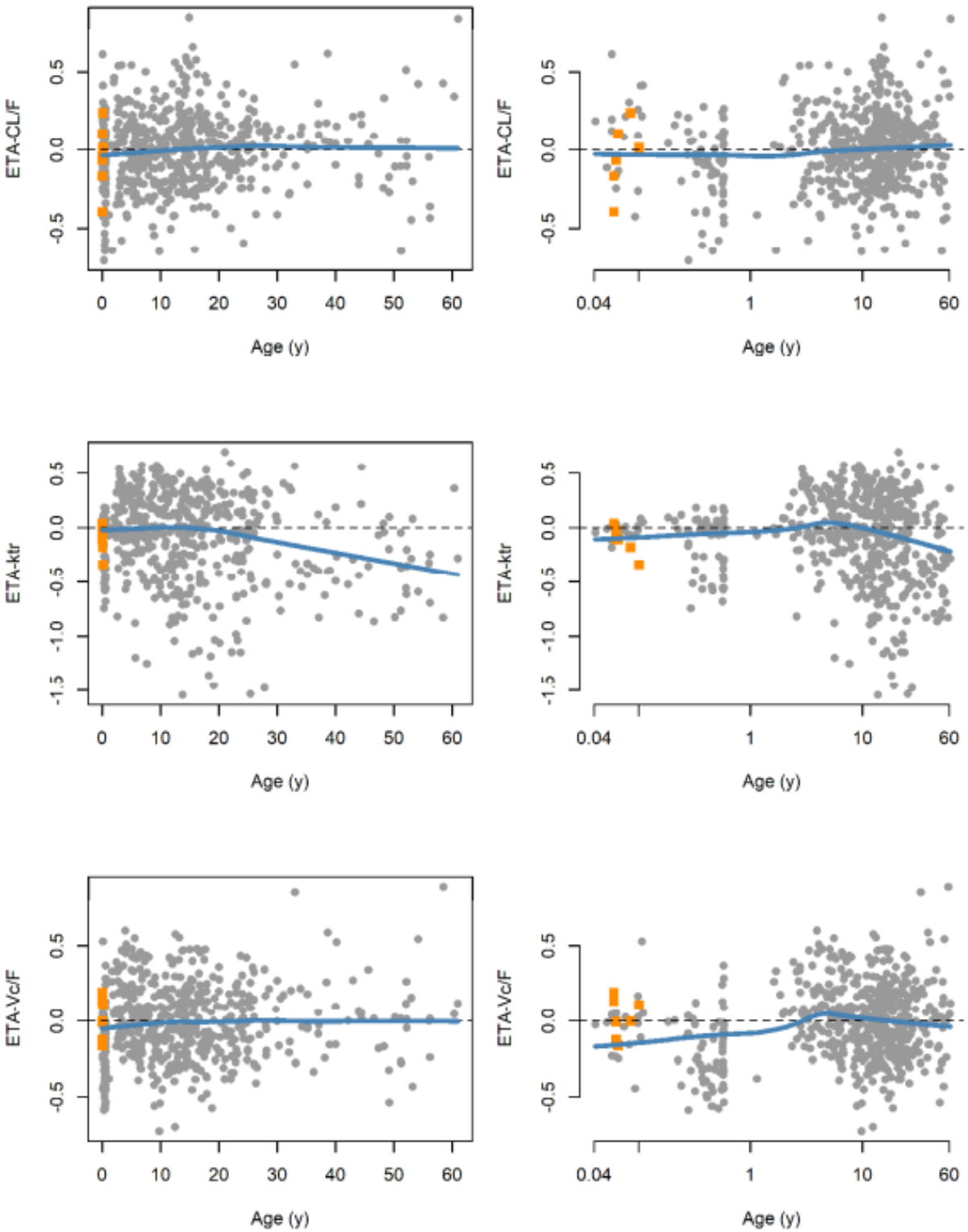
DV – Observed risdiplam concentrations [ng/mL], PRED (IPRED) – NONMEM predicted risdiplam concentrations [ng/mL] based on population (individual) PK parameters, CWRES – conditional weighted residual. The new additional observations collected from BN40703 are shown with orange squares. Black and blue lines indicate identity line and smooth, respectively.

Figure 14: Goodness-of-fit plots for the reference popPK model of risdiplam (SMA patients of Study BN40703 only)



DV – Observed risdiplam concentrations [ng/mL], PRED (IPRED) – NONMEM predicted risdiplam concentrations [ng/mL] based on population (individual) PK parameters, CWRES – conditional weighted residual. The new additional observations collected from BN40703 are shown with orange squares. Black and blue lines indicate identity line and smooth, respectively.

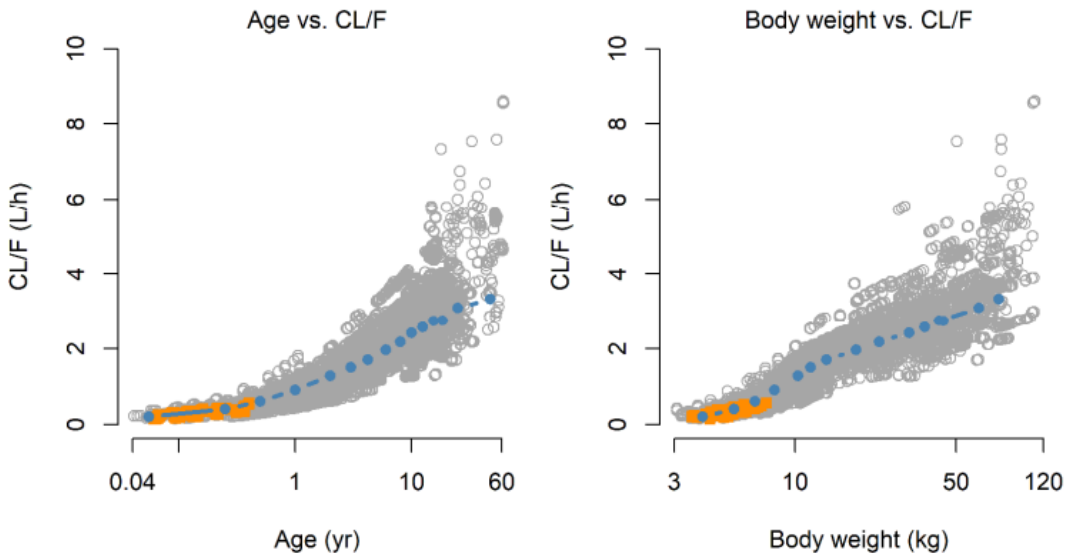
Figure 15: Goodness-of-fit plots for the reference popPK model of risdiplam (all populations) against Age



The new additional observations collected from BN40703 are shown with orange squares. Black and blue lines indicate identity line and smooth, respectively.

The *post hoc* CL/F over the range of age and body weight are compared with the population estimate of CL/F accounting for the median age and body weight per age category in Figure 16.

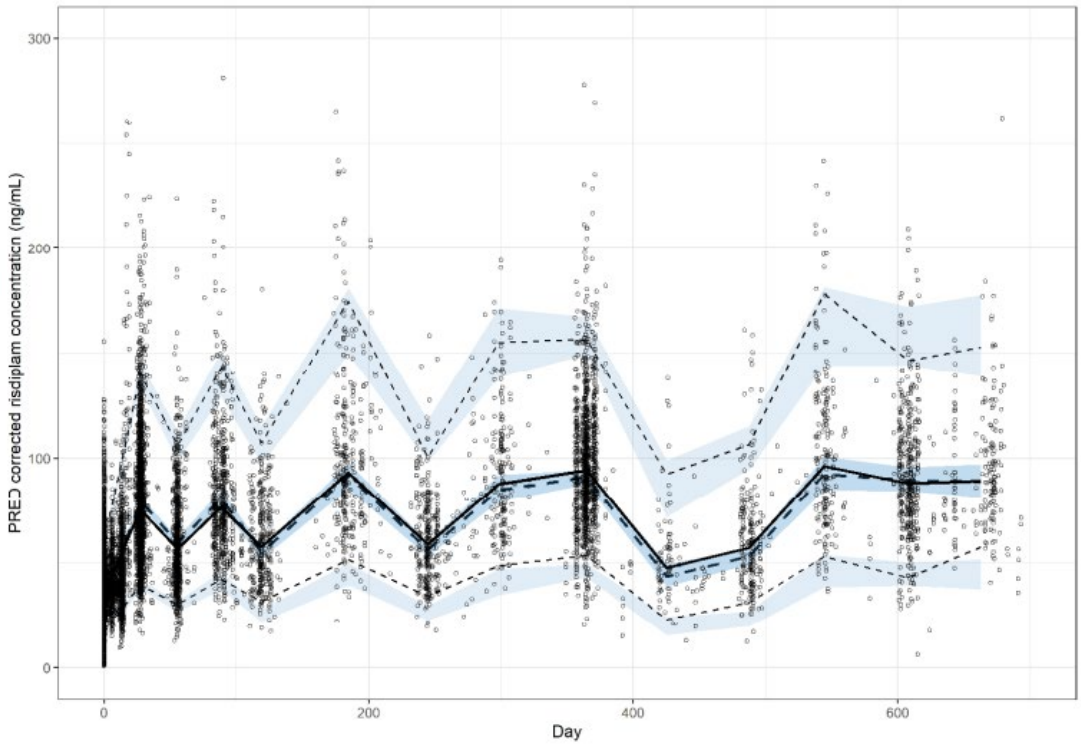
Figure 16: Population and Individual estimates of risdiplam CL/F vs. Age or Body Weight



Individual post-hoc CL/F (gray open circles) over the range of age and body weight are shown. The *post hoc* CL/F of the new seven patients of Study BN40703 are shown with orange squares. Population estimate of CL/F (blue circles and lines) were calculated using the model parameters and actual age and median body weight for each age group of the data base.

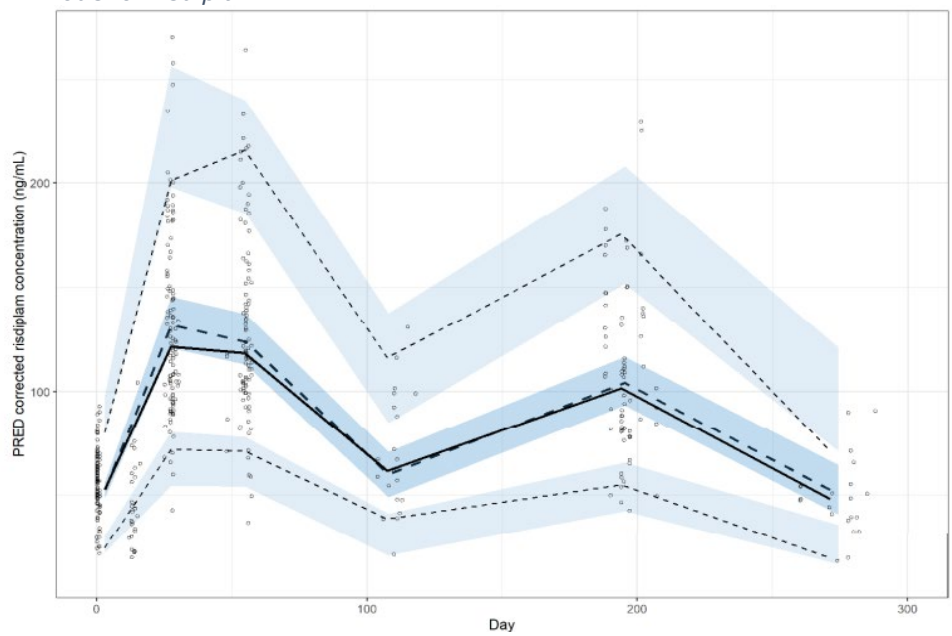
The pc-VPC with time after the first dose for the entire data set and for BN40703 patients only are shown in Figure 17 and Figure 18.

Figure 17: Prediction Corrected Visual Predictive Check (All populations) of the reference popPK model of risdiplam



Individual observations corrected by the respective prediction are shown with solid circles. Blue areas are 95% prediction intervals of the 2.5th, median and 97.5th percentiles of predictions. Dotted and solid lines show 2.5th and 97.5th, and median of the observations, respectively

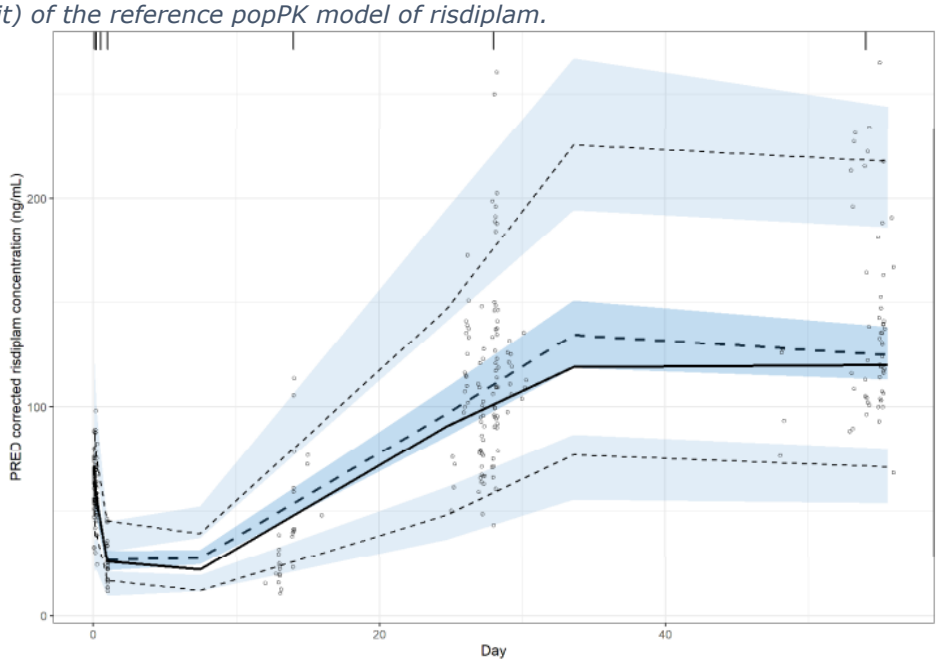
Figure 18: Prediction Corrected Visual Predictive Check (SMA patients of Study BN40703) of the reference popPK model of risdiplam.



Individual observations corrected by the respective prediction are shown with solid circles. Blue areas are 90% prediction intervals of the 5th, median and 95th percentiles of predictions. The 90% interval was selected due to the sample size (n=26). Dotted and solid lines show 5th and 95th, and median of the observations, respectively.

The pc-VPC of the model for all 26 patients of BN40703 up to Day 56 visit is also shown in Figure 19. The median, 5th and 95th percentiles of the observations of Study BN40703 up to Day 56 visits were mostly within the corresponding prediction interval of the pc-VPC (Figure 19). Therefore, the ability of the model to predict the central tendency and variability of risdiplam plasma concentrations of the SMA patients of Study BN40703 was considered satisfactory.

Figure 19: Prediction Corrected Visual Predictive Check (SMA patients of Study BN40703 up to Day 56 Visit) of the reference popPK model of risdiplam.



Individual observations corrected by the respective prediction are shown with solid circles. Blue areas are 90% prediction intervals of the 5th, median and 95th percentiles of predictions. The 90% interval was selected due to the sample size (n=26). Dotted and solid lines show 5th and 95th, and median of the observations, respectively.

Since adequacy of the reference popPK model was demonstrated by the GOFs and pcVPC, and no

appreciable improvement was noted in the model with updated parameter estimates, the reference popPK model was selected as a suitable popPK model for the analysis of the updated data including 26 patients from Study BN40703. A summary of risdiplam $AUC_{0\text{-}24h}$ and C_{av} on Days 14, 28 and 56 after treatment start is shown in Table 11, and $AUC_{0\text{-}24h}$ summarized by age (infants 1 to 2 months old, and infants 2 to 3 months old) is provided in Table 12.

Table 11: Summary of estimated Individual Secondary PK Parameters for the SMA patients of Study BN40703

Parameters	Day 14	Day 28	Day 56
Risdiplam 0.2 mg/kg	n=20	n=20	n=18[a]
Age (days)			
mean	41.9	56.0	82.7
median [range]	38.0 [35.0, 55.0]	52.0 [49.0, 69.0]	80.0 [70.0, 96.0]
Body weight (kg)			
mean	4.62	5.09	5.88
median [range]	4.58 [3.79, 6.12]	5.03 [4.30, 6.57]	5.83 [5.10, 7.20]
$AUC_{0\text{-}24h}$ (ng•h/mL)			
mean	2690	2840	2540
median [range]	2790 [1430, 3960]	2870 [1520, 4580]	2500 [1400, 4120]
C_{av} (ng/mL)			
mean	94.5	107	108
median [range]	96.8 [37.8, 128]	108 [58.3, 156]	109 [58.7, 169]
Dose normalized to 0.2 mg/kg	n=26	n=26	n=24[a]
Age (days)			
mean	42.1	56.0	82.8
median [range]	38.0 [29.0, 55.0]	52.0 [44.0, 69.0]	80.0 [70.0, 96.0]
Body weight (kg)			
mean	4.59	5.06	5.79
median [range]	4.54 [3.63, 6.44]	4.99 [4.03, 6.77]	5.80 [4.53, 7.20]
$AUC_{0\text{-}24h}$ (ng•h/mL)			
mean	2660	2740	2560
median [range]	2650 [1430, 3960]	2780 [1190, 4580]	2500 [1400, 4120]

$AUC_{0\text{-}24h}$ and C_{av} were calculated using simulated plasma concentration of risdiplam at each visit reflecting actual individual age, body weight and dosing information of each patient. A Two patients had observations up to Day 28.

Table 12: Summary of risdiplam $AUC_{0\text{-}24h}$ of the SMA patients of Study BN40703 by age

	Infants 1 month to 2 months	Infants 2 month to 3 months
Risdiplam 0.2 mg/kg	n=20	n=19[b]
Age (days)	50.0 [35.0, 60.0]	79.0 [61.0, 88.0]
$AUC_{0\text{-}24h}$ (ng•h/mL)[a]		
mean	2790	2660
median [range]	2860 [1430, 4580]	2640 [1400, 4120]
Dose normalized to 0.2 mg/kg	n=26	n=25[b]
Age (days)	50.0 [35.0, 60.0]	78.0 [61.0, 89.0]
$AUC_{0\text{-}24h}$ (ng•h/mL)[a]		
mean	2710	2670
median [range]	2860 [1190, 4580]	2660 [1400, 4120]

Median [range] of age is shown. a Individual $AUC_{0\text{-}24h}$ estimates on Day 14 or later were included. Multiple estimates per patient were included when they were available in the specified age range. B One patient was < 2 months old at the latest visit.

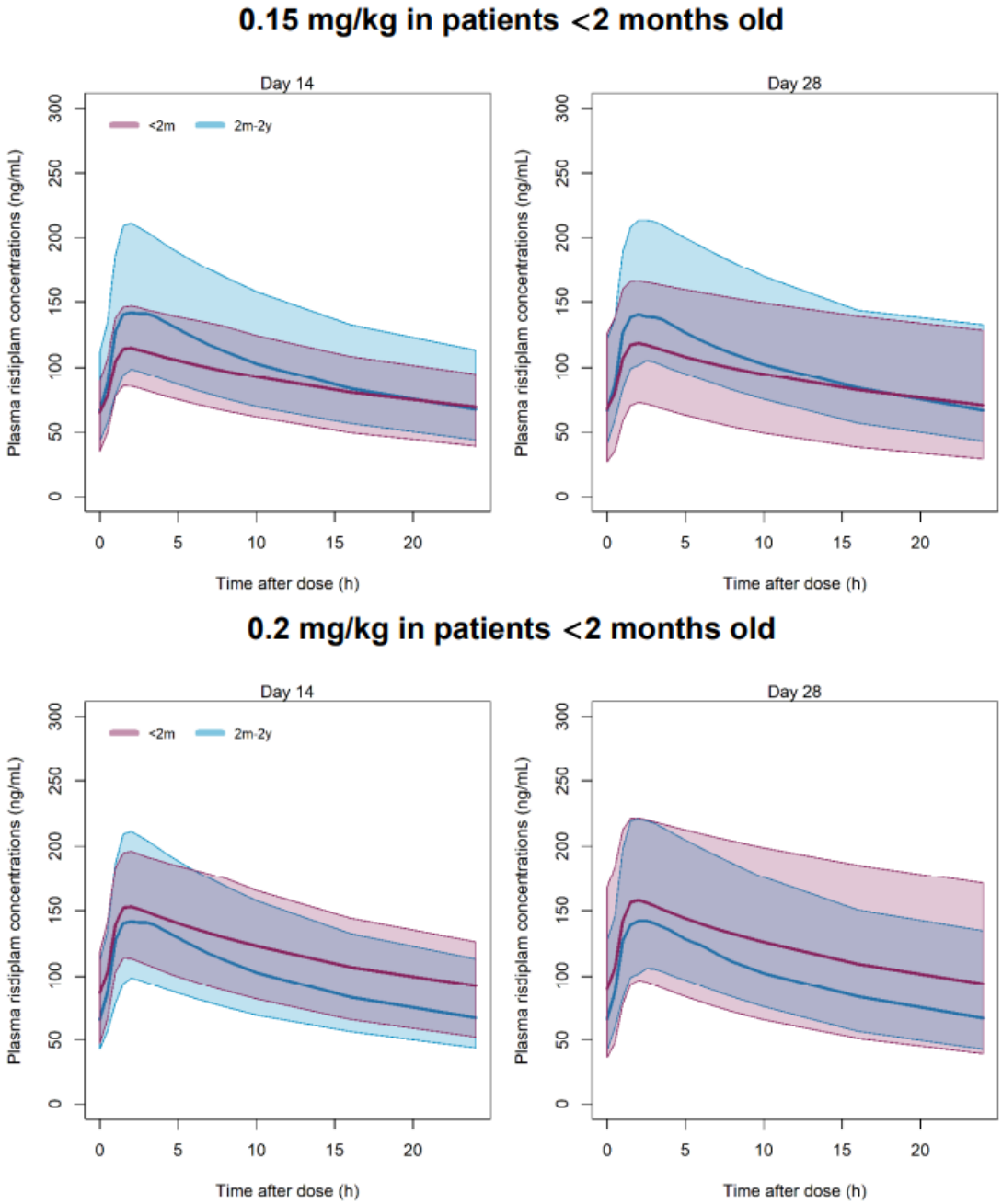
The median risdiplam AUC_{0-24h} of the 20 patients initiated with 0.2 mg/kg on Days 14 and 28 was 2790 and 2870 ng□h/mL, respectively, and decreased to 2500 ng□h/mL on Day 56. Similar values are reported when the dose normalized risdiplam AUC_{0-24h} values for the 6 patients who started with 0.04 or 0.08 mg/kg were included. The median risdiplam AUC_{0-24h} for infants aged 1 to 2 months and age 2 to 3 months were 2860 and 2640 ng.h/mL, respectively, in the patients initiated with 0.2 mg/kg; and were 2860 and 2660 ng.h/mL, respectively, when the dose normalized risdiplam AUC_{0-24h} values of the 6 patients who started with 0.04 or 0.08 mg/kg were included. In the previous analysis with 19 patients with SMA from Study BN40703, the median risdiplam AUC_{0-24h} of the 13 patients initiated with 0.2 mg/kg were 2380, 2440 and 1930 ng.h/mL on Days 14, 28 and 56 respectively. The median risdiplam AUC_{0-24h} for infants age 1 to 2 months and age 2 to 3 months were 2440 and 2110 ng.h/mL, respectively. The updated analysis with 26 patients with SMA in Study BN40703 demonstrated approximately 10□20% higher risdiplam AUC_{0-24h}. The individual AUC_{0-24h} results derived from the popPK model are presented in Table 13 (new patients shown in red boxes).

Table 13: Individual risdiplam AUC_{0-24h} of the SMA patients of Study BN40703

ID	Age (days)[a]	Dose (mg/kg)[a]	Day 14	Day 28	Day 56
[redacted]	23	0.2	3960	4580	4120
	23	0.2	1710	3350	3000
	32	0.2	2310	2230	NA
	37	0.2	2730	2640	2370
	22	0.2	1430	1520	1400
	22	0.2	2540	2510	2220
	20	0.2	2960	3070	2950
	38	0.2	2570	2680	2320
	24	0.2	3530	3320	2870
	22	0.08	1000	1630	2030
	28	0.2	2880	2890	2420
	25	0.2	3700	3790	3420
	39	0.2	1840	1830	1710
	31	0.2	1680	2140	1950
	24	0.2	2850	2960	2740
	25	0.2	3130	2860	2570
	40	0.04	504	541	654
	37	0.08	1440	2260	2180
	41	0.2	1930	1910	1740
	37	0.04	657	707	3130
	24	0.2	2860	2870	2590
	24	0.04	664	2950	3160
	35	0.2	3780	3970	NA
	16	0.04	464	1190	2010
	29	0.2	2190	2280	1910
	24	0.2	3270	3480	3330

Simulations with different risdiplam dosing regimens for infants < 2 months old were performed to explore risdiplam exposures in this population. Actual patients demographics and *post hoc* PK parameters estimated by the popPK model were used. The simulated plasma concentration-time profiles of risdiplam in patients <2 months old after 0.15 mg/kg or 0.2 mg/kg are compared to the simulations in patients 2 months to 2 years old after 0.2 mg/kg (Figure 20).

Figure 20: Simulated plasma concentration-time profiles of risdiplam for patients aged < 2months receiving 0.15 or 0.20mg/kg Risdiplam compared to patients aged 2 Months – 2 Years.



The 5th to 95th percentiles, except for patients < 2 months old on Day 28 where range was shown due to sample size (n<20), and the median of the predictions are shown.

In Table 14, a summary of the simulated maximum serum concentration(C_{max}) and AUC_{0-24h} in patients <2 months old after 0.15 mg/kg or 0.2 mg/kg are compared with older patients from Studies BP39054, BP39055 and BP39056 and BN40703. In Table 15, the simulated C_{max} and AUC_{0-24h} are summarized by age: 1□2 months old or 2□3 months old within BN40703 patient population.

Table 14: Simulated PK parameters of risdiplam summarized by age groups

Age group	Day 14		Day 28		Day 56	
	$AUC_{0\text{-}24h}$ (ng•h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng•h/mL)	C_{max} (ng/mL)	$AUC_{0\text{-}24h}$ (ng•h/mL)	C_{max} (ng/mL)
16d - 2m	**n=26, 38 [29-55] days old**		**n=18, 51 [44-60] days old**			
0.15 mg/kg	2080	113	2200	119	All patients of Study BN40703 were >2 months old	
	2130 [1410, 2890]	115 [85.4, 147]	2190 [1510, 2990]	119 [92.5, 155]		
0.2 mg/kg	2780	151	2930	158		
	2840 [1880, 3850]	153 [114, 197]	2910 [2010, 3980]	158 [123, 207]		
2m - 2y	**n=62, 6.1 [2.6-23.7] months old**		**n=70, 6.3 [2.0-21.1] months old**		**n=80, 6.1 [2.3 – 10.2] months old**	
	2500	150	2570	152	2440	144
	2320 [1580, 3620]	143 [99.5, 211]	2320 [1740, 4080]	144 [106, 222]	2270 [1650, 3450]	139 [105, 200]
2 - 6y	**n=64, 4.0 [2.1-6.0] years old**		**n=61, 4.1 [2.0-6.0] years old**		**n=47, 4.2 [2.4-6.0] years old**	
	2020	124	2090	127	2130	130
	1910 [1410, 2960]	119 [90.7, 168]	1980 [1350, 3090]	123 [94.6, 177]	2090 [1490, 2920]	127 [99.1, 173]
6 - 12y	**n=73, 9.1 [6.0-11.8] years old**		**n=69, 9.1 [6.1-11.9] years old**		**n=49, 9.2 [6.1-12.0] years old**	
	2070	120	2200	127	2200	127
	2070 [1430, 2740]	117 [81.5, 162]	2220 [1480, 2980]	126 [83.5, 173]	2190 [1550, 2870]	125 [91.4, 163]
12 - 18y	**n=101, 14.4 [12.0-18.8] years old**		**n=105, 14.5 [12.0-18.9] years old**		**n=49, 14.6 [12.1-18.96] years old**	
	1620	87.9	1740	93.1	1740	90.8
	1570 [935, 2410]	83.1 [55.1, 134]	1690 [1060, 2500]	87.7 [59.1, 138]	1660 [1150, 2330]	84.6 [66.3, 126]
≥ 19y	**n=71, 24.8 [19.0-61.0] years old**		**n=68, 24.8 [19.0-61.1] years old**		**n=21, 23.0 [19.1-52.3] years old**	
	1490	78.2	1600	82.9	1650	84.3
	1510 [921, 2050]	79.8 [46.0, 110]	1590 [972, 2220]	83.3 [47.7, 122]	1660 [1130, 2130]	86.3 [56.4, 107]

Median [range] are shown for age, mean, median[5th -95th percentiles] are shown for the PK parameters. The patients of Study BN40703 older than 2 months old at Days 28 and/or 56 visit were included in the summary for 2 months-2 years old group

Table 15: Simulated risdiplam $AUC_{0\text{-}24h}$ and C_{max} after 0.15 or 0.20mg/kg in the SMA patients of Study BN40703 summarized by age.

	Infants		**Infants**	
	1 month to 2 months		**2 months to 3 months**	
Dose	50.0 [35.0, 60.0] days old (n=26)		78.0 [61.0, 89.0] days old (n=25[a])	
	$AUC_{0\text{-}24h}$ (ng•h/mL)[b]	**C_{max} (ng/mL)[b]**	**$AUC_{0\text{-}24h}$ (ng•h/mL)[b]**	**C_{max} (ng/mL)[b]**
0.15 mg/kg[c]	2140	116	2430	135
	2140 [1410, 2930]	117 [84.5, 152]	2410 [1720, 3210]	133 [109, 170]
0.2 mg/kg	2850	154	2700	147
	2860 [1880, 3900]	156 [113, 203]	2650 [1840, 3920]	144 [115, 194]

Mean, Median [5-95th] of age is shown. A One patient was < 2 months old at the latest visit and not included in the summary for 2□3 months old. b Individual $AUC_{0\text{-}24h}$ estimates on Day 14 or later were included. Multiple estimates per patient were included when they were available in the specified age range. c0.15 mg/kg was given until age of 2 months old and 0.2 mg/kg was given thereafter.

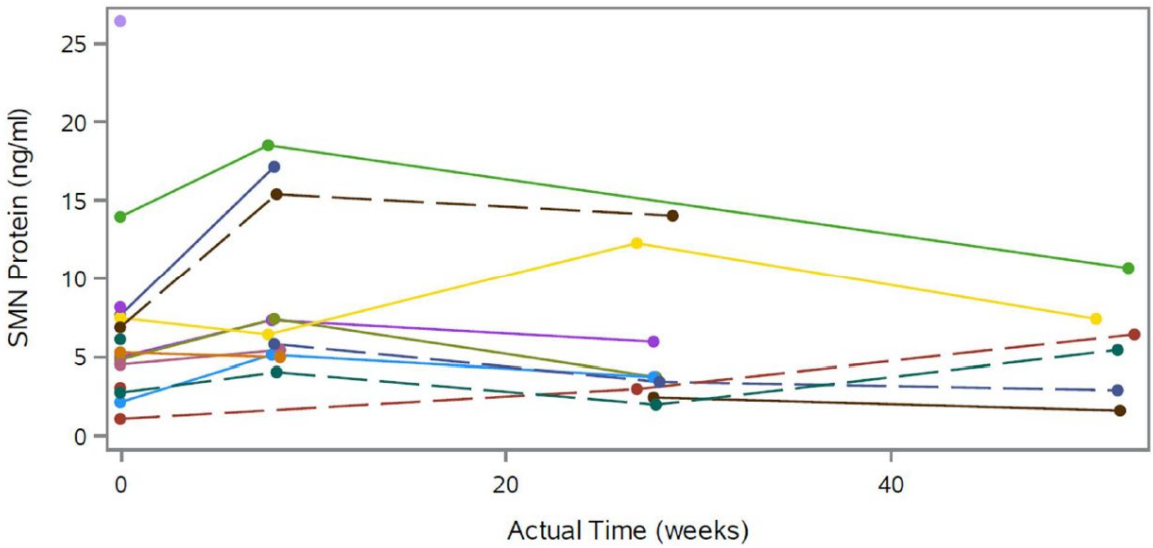
The simulations with 0.2 mg/kg or 0.15 mg/kg in patients <2 months old indicated that the median simulated $AUC_{0\text{-}24h}$ on Days 14 and 28 were 2840 and 2910 ng.h/mL after 0.2 mg/kg, and 2130 and 2190 ng.h/mL after 0.15 mg/kg, respectively. The median simulated $AUC_{0\text{-}24h}$ of 1 to 2 months old and 2 to 3 months old were 2860 and 2650 ng.h/mL after 0.2 mg/kg and 2140 and 2410 ng.h/mL after 0.15 mg/kg followed by 0.2 mg/kg at age of 2 months. Therefore, simulations suggested a dose of 0.15 mg/kg for patients 20 days to <2 months old, ensuring that the exposure obtained in these young patients is well within the exposure range observed for older children, i.e. mean of 2130 on Day 14 and 2190 ng.h/mL on Day 28, more compliant with the specified exposure cap of a mean $AUC_{0\text{-}24,ss}$ of 2000 ng.h/mL. Despite these simulations results, the MAH has not provided additional data supporting the ontogeny of the flavin monooxygenase 3 (FMO3) enzyme, which could be included in the final popPK model for more accurate predictions of risdiplam exposure in neonates below 20 days administered with risdiplam 0.15 mg/kg.

2.4.3. **Pharmacodynamics**

PD biomarkers (SMN protein and SMN2 mRNA) measured in blood samples from 7 children (4 with 2 SMN2 copies, 2 with 3 copies and 1 with ε 4 copies) who completed at least 12 months of treatment in Study BN40703 have shown the following individual measurements over time per patient:

- An overall trend towards increase in SMN Protein in blood over time (Figure 21).

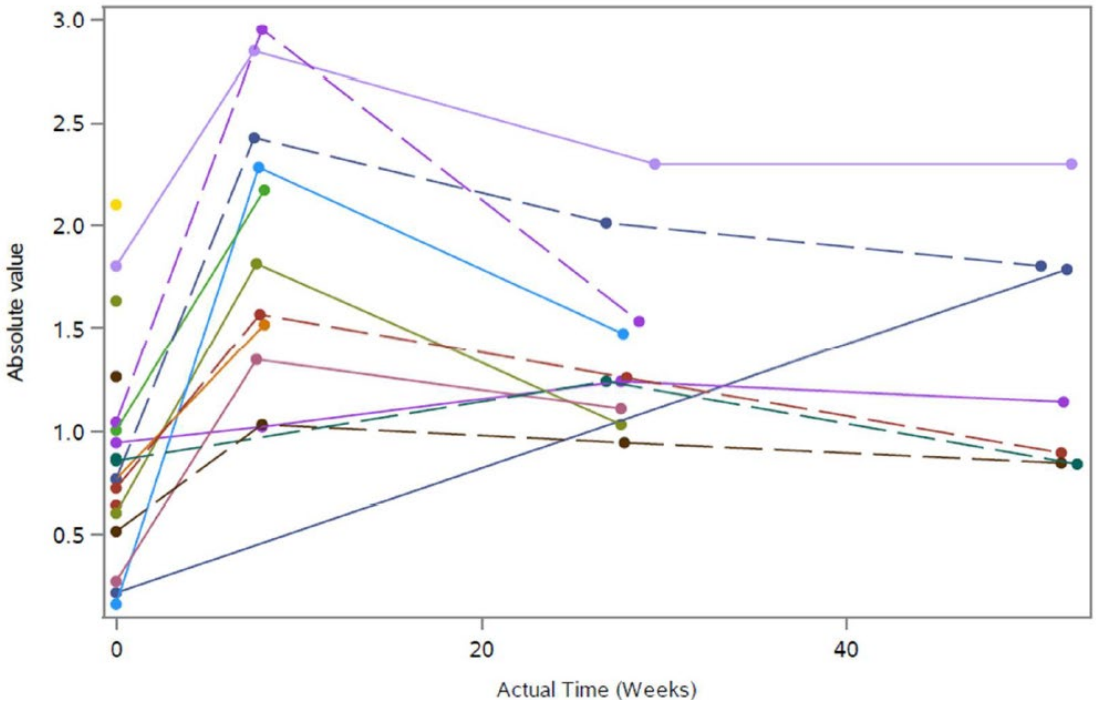
Figure 21: Study BN40703: SMN protein in blood versus time



SMN = Survival Motor Neuron

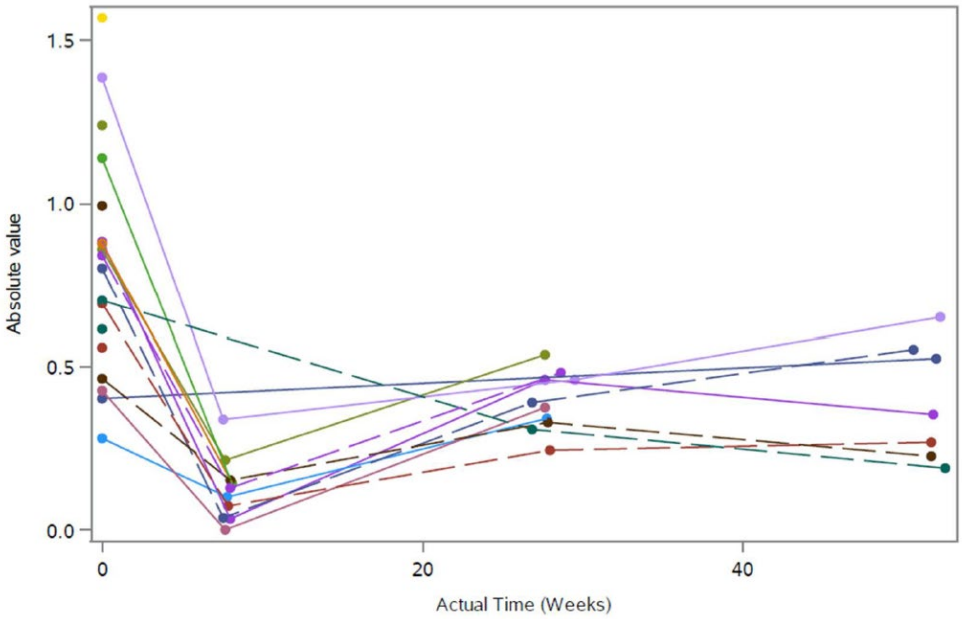
- An increase trend in SMN2 mRNA in blood over time (Figure 22) and a concomitant decrease in SMN⊗7 mRNA in blood over time (Figure 23) that supports risdiplam's mode of action (shift from the SMN⊗7 mRNA to full-length mRNA) in children from birth to 6 weeks

Figure 22: Study BN40703: fully-length SMN2 mRNA in blood versus time



mRNA = messenger ribonucleic acid; *SMN2*=Survival of Motor Neuron 2 (gene/RNA)

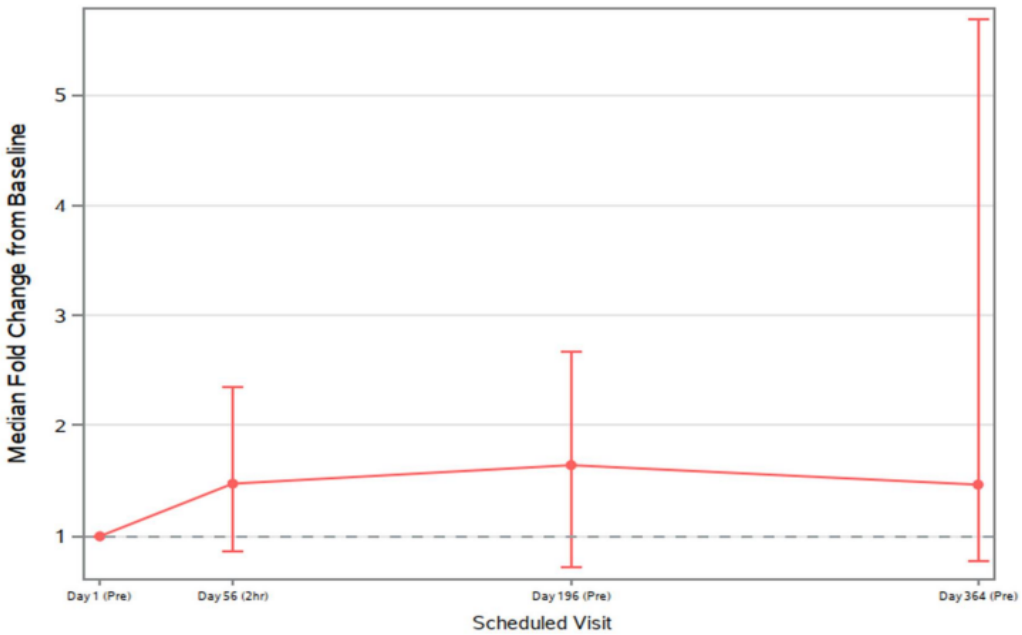
Figure 23: Study BN40703: SMN⊗7 mRNA in blood versus time



mRNA =messenger ribonucleic acid; *SMN⊗7*=Survival of Motor Neuron 2 mRNA with exon 7 missing.

Upon request, the MAH provided a graph reporting the SMN protein median fold change from baseline for study RAINBOWFISH as already done for FIREFISH study in order to better compare the PD profile between patients. The median fold change from baseline for SMN protein in Study BN40703 (RAINBOWFISH) is shown in Figure 24.

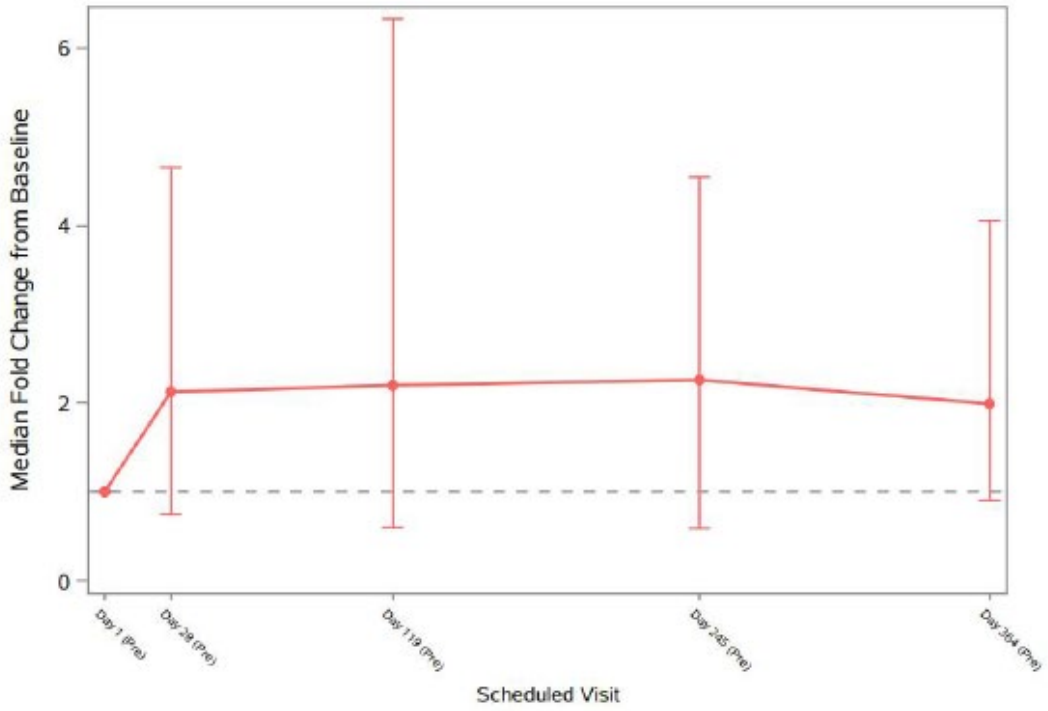
Figure 24: Study BN40703: SMN Protein (change from baseline) after risdiplam treatment



Scheduled Visit			
Day 1 (Pre)	**Day 56 (2h)**	**Day 196 (Pre)**	**Day 364 (Pre)**
[n=15]	[n=10]	[n=7]	[n=4]
1.00	1.47	1.63	1.46
(1.00–1.00)	(0.85–2.35)	(0.71–2.67)	(0.77–5.69)

PD profile for patients under 2 months of age can be considered different compared to older children (Figure 25) given that the 2-fold change has not been reached.

Figure 25: Study BP39056 Part 2: SMN Protein (change from baseline) in SMA type 1 infants after risdiplam treatment



2.4.4. Discussion on clinical pharmacology

Analytical method

The analytical method used to determine risdiplam, its main metabolite is the same used within the initial marketing authorisation application, and it has undergone a full validation in accordance with the current EMEA/CHMP/EWP/192217/2009 Rev.1 Guideline and complies with it in terms of selectivity, calibration curve, accuracy, precision, dilution integrity, matrix effect. No concerns are raised about the bioanalytical report SPI_S_18080 relevant to RAINBOWFISH study, which is in line with both validation and above-mentioned guideline.

Clinical PK-PD

In order to compare the exposure achieved in Study BP39056 (FIREFISH) and Study BN40703 (RAINBOWFISH), the MAH has provided only a graphical representation, with only simulated data being compared.

The proposed oral dose (0.2 mg/kg) was selected for children from birth to 6 weeks of age, to the target exposure of mean $AUC_{0\text{-}24h,ss} \leq 2000$ ng•h/mL per protocol, instead, the estimated mean exposure for infants age 1 to 2 months in Study BN40703 was higher, i.e. 2500 ng•h/mL. The MAH was asked to justify the dose appropriateness in light of the discrepancy between the target AUC value of 2000 ng • h/mL (approved as cap in the PIP) and the observed higher median AUC value of 2500 ng • h/mL. This also considering that at least ¼ of patients for each time point have AUC values greater than 2000 ng • h/mL.

During the procedure and as a response to the above-mentioned request, the MAH updated the PK analysis with data available as of April 2022 from all 26 patients enrolled into Study BN40703 (RAINBOWFISH), using the final reference popPK model. The new model is considered to better fit the combined data, based on the numerical stability, GOFs and pc-VPC. Based on the model, simulations suggested a dose of 0.15 mg/kg for patients 20 days to <2 months old, ensuring that the exposure obtained in these young patients is well within the exposure range observed for older children, i.e. mean of 2130 on Day 14 and 2190 ng.h/mL on Day 28, more compliant with the specified exposure cap of a mean $AUC_{0\text{-}24,ss}$ of 2000 ng.h/mL. For the other age groups, it is proposed a dose of 0.20 mg/kg for patients from 2 months to <2 years of age, a dose of 0.25 mg/kg for patients ≥2 years of age (<20 kg) and a dose of 5 mg for patients ≥2 years of age (≥20 kg), which enable to attain a similar exposure.

During the procedure, the MAH discussed the potential involvement of the FMO1 and FMO3 activity modification in the target population. While it can be agreed that the higher than expected AUC levels could be a consequence of the expected reduced activity of FMO3 in paediatric patients < 2 months of age, the MAH acknowledged that there is a correlation between higher dose to risdiplam (in terms of AUC) and low levels of FMO3 in the children below 2 months of age Moreover, no additional data supporting the ontogeny of the FMO3 enzyme could be included in the final popPK model which could only be considered explorative as a full qualification and validation cannot be provided (mainly with respect to FMO3).

From available PK data no recommendation on posology may be made below 20 days of age because only one 16 days old neonate received risdiplam at a considerably lower dose, compared to the one proposed for marketing. However, the MAH provided data on the use of risdiplam in patients below 20 days of age who were treated with risdiplam 0.15mg/kg once daily in countries where it is indicated from birth. Given the well-recognized need for an early initiation of treatment in SMA and the absence of safety signals in this subpopulation treated with the proposed dose of 0.15mg/kg/day, the CHMP agreed on recommending the 0.15mg/kg/day dose for newborns up to 2 months of age. Section 4.2 of the SmPC has been updated to reflect the updated posology in patients 2 months of age and younger. Section 5.2 of the SmPC has also been updated with the new PK data.

In order to strengthen the confidence on the optimal recommended dose in this very young population, the MAH has developed Study BN44619 (PUPFISH) to assess the PK and safety of risdiplam in SMA patients from birth (day 1) to under 20 days of age at first dose. Study BN44619 (PUPFISH) has been added as additional pharmacovigilance activity in the RMP to enlarge evidence on the safety profile in patients below 1 month of age – currently considered limited (see discussion on safety for further details).

From a PD perspective, the MAH provided- upon request -median fold change from baseline for SMN protein in Study BN40703 (RAINBOWFISH). However, these data are currently difficult to interpret for Study BN40703, due to the small number of patients and limited follow-up duration. Further, literature indicates that SMN protein levels change in the first weeks and months of life, which would make the calculation of the true change from baseline (which occurs, by definition, earlier than the subsequent post-treatment time-points) difficult, as the baseline shifts over time (Alves et al., 2020; Ramos et al., 2019). These interim data are therefore not comparable with the previously provided SMN protein data from Study BP39056 (FIREFISH) and BP39055 (SUNFISH) in the SmPC for which SMN protein information was available from all patients for all timepoints up to at least one year of treatment. This information has been clarified in section 5.1 (pharmacodynamic effects) of the SmPC.

Finally, Exposure – Efficacy analyses have not been conducted due to the low number of patients enrolled and the very variable treatment duration, with limited follow-up. Upon request, the MAH provided exposure safety correlations with updated safety data (CCOD: 25 February 2022) (see below Exposure- Safety analysis in the Clinical safety section).

2.4.5. Conclusions on clinical pharmacology

Although no recommendation on posology can be inferred for patients below 20 days of age based on PK data, the dose of 0.15mg/kg for this subpopulation can be agreed based on the well-recognized need for an early initiation of treatment in SMA and the absence of safety signals in this subpopulation already treated with the proposed dose of 0.15mg/kg/day in countries where risdiplam is indicated from birth.

2.5. Clinical efficacy

Title of Study

Study BN40703 (RAINBOWFISH)

Methods

Study BN40703 is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, PK, and PD of risdiplam in patients aged from birth to 6 weeks (at first dose) who are genetically diagnosed with SMA (SMN1 deletion and any SMN2 copies) but not yet presenting with symptoms (Table 16).

The study consists of a screening period, a treatment phase, an open-label extension phase of at least 36 months (Month 24 up to Month 60) and a follow-up period, for a total treatment duration of at least 5 years

for each infant enrolled. During the treatment phase, all patients will receive risdiplam orally once daily for 2 years at a dose selected to achieve the targeted exposure range.

At the time of the application, the study is ongoing, and enrollment will continue until at least 25 patients are enrolled (including a minimum of 5 patients who meet the criteria for the primary efficacy population) or until a total of 10 patients who meet the criteria for the primary efficacy population are enrolled. The primary efficacy analysis population is defined as all infants in the intent-to-treat population with 2 SMN2 copies (excluding the known SMN2 gene modifier mutation c.859G > C) and a baseline compound muscle action potential (CMAP) amplitude ε1.5 mV.

This submission provides PK, PD, safety, and efficacy data from Study BN40703 at the time of an interim analysis (CCOD 1 July 2021 for PD, efficacy and safety data, and 31 August 2021 for PK data) in order to support the dose determination for patients below 2 months of age. The primary endpoint (sitting without support for 5 seconds, as assessed by Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID III) Gross Motor Scale) was not evaluated at this time, in order to preserve the type 1 error for the future primary efficacy analysis. Interim results for some secondary efficacy endpoints are presented, including data from the Hammersmith Infant Neurological Examination, Module 2 (HINE-2), which includes an assessment of sitting.

Table 16: Overview of Clinical Study Contributing to the Application

Study Number	Study Design and Objectives	Population	Number of Patients and Data Contributing to Application
BN40703 (RAINBOWFISH), an ongoing Phase II study	Open-label, single-arm, multicenter study. Objectives: Efficacy, safety, PK and PD	Infants aged from birth to 6 weeks with genetically diagnosed presymptomatic SMA	At least 25 patients planned. 18 patients enrolled as of 1 July 2021, including 7 patients treated for at least 12 months 19 patients with PK data as of 31 August 2021

PD = pharmacodynamics; PK = pharmacokinetics; SMA = spinal muscular atrophy.

The MAH sought written input from the CHMP Rapporteur and Co-Rapporteur in May 2021 on an initial proposal for a variation to update the label based on the Study BN40703 interim analysis, and their feedback was supportive. Previous health authority feedback on the nonclinical, clinical, and technical development programs for risdiplam can be found in the original submission.

Study BN40703 is being conducted in accordance with the protocol and with the following: consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines, applicable ICH Good Clinical Practice Guidelines, applicable laws and regulation. No audits were conducted for this study.

Study participants

The RAINBOWFISH Study was open for inclusion of infants aged from birth to 6 weeks, with genetically diagnosed presymptomatic SMA.

Treatments

A once daily oral dose of 0.2 mg/kg risdiplam was selected as the pivotal dose for Study BN40703 and was, therefore, initially proposed as the recommended dosing regimen for infants 16 days to 2 years of age.

Table 17: Risdiplam Dosing Regimen

Age	Body Weight	Recommended Daily Dose
16 days to < 2 years of age	-	0.20 mg/kg
ε 2 years of age	< 20 kg	0.25 mg/kg
ε 2 years of age	ε 20 kg	5 mg

Objectives

The objective was to evaluate the efficacy of risdiplam in patients with two copies of the SMN2 gene (excluding the known SMN2 gene modifier mutation c.859G > C) and baseline CMAP amplitude ε1.5 mV.

Outcomes/endpoints

The primary endpoint of the study is the proportion of infants who are sitting without support after 12 months of treatment, as assessed in Item 22 of the BSID III Gross Motor Scale. Per protocol, the primary efficacy analysis will be conducted when the last patient enrolled (irrespective of SMN2 copy number) has reached 12 months of treatment (expected in mid-2023). Results from BSID-III (primary endpoint) have not been provided in this analysis, in order to preserve the type 1 error for the primary endpoint.

Similarly, the proportion of patients developing clinically manifested SMA (listed among secondary endpoints) has not been reported in this interim-CSR as the definition includes motor milestone development, one of which includes Item 22 of the BSID-III Gross Motor Scale. By SAP definition, clinically manifested SMA, also includes growth measures. Growth measures (listed among secondary endpoints) have not been provided in this interim CSR. Also, respiratory endpoint (proportion of patients who do not receive any pulmonary care at month 12) (listed among secondary endpoints) have not been provided in this interim CSR. These results will be provided at the time of the primary analysis, when all patients have completed 12 months of treatment.

Efficacy endpoints:

- Proportion of patients who achieve the attainment levels of the motor milestones assessed in the HINE-2 (at Month 12 of treatment)
- Change from baseline in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) motor function scale (at Month 12 of treatment)
- Proportion of patients who achieve a score of 40 or higher, 50 or higher, and 60 or higher in the CHOP-INTEND motor function scale (at Month 12 of treatment)
- Change from baseline in CMAP amplitude (at Month 12 of treatment)
- Ability to swallow and to feed orally (at Month 12 of treatment)
- Number of hospitalizations
- Time to death and/or permanent ventilation (at Month 12 of treatment)

Safety endpoints

- Incidence and severity of AE and serious adverse events (SAE)
- Incidence of treatment discontinuation due to AE
- Incidence of abnormal laboratory values
- Incidence of abnormal electrocardiogram (ECG) values
- Vital signs abnormalities

Sample size

The MAH changed the primary analysis population -due to the difficulty and slow enrolment in the ongoing RAINBOWFISH Study- from "*at least 10 infants at inclusion with 2 SMN2 copies and a baseline CMAP ≥1.5 evaluable for the primary endpoint"* to: "*at least 25 infants, including a minimum of 5 patients who meet the criteria for the primary efficacy population are enrolled OR a total of 10 infants who meet the criteria for the primary efficacy population are enrolled.*

This interim CSR presents data from the first 18 patients enrolled at the time of the CCOD, including 7 patients who had reached at least 12 months of treatment.

Randomisation

There was no randomisation as this was a non-controlled, open label trial.

Blinding (masking)

By design, there was no blinding.

Statistical methods

Descriptive statistics are provided for the efficacy and safety endpoints listed above.

Results

Recruitment

The first patient was enrolled on 7 August 2019 and the CCOD for this report was on 1 July 2021.

After almost 2 years of enrolment, out of 14 active sites, only 6 centres across 6 countries enrolled at least 1 patient (Australia, Belgium, Brazil, Russia, Taiwan, U.S.A.).As regards to sites from EU countries, out of the 4 active sites (1 in Belgium and 1 in Italy and 2 sites in Poland), only the site from Belgium had enrolled at least 1 patient.

Baseline data

A total of 20 patients were screened for the study, of whom 2 patients were screening failures (2/20, 10%); reasons for screening failure was not provided in a patient from Australia and was unclear (explanation provided: "*Absence of clinical signs or symptoms at screening*") in a patient from Brazil.

Overall, 18 patients were enrolled in the study across 6 different sites in 6 countries. 2/18 were Asian patients (both from Taiwan). Only 2 patients from Belgium were enrolled in EU Countries. Other 4 patients (included in the "Europe" Region) were enrolled in Russia. 6 further patients were enrolled in Australia, 1 in US and 3 in Brazil.

All patients received treatment with risdiplam. At the time of the CCOD for this report, all 18 patients (100%) were still in the study, and 7 patients had completed 12 months of treatment.

SMA identification occurred through: newborn screening in 13/18 (72%) of the enrolled newborns; family history (4/18, 22%) and other (1/18, patient, 6%).

Overall, 10 patients had previous conditions. Prior conditions occurring in more than 1 patient were jaundice and abdominal pain. All other conditions occurred in single patients. One of the enrolled patients reported retinopathy among prior diseases. Only one patient reported SMA as congenital, familial and genetic disorders (even though SMA identification occurred through family history in 4/18 of the enrolled patients)

At the time of the CCOD for this report, 18 patients (100%) were still on study, and 7 patients had completed 12 months of treatment. No patients had withdrawn from treatment, reached the open label extension (OLE) phase or entered the safety follow-up period at the time of this report.

There was a similar number of male/female patients (44.4%/55.6%), and most patients (83.3%) were White. The median age at first dose was 26.5 days (range: 16-40 days).

Most patients (72.2%) were identified via newborn screening. Median scores at baseline were as follows: CHOP-INTEND: 49.0 (range: 35.0-58.0); HINE-2: 2.0 (range: 0.0-6.0); CMAP amplitude: 3.6 (range: 0.5-6.7).

Based on PK data (reported separately), the dose of risdiplam selected to achieve the target exposure was 0.2 mg/kg. A total of 18 patients received at least one dose of study treatment. The median duration of treatment exposure was 8.7 months (range: 0.5-22.8 months). The median dose intensity was 100.4% (range: 97.3%-103.4%). All patients eventually received a dose of 0.2 mg/kg.

Numbers analysed

The efficacy data includes 7 patients (4 patients with 2 SMN2 copies, 2 patients with 3 SMN2 copies and 1 patient with ≥4 SMN2 copies) who completed at least 12 months of treatment.

Outcomes and estimation

The efficacy data are reported in Table 18, Figure 26 and Figure 27 and summarized as follows:

- The median HINE-2 total score change from baseline seen at Month 12 reflects the fact that patients had achieved meaningful gains in motor function. The low HINE-2 total scores seen at baseline reflects the age range of enrolled patients (6 weeks of age)
- Results on motor function as assessed by HINE-2: At Month 12 all patients were sitting without support. Six of 7 patients achieved the highest levels of sitting (pivot/rotate); the remaining 1 patient with 2 SMN2 copies and baseline CMAP <1.5 mV achieved a stable sit. Six of 7 patients achieved the highest levels of rolling (supine to prone) and the remaining 1 patient with 2 SMN2 copies and baseline CMAP <1.5 mV achieved prone to supine rolling. Five of 7 patients could stand with support or stand unaided, the other 2 patients, both with 2 SMN2 copies and baseline CMAP <1.5 mV did not support weight. Three of 7 patients (including 1 patient with 2 SMN2 copies and baseline CMAP >1.5 mV) were walking independently and 1 patient was able to bounce (the remaining 3 patients [2 patients with 2 SMN2 copies; 1 patient with 4 SMN2 copies] were not tested at Month 12).
- Results on motor function as assessed by CHOP-INTEND: Patients achieved high levels of motor function prior to Month 12, with 10 of 13 patients (76.9%; 90% CI: 50.5, 93.4) achieving scores of ≥60 at Month 4 (Week 16). Four of 7 patients achieved the maximum score of 64 at Month 12.
- At baseline, the median CMAP amplitude for all patients (n=18) was 3.6 mV (range: 0.5-6.7 mV). Of the 7 patients who had reached Month 12 by the time of the CCOD, 5 of 7 patients showed an increase in CMAP amplitude between baseline and Month 12. The remaining 2 patients (both with 2 SMN2 copies) had the same CMAP amplitude at baseline and Month 12.
- Of the 7 patients who had reached Month 12 by the time of the CCOD, all patients (100%; 90% CI: 65.2%, 100.0%) had the ability to feed orally. All patients (100%) were fed exclusively by mouth.
- Of the 7 patients who had reached Month 12 by the time of the CCOD, all patients (100%; 90% CI: 65.2%, 100.0%) had the ability to swallow. All patients (100%) were able to swallow purees. At the time of the CCOD, 6 of 7 patients (85.7%) were reported to be able to swallow solid food. One patient (14.3%) with ≥4 SMN2 copies was reported to not be able to swallow solid food; however, after the CCOD, this was determined to be a data error and this patient was able to swallow solid food. Thus, all patients (100%) were able to swallow solid food at Month 12.
- No patients required any overnight hospitalization.
- All patients (100%) were alive without permanent ventilation at the time of the CCOD.

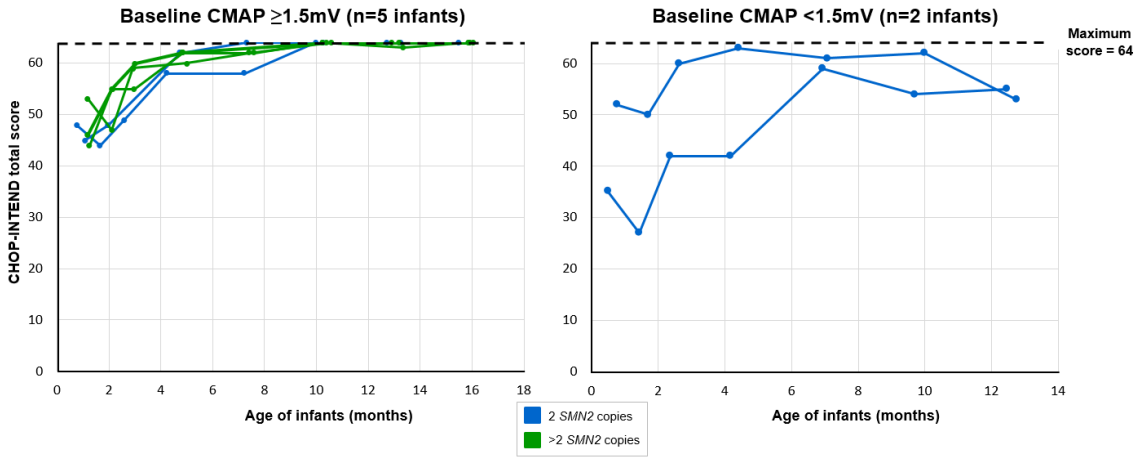
Of the 4 patients with 2 *SMN2* copies, 1 could stand unaided and walk independently, and 1 could stand with support and bounce at Month 12. The latter patient gained the ability to stand unaided and walk while holding on ("cruising") by Month 18 of treatment (at the time of the CCOD). The remaining 2 patients with 2 *SMN2* copies had low CMAP amplitude values at baseline (0.46 and 0.6 mV). Despite this finding, both patients were developing complex motor abilities, such as rolling and crawling (1 patient crawled on elbow and 1 crawled flat on abdomen) after 12 months of risdiplam treatment (their last visit before the CCOD).

Among the patients with 3 or ε4 *SMN2* copies, 2 patients could stand unaided and walk independently, and 1 patient could stand with support at Month 12. The latter patient (with ε4 *SMN2* copies) gained the ability to stand unaided and walk independently by Week 64 (approximately Month 15) of treatment.

Table 18: Results by endpoint and number of SMN2 copies

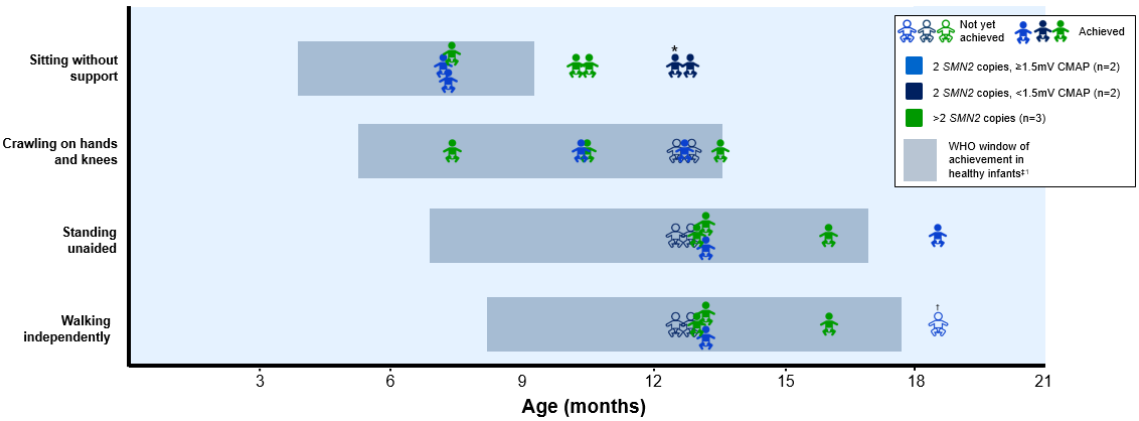
Endpoint	Patients with 2 *SMN2* copies (N = 4)	Patients with 3 *SMN2* copies (N = 2)	Patient with ≥4 *SMN2* copies (N = 1)	All Patients (N = 7)
Development Milestones and Motor Function				
Median (range) HINE-2 score	21.0 (13.0–26.0)	25.5 (25.0–26.0)	22.0 (22.0–22.0)	23.0 (13.0–26.0)
Proportion of patients achieving maximum score (26) on HINE-2	25.0%	50.0%	0%	28.6%
Proportion of patients able to sit as assessed by HINE-2 Stable sit Pivots (rotates)	 25.0% 75.0%	 - 100.0%	 - 100.0%	 14.3% 85.7%
Proportion of patients able to roll as assessed by HINE-2 Prone to supine Supine to prone	 25.0% 75.0%	 - 100.0%	 - 100.0%	 14.3% 85.7%
Proportion of patients able to crawl as assessed by HINE-2 On elbow Crawling flat on abdomen Crawling on hands and knees	 25.0% 25.0% 50.0%	 - - 100.0%	 - - 100.0%	 14.3% 14.3% 71.4%
Proportion of patients able to stand as assessed by HINE-2 Does not support weight Stands with support Stands unaided	 50.0% 25.0% 25.0%	 - - 100.0%	 - 100.0% -	 28.6% 28.6% 42.9%
Proportion of patients able to walk as assessed by HINE-2 Bouncing Walking independently Cannot test Not done	 25.0% 25.0% 25.0% 25.0%	 - 100.0% - -	 - - 100.0% -	 14.3%% 42.9% 28.6% 14.3%
Median (range) CHOP-INTEND score	59.5 (53.0–64.0)	64.0 (64.0–64.0)	63.0 (63.0–63.0)	64.0 (53.0–64.0)
Proportion of patients achieving maximum CHOP-INTEND score (64)	50.0%	100.0%	0%	57.1%
Proportion of patients who achieve a score of 40 or higher in the CHOP-INTEND (90% CI [a])	100.0% (47.3%, 100.0%)	100.0% (22.4%, 100.0%)	100.0% (5.0%, 100.0)	100.0% (65.2%, 100.0%)
Proportion of patients who achieve a score of 50 or higher in the CHOP-INTEND (90% CI [a])	100.0% (47.3%, 100.0%)	100.0% (22.4%, 100.0%)	100.0% (5.0% 100.0)	100.0% (65.2%, 100.0%)
Proportion of patients who achieve a score of 60 or higher in the CHOP-INTEND (90% CI [a])	50.0% (9.8%, 90.2%)	100.0% (22.4%, 100.0%)	100.0% (5.0%, 100.0%)	71.7% (34.1%, 94.7%)
Muscle Electrophysiology				
Median (range) change from baseline in CMAP amplitude [b], mV	0.6 (0.0–3.4)	1.9 (1.2–2.6)	0.6 (0.6–0.6)	1.1 (0.0–3.4)
Nutrition and Swallowing				
Proportion of patients with the ability to feed orally (90% CI [a])	100.0% (47.3%, 100.0%)	100.0% (22.4%, 100.0%)	100.0% (5.0%, 100.0%)	100.0% (65.2%, 100.0%)
Proportion of patients with the ability to swallow (90% CI [a])	100.0% (47.3%, 100.0%)	100.0% (22.4%, 100.0%)	100.0% (5.0%, 100.0%)	100.0% (65.2%, 100.0%)
Healthcare Utilization				
Proportion of patients with no hospitalizations [c, d]	100.0% (47.3%, 100.0%)	100.0% (22.4%, 100.0%)	100.0% (5.0%, 100.0%)	100.0% (65.2%, 100.0%)
Survival and Ventilation-Free Survival				
Proportion of patients alive without permanent ventilation (90% CI [e])	100.0% (100.0%, 100.0%)	100.0% (100.0%, 100.0%)	100.0% (100.0%, 100.0%)	100.0% (100.0%, 100.0%)

Figure 26: Study BN40703 (RAINBOWFISH): CHOP-INTEND Scores in Patients Treated for at Least 12 Months



CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP=compound muscle action potential; SMN=survival of motor neuron.
Note: 7 infants had received treatment with risdiplam for ε12 months and were included in this analysis. Clinical cutoff date: 1 July 2021

Figure 27: Study BN40703 (RAINBOWFISH): Gains in Motor Milestones (HINE-2) by Age in Patients Treated for at Least 12 Months



HINE-2=Hammersmith Infant Neurological Examination, Module 2; SMN=survival of motor neuron; WHO=World Health Organization.
* One infant achieved 'stable sit'. All other infants achieved 'pivots'.
† This infant achieved the 'cruising (walks holding on)' milestone.
‡ Shaded areas represent the 1st–99th percentile window for achievement of motor milestones based on the World Health Organization Motor Development Study.[1] Infants were included in this analysis after they reached 12 months of treatment. The age at which infants first achieved the most difficult milestone within each HINE-2 category up to the data cut-off (1 July 2021) is shown.
[1] WHO Multicentre Growth Reference Study Group.

2.5.1. Discussion on clinical efficacy

This variation application provides data from Study BN40703 at the time of an interim analysis (CCOD 1 July 2021) in patients below 2 months of age with presymptomatic SMA.

Design and conduct of clinical studies

The study design is adequate for this rare disorder and rarer in this age range.

Efficacy data and additional analyses

The efficacy data from the 7 patients (4 patients with 2 *SMN2* copies, 2 patients with 3 copies and 1 patient

with ε 4 copies) who completed at least 12 months of treatment show that, most patients achieved important motor milestones and high levels of motor function. Specifically, patients treated with risdiplam for 12 months:

- Developed complex motor abilities as assessed by the HINE-2 scale, including all patients achieving the ability of sitting without support (HINE-2 categories of 'Stable sit' and 'Pivots [rotates]').
- Achieved high levels of motor function illustrated by the median score on the CHOP-INTEND equal to the maximum score of the assessment at Month 12. Even the 2 patients with a baseline CMAP amplitude < 1.5 mV increased their motor function over time.
- Maintained their abilities to feed orally and to swallow.
- Did not require any overnight hospitalization throughout the 12 months of treatment.
- Did not require permanent ventilation.

The achievements were clearly not in line with the expected natural history of SMA type I.

The RAINBOWFISH study is enrolling pre-symptomatic patients, regardless of the number of SMN2 copies; however, the primary efficacy analysis is limited to the assessment of patients with two SMN2 copies (that are the patients who would most likely develop type 1 SMA, with onset before 6 months of age). Given the more heterogeneous phenotype in patients with ≥3 SMN2 copy numbers, a longer follow-up is needed to allow a meaningful interpretation of study results in this subgroup. This subgroup of patients is not foreseen to be included in the primary efficacy analysis of the RAINBOWFISH study.

The trial inclusion criteria required: "gestational age of 37-42 weeks for singleton births; gestational age of 34-42 weeks for twins". Body weight ≥3rd percentile for age, using appropriate country-specific guidelines. The lowest baseline weight of enrolled patients was 3.076 kg. The median age at first dose was 26.5 days (range: 16-40 days). During the procedure, the MAH was requested to clarify if there is data available in preterm neonates. During the procedure, the MAH proposed to take into account the aforementioned inclusion criteria by relying on the concept of corrected age, which better reflects the stage of maturation of the infant if they are born prematurely. This was agreed and specified in section 4.2 of the SmPC. The information on the weight range of the enrolled infants is provided in section 4.8 of the SmPC.

On 30 July 2021 the MAH submitted a request for a modification of the agreed PIP, proposing a change in the number of patients included in the primary analysis population of the RAINBOWFISH study and a deferral of the end of the study. The minimum number of patients for the primary analysis population was changed from "*at least 10 infants at inclusion with 2 SMN2 copies and a baseline CMAP ≥1.5 evaluable for the primary endpoint*" to: "at least 25 infants, including a minimum of 5 patients who m*eet the criteria for the primary efficacy population are enrolled OR a total of 10 infants who meet the criteria for the primary efficacy population are enrolled*"). The rationale for these changes were primarily due to the slower than expected enrolment, due to the increased competitive setting with two SMN-targeted therapies recently approved in SMA, added to risdiplam availability. After almost 2 years of enrolment (out of 14 active sites, only 6 centers enrolled at least 1 patient). As regards to sites from EU countries, out of 4 active sites (1 each from Belgium and Italy and 2 sites in Poland), only 1 site (from Belgium) enrolled at least 1 patient. Possibly COVID-19 pandemic may have played a role in the difficulties in enrolment.

As commented by the PDCO Rapporteur and by the Paediatric Coordinator at the time of the EMA/PDCO Modification report, a minimum of 7 neonates/young infants meeting the criteria for the primary efficacy population with at least 2 achieving the primary endpoint should be kept for the primary analysis, in order to maintain power above 80%. Thus, it is agreed with the PDCO Rapporteur and with the Paediatric Coordinator to keep a minimum of 7 pre-symptomatic neonates and young infants with 2 SMN2 copies and a baseline CMAP ≥1.5 mV (=who meet the criteria for the primary efficacy population), and at least 25 infants, to be enrolled prior to study completion (OR a total of 10 infants who meet the criteria for the primary efficacy population, as initially pre-specified). A total of 25 patients would be welcome, and is not mutually exclusive with the 10 patients evaluable for primary efficacy. ". During the procedure, the MAH confirmed the recruitment was closed in February 2022 due to feasibility issues with a total of 26 patients enrolled (8 patients with 2 SMN2 copies and 5 patients with 2 SMN2 copies and CMAP ≥ 1.5 mV). The MAH confirmed that none of the 8 patients with 2 SMN2 copies enrolled in the Study BN40703 (RAINBOWFISH) carries the SMN2 gene modifier mutation c.859G > C. The baseline CMAP is not considered a critical issue by the MAH. A minimum of 7 pre-symptomatic neonates and young infants who meet the criteria for the primary efficacy population (=with 2 SMN2 copies and a baseline CMAP ≥1.5 mV) would have been preferable, as it would have allowed to maintain power above 80%.

In the submitted interim analysis of the RAINBOWFISH study, the primary focus is not efficacy but PK evaluation, to support dose determination for patients below 2 months of age. As discussed by PDCO Rapporteur at the time of the EMA/PDCO Modification report, the minimum required number of patients submitted in this interim analysis is no longer based, at this step, on primary endpoint and statistical power

but on a sufficient number of patients (not especially meeting the criteria for the primary efficacy population) required for an appropriate PK dose finding. In this interim-analysis, results from BSID-III (primary endpoint) have not been provided, to preserve the type 1 error for the primary endpoint. Similarly, the proportion of patients developing clinically manifested SMA, growth measures and respiratory endpoint included as secondary endpoints have not been provided in this interim CSR. These results will be provided at the time of the primary analysis when all patients have completed 12 months of treatment.

As already discussed at the time of the Marketing Authorization (please refer to risdiplam EPAR) - it may be acknowledged that the overall findings of the risdiplam studies and the literature support the early initiation of treatment with risdiplam. The uncertainties of such extrapolation of the data from symptomatic patients to pre- or pauci-symptomatic patients that have not yet reached the criteria for clinical diagnosis are also expected to be clarified by the data generated in the agreed PAES (see Annex II).

The efficacy data has shown similitude to the older infant efficacy data. However, given the heterogeneity of the expected phenotype in patients with 3 and especially 4 SMN2 copies, a follow up longer than 12 months is needed. In pre-symptomatic patients with 4 copies a follow up longer than 24 months is needed in order to assess if patients deviate from the natural history of untreated SMA patients. Section 5.1 of the SmPC has been updated with efficacy data from pre-symptomatic SMA population (RAINBOWFISH).

During the procedure, the MAH has submitted data from Roche Global Safety Database and the United States Evrysdi patient access database, which, as of 8MAY2023 had included 47 babies below 20 days of age treated with risdiplam. The MAH contacted U.S. physicians' and received orally their experience regarding 12 newborns below 20 days of age at the time of risdiplam treatment start. The physicians orally reported that treated newborns did well on risdiplam, progressed normally, and reached milestones on time.

2.5.2. Conclusions on the clinical efficacy

It is acknowledged that there is evidence - both from the risdiplam studies as well as studies with other disease modifying drugs- that earlier treatment initiation is associated with better clinical outcomes. For this reason, extrapolation of efficacy from symptomatic to pre- or pauci-symptomatic patients that have not yet reached the criteria for clinical diagnosis has been accepted since the initial marketing authorization. The preliminary efficacy results provided for some of the secondary endpoints in this interim analysis of the RAINBOWFISH Study in the 4 subjects with 2 SMN2 copies with a 12-months follow-up also support the early initiation of treatment with risdiplam.

2.6. Clinical safety

Introduction

Clinical safety was also assessed in the RAINBOWFISH study. The observed safety profile up to the CCOD was reflective of the age of the patients.

Patient exposure

Based on PK data (reported separately), the dose of risdiplam selected to achieve the target exposure was 0.2 mg/kg. A total of 18 patients received at least one dose of study treatment. The median duration of treatment exposure was 8.7 months (range: 0.5-22.8 months). The median dose intensity was 100.4% (range: 97.3%-103.4%). All patients eventually received a dose of 0.2 mg/kg.

Overall, 14 patients (77.8%) received at least one concomitant medication[1] in the study. The most frequently reported concomitant medications (in ε5 patients) were: Paracetamol (9 patients [50.0%]); Rotavirus vaccine live oral 1v (7 patients [38.9%]); Ibuprofen (6 patients [33.3%]); "6-in-1 DTaP/IPV/Hib/HepB vaccine" (refer to listing for full WHO Drug term) (6 patients [33.3%]); Pneumococcal vaccine conj 13v (crm197) (6 patients [33.3%])

[1] Concomitant medications with a start date on, or after first dose date.

Adverse events

In one subject a Grade 3 AE of cystoid macular edema was reported (observed at Spectral Domain Optical Coherence Tomography (SD-OCT) considered clinically significant and reported as AE); the Investigator assessed the event as unrelated to risdiplam treatment. The event was reported at week 8 (day 60) as a new cystoid macular edema (not present at baseline) in both eyes assessed as clinically significant. At week 13 (day 97) the event resolved. See below section.

Overall, 7 patients (38.9%) had at least 1 AE coding to the System Organ Class (SOC) Skin and subcutaneous tissue disorders. None of the 12 events were serious or led to a change in study medication. An event of non-serious skin discoloration (Grade 1) over the neck and back (whitish discoloration) (see below).

Overall, 9 patients (50.0%) had at least 1 AE coding to the SOC Gastrointestinal disorders. None of the 24 events were serious or led to a change in study medication. Two patients experienced a total of 2 treatment-related AEs (Diarrhoea: Grade 1, nonserious and Skin discoloration: Grade 1, non-serious).

When adjusted for patient-years at risk, the overall AE rate at the time of the CCOD was 558.2 events per 100 patient-years (PY) (90% CI: 460.3, 671.5; total PY at risk: 14.5 years).

The safety profile of risdiplam was comparable in patients who initiated therapy at <4 weeks of age and those who initiated therapy between > 4 to <6 weeks of age.

Haematological parameters were stable over time. Isolated shifts were observed in some patients but returned to normal without change to study medication. Isolated shifts in other laboratory parameters were observed; however, these were not sustained over time and generally were not clinically significant.

No Hy's law cases were observed. No AEs were reported in the SOC Hepatobiliary disorders. No AEs suggestive of liver abnormalities were reported in the SOC Investigations. Increased liver enzymes as laboratory findings occurred frequently (≤ 2x Upper limit of normal (ULN) bilirubin and ALT; ≤3 x ULN AST), and in particular AST elevation was sustained, with values not returned to within normal values at last visit: 7/18 patients (39%) had AST or ALT elevations post-baseline (< 2x ULN)) [where baseline values were either normal (3 patients) or unknown (4 patients)] which had not returned to within normal ranges at the last assessment (in 6/6 patients with AST elevation, AST had not returned to within normal values at last visit; 1/4 patients with ALT elevation, ALT had not returned to within normal values at last visit). 2/18 patients (11%) with normal bilirubin values at baseline, had elevated direct bilirubin levels (< 2x ULN) at Week 2, after which their direct bilirubin levels returned to within normal range at consequent tests. In most patients (2/2 bilirubin increase and 4/7 ALT and AST increase) increases started at week 2 (Day 14 or 15).

Isolated shifts in diastolic blood pressure, systolic blood pressure, temperature and pulse rate were observed; however, these were generally not sustained over time and were not clinically significant. The ECG data showed no clinically significant trends post-baseline versus baseline in mean ECG parameters. No AEs were reported in the SOC Cardiac disorders.

Seven of 18 patients (38.9%) were followed up with an SD-OCT assessment until at least 12 months. The longest follow-up was 78 weeks (achieved by 4 patients). Signs of retinal immaturity were observed in 50% of patients and resolved as expected with age in those with sufficient follow-up.

The proportion of patients with at least 1 AE was 77.8% (14 patients). Overall, there were 81 AEs reported. The AEs reported were as would be expected for infants of this age.

The majority of AEs were not considered by the Investigator to be related to study treatment; related AEs resolved or were resolving despite ongoing treatment with risdiplam.

Table 19: Overview of Adverse Events (Safety Population)

	SMN2 Copy Number			
	2 (N=7)	3 (N=7)	>=4 (N=4)	All Patients (N=18)
Total number of patients with at least one AE	5 (71.4%)	6 (85.7%)	3 (75.0%)	14 (77.8%)
Total number of AEs	22	35	24	81
Total number of deaths	0	0	0	0
Total number of patients withdrawn from study due to an AE	0	0	0	0
Total number of patients with at least one				
AE with fatal outcome	0	0	0	0
Serious AE	0	0	0	0
Serious AE leading to withdrawal from treatment	0	0	0	0
Serious AE leading to dose modification/interruption	0	0	0	0
Related Serious AE	0	0	0	0
AE leading to withdrawal from treatment	0	0	0	0
AE leading to dose modification/interruption	0	2 (28.6%)	0	2 (11.1%)
Related AE	0	1 (14.3%)	1 (25.0%)	2 (11.1%)
Related AE leading to withdrawal from treatment	0	0	0	0
Related AE leading to dose modification/interruption	0	0	0	0
Grade 3-5 AE	1 (14.3%)	1 (14.3%)	0	2 (11.1%)
Total number of adverse events which are				
Serious	0	0	0	0
Related	0	1	1	2
Grade 1	19	26	16	61
Grade 2	2	8	8	18
Grade 3	1	1	0	2
Grade 4	0	0	0	0
Grade 5	0	0	0	0
AEs with missing grade	0	0	0	0

Investigator text for AEs is coded using MedDRA version 24.0. Percentages are based on N in the column headings. Multiple occurrences of the same AE in one individual are counted only once except for "Total number of AEs" row in which multiple occurrences of the same AE are counted separately. Includes AEs with onset from first dose of study drug up to the clinical cutoff date. Safety-evaluable patients have received at least one dose of study drug. Clinical Cut-Off Date: 01JUL2021

Serious adverse event/deaths/other significant events

Up to the CCOD, no deaths, no SAEs and no AEs of Grade ε4 were reported.

Despite the limited data, no differences were observed in the safety profile of risdiplam in patients who initiated therapy at δ4 weeks of age and those who initiated between > 4 to δ6 weeks of age. There were no events or findings suggestive of risdiplam-induced effects on hematological parameters.

Table 20: Safety results by SMN2 copy number subgroups

MedDRA System Organ Class MedDRA Preferred Term	Outcome	SMN2 Copy Number 2 (N=7)	 3 (N=7)	 >=4 (N=4)	 All Patients (N=18)
- Any adverse events -	- Any Outcome -	22	35	24	81
	Recovered/Resolved	21	31	18	70
	Not Recovered/Not Resolved	1	3	6	10
	Unknown	0	1	0	1
Gastrointestinal disorders - Overall -	- Any Outcome -	7	12	5	24
	Recovered/Resolved	6	9	2	17
	Not Recovered/Not Resolved	1	2	3	6
	Unknown	0	1	0	1
Teething	- Any Outcome -	2 (100%)	4 (100%)	0	6 (100%)
	Recovered/Resolved	1 (50.0%)	2 (50.0%)	0	3 (50.0%)
	Not Recovered/Not Resolved	1 (50.0%)	1 (25.0%)	0	2 (33.3%)
	Unknown	0	1 (25.0%)	0	1 (16.7%)
Diarrhoea	- Any Outcome -	0	2 (100%)	2 (100%)	4 (100%)
	Recovered/Resolved	0	2 (100%)	1 (50.0%)	3 (75.0%)
	Not Recovered/Not Resolved	0	0	1 (50.0%)	1 (25.0%)
Vomiting	- Any Outcome -	1 (100%)	2 (100%)	1 (100%)	4 (100%)
	Recovered/Resolved	1 (100%)	2 (100%)	1 (100%)	4 (100%)
Constipation	- Any Outcome -	2 (100%)	1 (100%)	0	3 (100%)
	Recovered/Resolved	2 (100%)	1 (100%)	0	3 (100%)
Abdominal pain	- Any Outcome -	1 (100%)	0	1 (100%)	2 (100%)
	Recovered/Resolved	1 (100%)	0	0	1 (50.0%)
	Not Recovered/Not Resolved	0	0	1 (100%)	1 (50.0%)
Gastrointestinal pain	- Any Outcome -	0	1 (100%)	0	1 (100%)
	Not Recovered/Not Resolved	0	1 (100%)	0	1 (100%)
Gastrooesophageal reflux disease	- Any Outcome -	0	0	1 (100%)	1 (100%)
	Not Recovered/Not Resolved	0	0	1 (100%)	1 (100%)

Investigator text for AEs is coded using MedDRA version 24.0.
All counts represent number of events. Percentages are based on the number of events within each PT.
Recovered/Resolved includes Recovered/Resolved, Recovered/Resolved with Sequelae and Recovering/Resolving. Includes AEs with onset from first dose of study drug up to the clinical cutoff date.
Safety-evaluable patients have received at least one dose of study drug.
Clinical Cut-Off Date: 01JUL2021

Adverse Event Rate Adjusted for Patient Years at Risk by System Organ Class and Preferred Term - All Occurrences, Safety-Evaluable Patients
Protocol: BN40703

Time on Treatment: Overall

MedDRA System Organ Class MedDRA Preferred Term	SMN2 Copy Number 2 (N=7)	 3 (N=7)	 >=4 (N=4)	 All Patients (N=18)
Total patient-years at risk	6.2	5.7	2.6	14.5
Number of Adverse Events	22	35	24	81
Number of Adverse Events per 100 patient-years	352.90	615.49	926.64	558.21
90% CI	(238.91, 503.92)	(454.93, 816.04)	(638.96, 1303.18)	(460.26, 671.52)

Although it is acknowledged that the limited number of patients do not allow to draw definitive conclusions, when observing the outcome of AEs, it is noted that a higher proportion of AEs in patients with ≥4 copies (6/24, 25%) had an unresolved" outcome, in comparison to patients with a lower number of SMN2 copies (2 copies: 1/ 21, 5%; and 3 copies 3/31, 10%). The lower median treatment duration of the subgroup of patients with ≥4 copies (3.93 months), in comparison to patients with a lower number of copies (2 copies: 11.96 months; 3 copies: 8.94 months) could possibly have a role. However, also when observing AE rate adjusted for patient years at risk (that takes into account the different time of exposure), the number of adverse events per 100 patient-years (90% CI) are higher in the subgroup ≥4 SMN2 copies [926.64 (638.96, 1303.18)] in comparison to the subgroups with a lower number of SMN2 copies, with non-overlapping 90% CI when compared to the subgroup with 2 SMN 2 copies [352.90 (238.91, 503.92)].

Data are considered too limited to draw definitive conclusions. The MAH is monitoring safety data in all ongoing studies. In the event of a potential signal, signal evaluation will include an analysis of the impact of underlying SMA severity. Furthermore, the MAH plans to provide an analysis of safety by *SMN* copy number subgroups in the planned final CSR of all the ongoing clinical studies.

Two patients experienced a total of 2 treatment-related AEs (diarrhoea: Grade 1, nonserious, onset at Day 15 and resolved after 15 days without change to study treatment; and Skin discoloration: Grade 1, non-serious, onset at Day 29 and resolving at the time of the CCOD without change to study treatment).

Ophthalmology AE

One retinal abnormality was assessed as a clinically significant change compared with baseline and was reported as an AE which was also attributed to retinal immaturity and resolved under continued risdiplam therapy. The MAH discussed the Grade 3 AE of cystoid macula edema observed at SD-OCT upon request. The MAH reports that central reader assessed that the changes in this patient do not follow the pattern of abnormality observed in preclinical studies in which all changes started in the retinal periphery especially the outer nuclear layers and retinal pigment epithelium. The event resolved while continuing risdiplam

treatment. The Investigator assessed the event as unrelated to risdiplam treatment. Although the new cystoid macular edema started after risdiplam treatment and thus a possible causal relationship with treatment may not be definitely excluded, it is acknowledged that given the resolution of the event despite the continued risdiplam treatment, retinal immaturity could be a possible alternative explanation. The MAH provided a safety analysis by exposure quartiles. The infant with the AE of cystoid macular edema was in the higher exposure quartile (AUC value at week 4: 3790). During the procedure, the MAH proposed a lower dose (0.15 mg/kg) for infants <2 months of age based on updated popPK analysis. This is reassuring, as it is not expected that patients <2 months of age will be exposed to a risdiplam dose corresponding to the highest quartile of exposure in the RAINBOWFISH study (AUC value at week 4: >3070-4580).

AE of the Skin and Other Events Potentially Linked to Effects on Epithelial Tissues

An event of non-serious skin discoloration (Grade 1) over the neck and back (whitish discoloration) considered by the Investigator to be related to risdiplam. The event occurred on Study Day 29. On Study Day 168, discoloration over back had disappeared; but discoloration over neck persisted. There was no change in study drug due to this event. Among risdiplam important potential risks in the RMP there is "Effect on epithelial tissue". The MAH provided an update on the outcome of this event upon request. The MAH stated that the AE recovered on Study Day 263 without any additional treatment prescribed and without any change to study medication. The patient was seen by a dermatologist, but it is currently unknown if diagnostic measures were taken to establish a more precise diagnosis. Hypopigmentation macules are very common (both in children and adults) and that the clinical presentation of this event (hypopigmentation of the skin) as well as the resolution of the event despite ongoing risdiplam strongly suggest that the event reported in this patient is distinct from the findings observed in nonclinical studies. It may be acknowledged that the resolution of the event despite ongoing risdiplam treatment may point in the direction of an alternative explanation.

AE coding to the SOC Gastrointestinal disorders

In RAINBOWFISH study there were 6 AEs of diarrhoea reported in 6 patients (6/6= 2.3%). Diarrhoea is already included as a very common adverse drug reaction in both early-onset and late-onset SMA. In the poster presentation describing preliminary results of the RAINBOWFISH Study, submitted during this procedure, one SAE of gastroenteritis norovirus was reported that was not discussed in the interim CSR. The MAH clarified that gastroenteritis was downgraded to non-serious. The MAH further reviewed the events of diarrhoea in RAINBOWFISH and in FIREFISH studies and concluded that clinical presentation of diarrhoea AEs in Study BN40703 (RAINBOWFISH) is consistent with observations of diarrhoea in patients with symptomatic SMA in Study BP39056 (FIREFISH).

Laboratory findings

In the submitted CSR, no Hy's law cases were observed. No AEs were reported in the SOC Hepatobiliary disorders. No AEs suggestive of liver abnormalities were reported in the SOC Investigations.

In the poster presentation describing preliminary results of the RAINBOWFISH Study, submitted for the procedure two related AEs of increased ALT and increased AST (both reported in one infant) have been described. These events were later updated and were not discussed in the interim CSR as presented in the poster. This was justified by the MAH upon signaling.

Exposure- Safety analysis

During the first 6 months of treatment, the overall AE rate was 681.0 events per 100PY (90% CI: 526.2, 868.4; total PY at risk: 6.9 years). This decreased to a rate of 401.1 events per 100PY during the second 6 months on treatment (90% CI: 255.6, 601.7; total PY at risk: 4.2 years).

Upon request, the MAH provided exposure safety correlations with updated safety data (CCOD: 25 February 2022). The MAH provided an analysis of AEs, SAEs, and safety laboratory parameters by exposure quartiles: the 26 infants enrolled into Study BN40703 were allocated into 4 groups based on their AUC observed at Week 4, i.e. exposure quartiles, and safety data was compared across the quartiles. The MAH considers the AUC value at Week 4 the "worst case" as it is in general the highest value: as risdiplam accumulates with continued administration, the exposure reaches steady-state approximately 2 to 4 weeks after treatment start, and then generally declines for most infants as they mature and grow. As the exposure to risdiplam is dependent on the general maturation of the infants and in particular maturation of liver function, patients in the lower exposure quartiles (Quartiles 1 and 2) tended to be slightly older (mean age 30 days) than the patients in the higher exposure quartiles (Quartiles 3 and 4) (mean age 25 days). The only 2 Grade 3 AEs, occurred one (cystoid macular oedema) in a patient in the highest exposure quartile (>3070-4580) and the

other (gastroenteritis norovirus) in a patient in the first exposure quartile (541-1910). The only 2 SAEs (neonatal jaundice and gastroenteritis) were both reported in two patients in the highest exposure quartile (>3070-4580). Even though the investigator considered these two events as not related to risdiplam, considering the limited available data, it is not possible to exclude a worst safety in the highest quartile of risdiplam exposure (AUC at 4 weeks: >3070-4580). Nevertheless, the MAH has finally proposed a lower dose (0.15 mg/kg) for infants <2 months of age based on updated popPK analysis. This is considered reassuring, as it is not expected that patients <2 months of age will be exposed to a risdiplam dose corresponding to the highest quartile of exposure in the RAINBOWFISH study (AUC value at week 4: >3070-4580).

Section 4.8 of the SmPC has been updated with safety data from pre-symptomatic SMA population (RAINBOWFISH).

Overdose

At the time of the CCOD, 4 patients (22.2%) were reported to have received ε 10% above the planned dose (defined as an overdose). In 2 patients (11.1%) the overdoses were single occurrences; in the other 2 patients the overdoses were determined to be noted in error.

Of the 4 patients who had an overdose, AEs of Accidental overdose were reported for 2 patients. The overdose in these patients did not lead to any other AEs. The other 2 patients were reported (at the time of the CCOD) to have doses that were 10% above the planned dose; however, these were determined to be discrepancies due to data entry error relating to recording of the patients' weights. The actual doses received by the patients were correct per protocol dosing regimen.

No cases of overdose were associated with any AEs due to risdiplam.

Post Marketing Data

Risdiplam is currently approved in the U.S., E.U. and over 90 international markets for the treatment of SMA. Since the International Birth Date (7 August 2020) through 6 August 2021 (data lock point for the Periodic Benefit-Risk Evaluation Report [PBRER]), an estimated total of 2728 patients received risdiplam from marketing experience (European Economic Area [EEA] n = 433; Rest of the World n = 2295). Exposure was similar between the sexes (male n = 1363; female n = 1363; unknown n = 1).

Based on the evaluation of these data, one new identified risk (cutaneous vasculitis) not categorized as important was identified. The information that became available did not alter the known benefit-risk profile of risdiplam. The benefit-risk profile of risdiplam in the authorized indication remains favorable.

The worldwide exposure in patients below 20 days of age is unknown. However, in the United States, per the Evrysdi patient access database, as of 8 May 2023, 47 babies below 20 days of age have been prescribed risdiplam. Data submitted upon response to the 3rd RfSI covered 8 neonates identified in the MAH safety database. While some patients had adverse events, the single SAEs of cardiac arrhythmia and troponin value elevated and the non-serious event of icterus prolungatus occurred in a child who had been just treated with gene therapy and was also receiving risdiplam. The outcome of these events was resolved; it is not known if therapy with risdiplam was altered or not in response to these events. There were two other children with diarrhoea described as non-serious AEs.

2.6.1. Discussion on clinical safety

No deaths or SAEs occurred up to the CCOD for the interim analysis. No new risks were identified following the review of the type and frequency of AEs as well as vital signs, physical examinations, ECG.

Upon request, the MAH provided updated safety data from RAINBOWFISH study (CCOD: 25 February 2022). Eight more patients have been enrolled, thus safety data from 26 patients <2 months of age who received at least 4 weeks of risdiplam treatment are now available. Since the previous CCOD, two new SAEs occurred (neonatal jaundice and gastroenteritis), both grade 1, resolved without study drug interruption and considered not related to study drug by the investigator. Furthermore, since the previous CCOD, two new related AEs occurred (Grade 1 non-serious Diarrhoea, resolved after 4 days, without change to study treatment; one Incorrect dose administered: Grade not stated, non-serious, onset at Day 1 and resolved after 13 days. No additional AE was reported due to this incorrect dose administered.

The only 2 SAEs were both reported in two patients in the highest exposure quartile at week 4 (>3070-4580), with both SAEs occurring in proximity to week 4. Even though the investigator considered these two events as not related to risdiplam, considering the limited available data, it is not possible to exclude a

worst safety in the highest quartile of risdiplam exposure (AUC at 4 weeks: >3070-4580). Nevertheless, the MAH finally proposed a lower dose (0.15 mg/kg) for infants <2 months of age based on updated PK analysis. This may be considered reassuring from a safety perspective, as it is not expected that patients <2 months of age will be exposed to a risdiplam dose corresponding to the highest quartile of exposure in the RAINBOWFISH study.

The limited post marketing exposure in countries where the dose of 0.15 mg/kg was approved in children aged 0-20 days of life has not triggered safety signals and seems consistent with the approved treatment 2 months and above.

Given the well-recognized need for an early initiation of treatment in SMA and the lack of safety signals on newborns already treated with 0.15mg/kg, the indication from birth has been accepted.

However, safety in patients <1 month of age has been added as missing information in the RMP due to the extremely limited evidence available in this patient population that represent the most vulnerable subgroup of the paediatric population and the need to further strengthen the confidence on the optimal recommended dose in this very young population.

The MAH proposed to include the PK study BN44619 (PUPFISH) as an additional pharmacovigilance activity (category 3 PASS) in the RMP. A total of 10 patients are expected to be enrolled, with a minimum of 3 patients aged < 7 days at first dose, in order to generate data in the most vulnerable phase right after birth. The MAH has committed to provide regular updates in upcoming PSURs on the progress of the PK study BN44619 (PUPFISH).

Further, the MAH has committed to collect data in the real world setting in very young patients through a retrospective chart review, Study ML44811. The study is a retrospective chart review data collection from clinicians across multiple centers in the US who have initiated treatment with risdiplam in newborn infants with SMA younger than 2 months, between May 2022 and the study cutoff date (date to be set at protocol finalization). Research coordinators who are doing the chart abstraction will be provided with a standard template to collect required data for this descriptive real world study. Sample size is expected to be up to 50 patients from across the US.

The primary objective for this study is to describe the demographics and clinical characteristics (including dose, age at diagnosis, *SMN2* copy number, etc.) at the initiation of treatment with risdiplam of SMA newborns (0-2 months old) in the U.S. to date.

If feasibility is confirmed, the planned secondary objectives for this study, ideally at a 1 year follow-up time point is as follows:

- To describe risdiplam use and SMA disease-modifying treatment patterns post risdiplam initiation.
- In order to collect the most relevant adverse events in these patients, the chart review will extract all hospitalizations (including date of admission, length of stay) and reasons for hospitalisation.

Given that site enrollment is unpredictable as there are many ongoing SMA studies competing for site resources, an exact timeline for this study read-out cannot be ascertained at this point in time.

The MAH's proposal for real-world data is endorsed and the MAH was made aware that data from this study is needed, since the presently discussed positive benefit-risk balance is based on the hypothetical benefit of risdiplam being higher than the risk of the very early use. Therefore, to substantiate this theoretical reasoning, RWE is required, and should be presented as early as possible. Otherwise, should safety issues emerge on the early usage in the absence of supportive efficacy and safety (for contextualisation on the frequency of safety issues), the use on the very young must be revised.

2.6.2. Conclusions on clinical safety

Limited safety data is available in neonates and young infants with pre-symptomatic SMA (n=18 up to the CCOD for the interim analysis).

Given the limited available data and due to neonates representing the most vulnerable subgroup of the paediatric population, all single AE with an at least reasonable possibility of a causal relationship with risdiplam are considered relevant. Available data in neonates and young infants <2 months of age do not provide enough reassurance on the absence of a clinically relevant unfavourable effect of the higher-than-expected median AUC observed in the interim analysis of the RAINBOWFISH study. Nevertheless, the new proposed lower dose (0.15mg/kg) for infants <2 months is considered reassuring, and it can be accepted

that there are no major safety concerns for infants aged at birth and above, treated with the lower dose of 0.15mg/kg.

However, safety in patients <1 month of age has been added as missing information in the RMP. The MAH proposed to include the PK study BN44619 (PUPFISH) as an additional pharmacovigilance activity (category 3 PASS) in the RMP and has committed to provide regular updates in upcoming PSURs on the progress of the PK study BN44619 (PUPFISH). Further, the MAH has committed to conduct a real-world data collection in newborn infants with SMA younger than 2 months who have initiated treatment with risdiplam in the US (Study ML44811) to support the benefit risk in this subpopulation.

2.6.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.5 is acceptable.

The CHMP endorsed the Risk Management Plan version 1.5

Safety concerns

Table 21: Summary of Safety Concerns

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

Pharmacovigilance plan

Table 22: Ongoing and Planned Additional Pharmacovigilance Activities

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

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones/Due Date(s)
BP39055 (SUNFISH) OLE Ongoing	Target population: patients with Type 2 and 3 SMA (aged 2 to 25 years) OLE: Continued general safety as well as ophthalmological monitoring.	Retinal toxicity Long-term safety Effect on epithelial tissues	Initial protocol: Version 1, 03 May 2016 Current protocol: Version 6, 22 June 2020 Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the OLE phase Final CSR: Estimated Q2 2024
BP39054 (JEWELFISH) OLE Ongoing	Target population: patients previously enrolled in Roche Study BP29420 (MOONFISH) who were previously treated with the splicing modifier RO6885247 (development discontinued) or patients previously treated with SPINRAZA→ (nusinersen), Zolgensma→ (onasemnogene abeparvovec, AVXS-101), or olesoxime (previous Roche acquired development compound, since discontinued) OLE: Continued general safety as well as ophthalmological monitoring.	Retinal toxicity Long-term safety Effect on epithelial tissues	Initial protocol: 02 November 2016 Current protocol: Version 4, 23 June 2020 Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the OLE phase Final CSR: Estimated Q4 2025
BN40703 (RAINBOWFISH) OLE Ongoing	Target population: infants with genetically diagnosed and presymptomatic spinal muscular atrophy OLE: Continued general safety as well as ophthalmological monitoring.	Retinal toxicity Long-term safety Effect on epithelial tissues	Initial protocol: 13 July 2018 Current protocol: Version 4, 30 March 2021 Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the OLE phase Final CSR Estimated: Q3 2027
BN42833 Phase IV, non-interventional pregnancy surveillance study Planned	To collect and describe selected pregnancy outcomes (i.e., live birth, spontaneous abortions, stillbirths, elective abortions, and preterm births) and pregnancy complications in women with SMA exposed to risdiplam during the defined exposure window. To collect and describe selected fetal/neonatal/infant outcomes (i.e., major and minor congenital malformations, small for gestational age, and postnatal growth and development) at birth and through up to the first year of life of infants born to women exposed to risdiplam during the defined pregnancy exposure window.	Embryofetal toxicity	Protocol v1 (Submitted to EMA in Q3 2021) Current Protocol: Version 2, 30 November 2021 (Submitted to EMA in Q4 2021) Final report: Estimated Q4 2031
BP42817 Phase I, double-blind, placebo- and positive-controlled crossover study to investigate the effects of risdiplam on QTc interval in healthy subjects Ongoing	To estimate the effects of single oral doses of risdiplam on QT interval of the ECG (QT)/QT corrected for heart rate (QTc) interval in healthy subjects.	Missing information : long-term safety	Current Protocol: Version 1, 21 May 2021 (Submitted to EMA in Q2 2021) Final report: Estimated Q2 2023

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones/Due Date(s)
BN44619 Phase II, open-label study Planned	To evaluate the pharmacokinetics and safety of risdiplam in patients with SMA under 20 days of age at first dose.	Missing information : Safety in patients < 1 month of age	Biannual/Annual: Data to be reported as part of the PSUR/PBRER until completion of the study. Final report: Estimated Q1 2026

Risk minimisation measures

Table 23: Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Potential Risk: Retinal toxicity	**Routine risk minimization measures:** ● Section 4.4 of the SmPC (Special warnings and precautions for use) ● Section 5.3 of the SmPC (Preclinical safety data; Effect on retinal structure) **Routine risk-minimization activities recommending specific clinical measures to address the risk:** ● Section 4.5 of the SmPC (Interaction with other medicinal products and other forms of interaction) **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** ● None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** ● None **Additional pharmacovigilance activities:** OLE until 5 years of treatment for all patients in following studies: ● Study BP39056 (FIREFISH) ● Study BP39055 (SUNFISH) ● Study BP39054 (JEWELFISH) ● Study BN40703 (RAINBOWFISH)
Important Potential Risk: Effect on Epithelial tissues	**Routine risk minimization measures:** ● SmPC Section 5.3 (Preclinical safety data; Effect on Epithelial tissues) **Other risk minimization measures beyond the Product Information:** Medicine's legal status: Risdiplam is a medicinal product subject to restricted medical prescription. **Additional risk-minimization measures:** ● None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** ● None **Additional pharmacovigilance activities:** OLE until 5 years of treatment for all patients in following studies: ● Study BP39056 (FIREFISH) ● Study BP39055 (SUNFISH) ● Study BP39054 (JEWELFISH) ● Study BN40703 (RAINBOWFISH)
Important Potential Risk: Embryofetal toxicity	**Routine risk minimization measures:** ● SmPC Section 4.4 (Special warnings and precautions for use) ● SmPC Section 4.6 (Fertility, pregnancy and lactation) ● SmPC Section 5.3 (Preclinical safety data) ● Section 2 of the Package Leaflet (What you need to know before you or your child take Evrysdi; Pregnancy, contraception, breastfeeding and male fertility) **Routine risk-minimization activities recommending specific clinical measures to address the risk:** ● SmPC Section 4.6 (Fertility, pregnancy and lactation)	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** ● None **Additional pharmacovigilance activities:** ● Study BN42833 (Risdiplam Pregnancy Surveillance Study)

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

2.8. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make some editorial improvements in the product information.

As a consequence of the variation to update Evrysdi pack configuration with the addition of a new 1 mL oral syringe into the product carton allowing precise dosing of infants below 2 months of age and the , variation to remove the spare unit of 12 mL oral syringe out of the two units currently provided in the product carton, section 6.5 of the SmPC has been updated and the labelling and Package Leaflet have been updated in accordance.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: there are few changes included in the PL and IFU, and these changes do not introduce any new safety message and there is no new information that impacts the general readability of the PL for users.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

SMA is a monogenic neuromuscular disorder resulting in severe weakness of the limbs, trunk, bulbar and respiratory muscles secondary to the dysfunction of alpha motor neurons within the anterior horn of the spinal cord, leading to skeletal muscle weakness and atrophy. Clinically, patients may experience failure to gain motor milestones and motor function, recurrent respiratory infections, swallowing difficulties, contractures, scoliosis, and reduced life expectancy. It is the most frequent cause of inherited death in early childhood. The severity of spinal muscular atrophy is highly variable and patients with heterogeneous clinical features can be classified into phenotypes (Types 0 through 4) on the basis of age at onset and the most advanced motor milestone achieved during development.

This variation application provides interim results from Study BN40703 (RAINBOWFISH) in order to support the risdiplam dose determination for patients below 2 months of age.

3.1.2. Available therapies and unmet medical need

For patients with SMA below 2 months of age, there are currently two approved therapies: Spinraza® (nusinersen) and Zolgensma® (onasemnogene abeparvovec). Spinraza is an SMN2-directed antisense oligonucleotide administered intrathecally, thus largely limiting the effects to the CNS only. The first 3 loading doses of Spinraza are administered at 14-day intervals, followed by a 4th loading dose after 30 days and maintenance dose every 4 months thereafter. Zolgensma is a one-time intravenously administered gene-replacement therapy that uses a nonreplicating AAV capsid to deliver a functional copy of the SMN1 gene. High-dose, systemic corticosteroid treatment is required prior to and following Zolgensma administration.

Despite the availability of these therapies, there remains an unmet medical need for additional treatment options for patients below 2 months of age, especially when considering prompt treatment initiation. Specific factors contributing to the current unmet medical need:

- Required hospital setting for Zolgensma and Spinraza administration presents challenges for patients;
- Zolgensma administration may be delayed in patients with elevated anti-AAV9 antibody titers or infections;
- Safety risks are associated with Zolgensma therapy and concomitant corticosteroid treatment;
- Safety risks are associated with intrathecal route of administration of Spinraza.

3.1.3. Main clinical studies

The main clinical study submitted in this application is an interim CSR of the ongoing RAINBOWFISH (BN40703) study, which is an open-label, single-arm, multicenter clinical study to investigate the efficacy, safety, PK, and PD of risdiplam in patients aged from birth to 6 weeks (at first dose) who are genetically diagnosed with SMA (SMN1 deletion and any SMN2 copies) but not yet presenting with symptoms.

3.2. *Favourable effects*

Most treated children have reached milestones which could not be attained by children with 2 *SMN2* copies as known from natural history cohorts.

No new favourable effect was identified in this population that had not been observed with the older population.

3.3. *Uncertainties and limitations about favourable effects*

The study was noncontrolled.

The RAINBOWFISH study is enrolling pre-symptomatic patients, regardless of the number of SMN2 copies; however, the primary efficacy analysis is limited to the assessment of patients with two SMN2 copies (that are the patients who would most likely develop type 1 SMA, with onset before 6 months of age). Given the heterogeneity of the expected phenotype in patients with 3 and especially 4 SMN2 copies and given the limited number of patients enrolled, a follow up longer than 12 months is needed in order to assess if the 2 patients with pre-symptomatic SMA with 3 SMN2 copies and the only patient with ≥4 SMN2 copies treated with risdiplam in the RAINBOWFISH study, deviate from the natural history of untreated SMA patients.

Due to the slower than expected enrolment, due to the increased competitive setting with two SMN-targeted therapies recently approved in SMA, on 30 July 2021 the MAH submitted to the EMA a request for a modification of the agreed PIP, proposing a change in the number of patients included in the primary analysis population of the RAINBOWFISH study. The primary analysis population was changed from "*at least 10 infants at inclusion with 2 SMN2 copies and a baseline CMAP ≥1.5 evaluable for the primary endpoint*" to: "*at least 25 infants, including a minimum of 5 patients who meet the criteria for the primary efficacy population are enrolled OR a total of 10 infants who meet the criteria for the primary efficacy population are enrolled*"). However, a minimum of 7 neonates/young infants meeting the criteria for the primary efficacy population should have been kept for the primary analysis, in order to maintain power above 80%.

The primary efficacy endpoint and relevant secondary efficacy endpoints (e.g. development of SMA, respiratory endpoint) have not been reported in this interim CSR, only secondary efficacy endpoints have been included. However, the primary focus in the submitted interim analysis of the RAINBOWFISH study is not efficacy but PK evaluation, in order to support dose determination for patients below 2 months of age. The minimum required number of patients submitted in this interim analysis is no longer based, at this step, on primary endpoint and statistical power but on a sufficient number of patients (not especially meeting the criteria for the primary efficacy population) required for an appropriate PK dose finding.

3.4. *Unfavourable effects*

Given the limited available data and due to neonates representing the most vulnerable subgroup of the paediatric population, single AE with an at least reasonable possibility of a causal relationship with risdiplam are considered relevant.

In one subject (1/18, 5.5%) a Grade 3 AE of retinal abnormality (cystoid macular edema) was reported (observed at SD-OCT, considered clinically significant and reported as AE). Although the new cystoid macular edema started after risdiplam treatment and thus a possible causal relationship with treatment may not be definitely excluded, it is acknowledged that given the resolution of the event despite the continued risdiplam treatment, retinal immaturity could be a possible alternative explanation.

As regards to safety results by SMN2 copy number subgroups, when observing the outcome of AEs, it is noted that a higher proportion of AEs in patients with ≥4 copies (6/24, 25%) had an "unresolved" outcome, in comparison to patients with a lower number of SMN2 copies (2 copies: 1/ 21, 5%; and 3 copies 3/31, 10%). Also when observing AEs rate adjusted for patient years at risk (that takes into account the different time of exposure), the number of AEs per 100 patient-years (90% CI) are higher in the subgroup ≥4 SMN2 copies [926.64 (638.96, 1303.18)] in comparison to the subgroups with a lower number of SMN2 copies, with non-overlapping 90% CI when compared to the subgroup with 2 SMN 2 copies [352.90 (238.91, 503.92)]. Data are considered too limited to draw definitive conclusions. The MAH has committed to monitor in ongoing studies, risdiplam safety by SMN2 copy number subgroups

Increased liver enzymes as laboratory findings occurred frequently (≤ 2x ULN bilirubin and ALT; ≤3 x ULN AST), and in particular AST elevation was sustained, with values not returned to within normal values at last visit. In most patients (2/2 bilirubin increase and 4/7 ALT and AST increase) increases started at week 2 (Day 14 or 15). The MAH has committed to monitor laboratory findings of hepatic enzyme increased/ hepatic AEs in this very young patient population (<2 months) in ongoing studies and post-marketing in upcoming PSURs.

3.5. *Uncertainties and limitations about unfavourable effects*

The study duration prevents knowledge on types C, and D possible AEs, as well as type E, since no patient was followed after sudden discontinuation in a stable risdiplam treated patient.

Neonates represent the most vulnerable subgroup of the paediatric population and limited safety data are available in this subpopulation with pre-symptomatic SMA (n=18 at the CCOD of the interim analysis), with

no patient below 20 days of age receiving the dose 0.2 mg/kg (one 16-days neonate received an initial dose of 0.04 mg/kg), and only one patient of 20 days of age received the dose 0.2 mg/ kg. The absence of PK data or a PK model able to capture the ontogeny of the FMO3 enzyme questions the appropriateness of the proposed dosage for neonates below 20 days of age (0.15 mg/kg). However, the limited post marketing exposure in countries where the dose of 0.15 mg/kg was approved in children aged 0-20 days of life has not triggered safety signals and seems consistent with the approved treatment 2 months and above. This is considered reassuring enough for accepting the indication as proposed by the MAH. Nevertheless, safety in patients <1 month of age has been included as missing information in the RMP due to the extremely limited evidence available in this patient population; due to the need to further strengthen the confidence on the optimal recommended dose in this very young population and on the absence of risks associated with higher exposure to risdiplam, given the lack of PK data in infants below 20 days of age. Further, the MAH proposed to include the PK study BN44619 (PUPFISH) as an additional pharmacovigilance activity (category 3 PASS) in the RMP and has committed to provide regular updates in upcoming PSURs on the progress of the PK study BN44619 (PUPFISH). Additionally, the MAH has committed to conduct a real-world data collection in newborn infants with SMA younger than 2 months who have initiated treatment with risdiplam in the US (Study ML44811) to support the benefit risk in this subpopulation.

Evrysdi contains 0.375 mg of sodium benzoate per mL. The procedure of first authorization ended up in a post authorization measure (PAM) since the data on the adequacy of the proposed amount of sodium benzoate in the formulation were uncertain. However, in the proposed line extension the formulation maintains the same amount of sodium benzoate. According to the relevant guideline (EMEA/CHMP/QWP/396951/2006), the concentration of antimicrobial preservatives used should be at the lowest feasible level. Sodium benzoate is of particular concern in pre-term and full-term neonates where immaturity of metabolic enzymes until 8 weeks of age, may result in an accumulation of benzoic acid (please refer to EMA/CHMP/508189/2013). From the totality of available data and all the previous discussions, it's agreed that the inclusion of an antimicrobial preservative cannot be avoided, but since doubts remain on the selected amount of sodium benzoate the MAH has yet to demonstrate that the current concentration is the lowest effective level. Nevertheless, the CHMP agreed that this should be discussed as part of a separate Scientific Advice procedure. The PAM remains confirmed for the formulation.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

As already discussed at the time of the Marketing Authorization (please refer to risdiplam EPAR) - it may be acknowledged that the overall findings of previous risdiplam studies and the literature support the early initiation of treatment with risdiplam. The remaining uncertainties of such extrapolation of the data from symptomatic patients to pre- or pauci-symptomatic patients that have not yet reached the criteria for clinical diagnosis are also expected to be clarified by the data generated in the agreed PAES (see Annex II).

For this reason, it was agreed that the primary focus of the submitted interim analysis of the RAINBOWFISH study, is not efficacy but PK evaluation, in order to support dose determination for patients below 2 months of age. However, there were uncertainties in the previously selected dose, in relation to the discrepancy between the target AUC value of 2000 ng • h/mL (approved as cap in the PIP) and the observed higher median AUC value of 2500 ng • h/mL. together with the variability observed in the limited PK/PD available data in pre-symptomatic neonates and young infants < 2 months of age. A lower daily dose was proposed, which possibly mitigates the risk of the identified higher than target AUC values in the very young.

The preliminary efficacy results provided for some of the secondary endpoints in this interim analysis of the RAINBOWFISH Study in the 4 subjects with 2 SMN2 copies with a 12 months follow-up, seem to support the early initiation of treatment with risdiplam. The MAH has justified the difficulty in enrolment and the closure of the study due to not solvable recruitment issues; the ongoing population is expected to provide some responses to uncertainties which depend upon longer follow-ups.

Available data in neonates and young infants <2 months of age do not provide enough reassurance on the absence of a clinically relevant unfavourable effect of the higher-than-expected median AUC observed in the interim analysis of the RAINBOWFISH study. Nevertheless, the new proposed lower dose (0.15mg/kg) for infants <2 months is considered reassuring, and it can be accepted that there are no major safety concerns for infants aged at birth and above, treated with the lower dose of 0.15mg/kg.

3.6.2. Balance of benefits and risks

At present, the PK modelling together with the clinical PK data provided support the proposed dosage in children at least 20 days old (0.15 mg/kg). However, the absence of PK data or a PK model able to capture the ontogeny of the FMO3 enzyme questions the appropriateness of the proposed dosage for neonates below 20 days of age (0.15 mg/kg). Notwithstanding, limited available post marketing exposure in countries where the dose of 0.15 mg/kg was approved in children aged 0-20 days of life has not triggered safety signals.

The interim CSR included efficacy data on secondary endpoints. Although limited, results on asymptomatic subjects with 2 SMN2 copies support the early initiation of treatment with risdiplam.The safety data is limited in particular for neonates below 20 days of age. The absence of safety signals on this subpopulation treated with 0.15mg/kg in countries where risdiplam is indicated from birth is reassuring. The uncertainty remains and thus, "safety in patients <1 month of age" as missing information in the RMP. The MAH has committed to include PK study BN44619 (PUPFISH) in the RMP (cat.3 PASS) to address this safety concern. The MAH also committed to conduct a real-world data collection (Study ML44811) in newborn infants with SMA younger than 2 months.

All above considered, it is agreed to remove from section 4.1 of the SmPC the limitation of the indication starting from 2 months of age and the MAH proposal to recommend <2 months of age a 0.15 mg/kg dose is agreed.

3.7. *Conclusions*

At present available data from the interim analysis of the RAINBOWFISH study in the sought extension of indication below 2 months of age, can be accepted, from birth. The benefit-risk is considered to be positive in the sought indication.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends by consensus the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB
B.IV.1.b	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	Type IAin	I, IIIA and IIIB
B.IV.1.a.1	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	Type IAin	I, IIIA and IIIB

Grouping of three variations as follows:

Extension of indication to include treatment of patients below 2 months of age based on interim results from study BN40703 (RAINBOWFISH). The pivotal study RAINBOWFISH is an ongoing phase II multicentre, open-label, and single-arm study designed to evaluate the efficacy, safety, tolerability, and PK/PD of risdiplam in pre-symptomatic infants below 2 months of age who were genetically diagnosed with SMA. As a consequence, SmPC sections 4.1, 4.2, 4.8, 5.1 and 5.2 have been updated and the Package Leaflet has been updated in accordance. In addition, the MAH took the opportunity to make some editorial improvements in the product information. A revised RMP version 1.1 was also submitted as part of the application.

Type IAIN, B.IV.1.a.1 variation to update Evrysdi pack configuration with the addition of a new 1 mL oral syringe into the product carton allowing precise dosing of infants below 2 months of age. The 1 mL oral syringe is a CE-marked product provided by the same legal manufacturer as the current ones (6 mL and 12 mL syringes). As a consequence, section 6.5 of the SmPC has been updated and the labelling and Package Leaflet have been updated in accordance.

Type IAIN, B.IV.1.b variation to remove the spare unit of 12 mL oral syringe out of the two units currently provided in the product carton. As a consequence, section 6.5 of the SmPC has been updated and the labelling and Package Leaflet have been updated in accordance.

In view of the data submitted with the group of variations, amendments to Annex(es) I, IIIB and IIIA and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0470/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Evrysdi (risdiplam) is not similar to Spinraza® (nusinersen) and Zolgensma® (onasemnogene abeparvovec) within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1

5. EPAR changes

The EPAR will be updated following Commission Decision for this group of variations. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'EMEA/H/C/001899/II/0005/G

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 04 August 2023. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 04 August 2023. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.