CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213535Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	New Drug Application (NDA)
Application Number(s)	213535
Priority or Standard	Priority
Application Status Date(s)	September 24, 2019
PDUFA Goal Date	May 24, 2020
Division/Office	Division of Neurology 1/Office of Drug Evaluation-I
Reviewer Name(s)	Rainer W. Paine, MD, PhD
Review Completion Date	June 30, 2020
Established/Proper Name	Risdiplam (RO7034067)
(Proposed) Trade Name	EVRYSDI
Applicant	Genentech, Inc.
Dosage Form(s)	Powder for oral solution
Applicant Proposed Dosing Regimen(s)	Administer orally once daily using the provided oral syringe.

Age	Recommended Daily Dose
2 months to < 2 years of age	0.20 mg/kg
≥ 2 years of age (< 20 kg)	0.25 mg/kg
≥ 2 years of age (≥ 20 kg)	5 mg

Applicant Proposed Indication(s)/Population(s)	Spinal Muscular Atrophy (SMA)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Spinal Muscular Atrophy (SMA)

Reference ID: 4646272

Table of Contents

Glossary 10

1. Executive Summary 12
   1.1. Product Introduction 12
   1.2. Conclusions on the Substantial Evidence of Effectiveness 12
   1.3. Benefit-Risk Assessment 13
   1.4. Patient Experience Data 20

2. Therapeutic Context 21
   2.1. Analysis of Condition 21
   2.2. Analysis of Current Treatment Options 22

3. Regulatory Background 22
   3.1. U.S. Regulatory Actions and Marketing History 22
   3.2. Summary of Presubmission/Submission Regulatory Activity 22
   3.3. Foreign Regulatory Actions and Marketing History 25
   Risdiplam has not been marketed previously in any country. 25

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety 25
   4.1. Office of Scientific Investigations (OSI) 25
   4.2. Product Quality 25
   4.3. Clinical Microbiology 27
   4.4. Nonclinical Pharmacology/Toxicology 27
      4.4.1. In vitro Findings Relevant to Mechanism of Action Using Human-Derived Products 27
      4.4.2. Pharmacological Proof-of-Mechanism in Mouse Models 27
      4.4.3. Toxicology Studies 27
      4.4.4. Genotoxicity Studies 28
      4.4.5. Carcinogenicity Studies 28
      4.4.6. Reproductive and Developmental Toxicity 28
      4.4.7. Safety Pharmacology 29
   4.5. Clinical Pharmacology 29

Reference ID: 4646272

4.6. Devices and Companion Diagnostic Issues 30
4.7. Consumer Study Reviews 30

5. Sources of Clinical Data and Review Strategy 30
5.1. Table of Clinical Studies 30
5.2. Review Strategy 37

6. Review of Relevant Individual Trials Used to Support Efficacy 37
6.1. Study BP39055, SUNFISH: 37
A Two-Part Seamless, Multi-Center Randomized, Placebo-controlled, Double-blind Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam in Type 2 and 3 Spinal Muscular Atrophy Patients 37
6.1.1. Study Design 37
6.1.2. Study Results 56
6.2. Study BP39056, FIREFISH 68
A Two-Part Seamless, Open-Label, Multi-Center Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam in Infants with Type 1 Spinal Muscular Atrophy 68
6.2.1. Study Design 68
6.2.2. Firefish Study Results 81

7. Integrated Review of Effectiveness 93
7.1. Assessment of Efficacy Across Trials 93
7.1.1. Primary Endpoints 93
7.1.2. Secondary and Other Endpoints 94
7.1.3. Subpopulations 96
7.1.4. Dose and Dose-Response 100
7.1.5. Onset, Duration, and Durability of Efficacy Effects 100
7.2. Additional Efficacy Considerations 102
7.2.1. Considerations on Benefit in the Postmarket Setting 102
7.3. Integrated Assessment of Effectiveness 102

8. Review of Safety 104
8.1. Safety Review Approach 104
8.2. Review of the Safety Database 104

Reference ID: 4646272

8.2.1. Overall Exposure 104
8.2.2. Relevant Characteristics of the Safety Population: 105
8.2.3. Adequacy of the safety database: 106
8.3. Adequacy of Applicant's Clinical Safety Assessments 106
8.3.1. Issues Regarding Data Integrity and Submission Quality 106
8.3.2. Categorization of Adverse Events 106
8.3.3. Routine Clinical Tests 106
8.4. Safety Results 107
8.4.1. Deaths 107
8.4.2. Serious Adverse Events 108
8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects 113
8.4.4. Significant Adverse Events 113
8.4.5. Adverse Events and Adverse Reactions 114
8.4.6. Laboratory Findings 117
8.4.7. Vital Signs 120
8.4.8. Electrocardiograms (ECGs) 124
8.4.9. QT 125
8.4.10. Immunogenicity 126
8.5. Analysis of Submission-Specific Safety Issues 126
8.5.1. Retinal Toxicity 126
8.5.2. Effects on Epithelial Tissues 128
8.5.3. Hematological Effects 129
8.5.4. Risk of Liver Injury 130
8.6. Safety Analyses by Demographic Subgroups 135
8.7. Specific Safety Studies/Clinical Trials 136
8.8. Additional Safety Explorations 136
8.8.1. Human Carcinogenicity or Tumor Development 136
8.8.2. Human Reproduction and Pregnancy 136
8.8.3. Pediatrics and Assessment of Effects on Growth 137
8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound 137
8.9. Safety in the Postmarket Setting 137
8.9.1. Safety Concerns Identified Through Postmarket Experience 137

Reference ID: 4646272

8.9.2. Expectations on Safety in the Postmarket Setting 137
8.9.3. Additional Safety Issues From Other Disciplines 138
8.10. Integrated Assessment of Safety 138
9. Advisory Committee Meeting and Other External Consultations 139
10. Labeling Recommendations 140
10.1. Prescription Drug Labeling 140
10.2. Nonprescription Drug Labeling 140
11. Risk Evaluation and Mitigation Strategies (REMS) 140
12. Postmarketing Requirements and Commitments 140
13. Appendices 141
13.1. References 141
13.2. Financial Disclosure 144
13.3. CHOP INTEND Scoring Sheet. Source: Glanzman et al., 2010 145

Reference ID: 4646272

Table of Tables

Table 1: Classification of Spinal Muscular Atrophy. Source: Mercuri et al., 2012 21
Table 2: Composition of Risdiplam Powder for Oral Solution 0.75 mg/mL 26
Table 3: Overview of Risdiplam Clinical Development Program. Source: Clinical Overview, p. 13 31
Table 4: Listing of Placebo-Controlled Clinical Trials Relevant to this NDA 32
Table 5: Listing of Uncontrolled Clinical Trials Relevant to this NDA 34
Table 6: Classification of Spinal Muscular Atrophy. Source: Mercuri et al., 2012 41
Table 7: Sunfish Study Part 2 Schedule of Key Assessments 45
Table 8: Sunfish Study Schedule of Ophthalmology Assessments 46
Table 9: List of the 32 items of the Motor Function Measure with the starting position and exercises required. Source: Bérard et al. 2005 50
Table 10: The seven null hypotheses and the six families of the testing for Sunfish study Part 2. Source: Sunfish CSR 55
Table 11: Patient disposition (placebo-controlled period) 57
Table 12: Summaries of major protocol deviations that occurred during the placebo-controlled period of the Sunfish study. 58
Table 13: Demographics of Sunfish Study Part 2. Source: Submitted data 59
Table 14: Summary of Key Efficacy Results – ITT Population. 64
Table 15: Subgroup Analysis of Change from Baseline in MFM32 and RULM at Month 12 by Age Group 67
Table 16: Subgroup Analysis of Change from Baseline in MFM32 at Month 12 by Region 68
Table 17: Firefish Study Part 1 Schedule of Key Assessments 73
Table 18: Firefish Study Schedule of Ophthalmology Assessments, Parts 1 & 2 74
Table 19: Guidelines for Managing Specific Adverse Events 75
Table 20: Summary of Firefish Efficacy Endpoints in Part 1 at Month 12 (ITT Population) 84
Table 21: Summary of Additional Firefish Efficacy Endpoints in Part 1 at Month 12 (ITT Population) 85
Table 22: Risdiplam Safety Population, Size, and Denominators. Reviewer's assessment 105
Table 23: Exposure to Risdiplam. Note that 56 patients received the proposed labelling dose for up to 16 months (0.2 mg/kg for infants <2 years old, 0.25 mg/kg for infants and children >=2 years and <20 kg bodyweight, 5 mg for ≥20 kg bodyweight) 105
Table 24: Placebo-controlled Experience: Overview of Adverse Events 107
Table 25: Deaths in the Open-Label Firefish Study. All subjects received risdiplam. 108
Table 26: Serious Adverse Events in the Controlled Sunfish Part 2 Study that Occurred More Frequently in the Risdiplam (RO7034067) group. 109
Table 27: Serious Respiratory Adverse Events in the Sunfish Part 2 Study 109
Table 28: Serious Treatment-emergent Adverse Events from the Open-label Firefish Study that Occurred in More Than One Subject. 112
Table 29: Adverse Events in the Controlled Safety Database: MAED Analysis of Sunfish Part 2 Study 114

Reference ID: 4646272

Table 30: Adverse Events in the Controlled Safety Database that Occurred More Frequently in the Risdiplam Group: ODE-1 MedDRA Query for Sunfish Part 2 study. Terms highlighted in red occurred at least 5% more frequently in the Risdiplam group..... 114
Table 31: Treatment-emergent Adverse Events from the Open-label Firefish Study..... 115
Table 32: Treatment-emergent Adverse Events from the Open-label Jewelfish Study..... 116
Table 33: Mean Change (Standard Deviation) from Baseline Hematology Parameters in the Controlled Sunfish Study. Source: Reviewer Analysis..... 117

Reference ID: 4646272

Table of Figures

Figure 1: Sunfish Study Design of Part 1 Exploratory Dose-Finding 40
Figure 2: Sunfish Study Design of Placebo-controlled Part 2 40
Figure 3: Decision Tree for Part 2 Key Efficacy Endpoints for Hierarchical Testing. Source: Sunfish CSR..... 56
Figure 4: Firefish Study Design..... 70
Figure 5: Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) (Bayley, N., 2006)..... 76
Figure 6: Hammersmith Infant Neurological Examination (HINE) Section 2 – Motor Milestones. 80
Figure 7: FIREFISH Study Part 1: Assigned Doses for Each Infant 82
Figure 8: Kaplan-Meier survival curves in type 1 SMA infants as a function of type of respiratory support. Patients with Tracheostomy/Invasive Mechanical Ventilation (top, n=42); Non-invasive bilevel ventilation and mechanically assisted coughing (middle; n=31); Untreated (bottom, n=121). Source: Gregoretti et al., 2013 88
Figure 9: Mean Change from Baseline in CMAP Negative Peak Amplitude (ITT Population, Firefish Part 1 Patients)..... 91
Figure 10: Forest Plot of Patients Sitting without Support for 5 seconds at Month 12 by Subgroup (ITT Patients; Part 1 Patients)..... 96
Figure 11: Forest Plot of Patients who Achieved a CHOP-INTEND Score of 40 or Higher at Month 12 by Subgroup (ITT Population; Part 1 Patients)..... 97
Figure 12: Forest Plot of MMRM Analysis on the Change from Baseline in MFM32 Total Score at Month 12 by Subgroups (Placebo Controlled Period) (Part 2; ITT Population). Source: Sunfish CSR 97
Figure 13: Forest Plot of MMRM Analysis on the Change from Baseline in RULM Total Score at Month 12 by Subgroups (Placebo Controlled Period) (Part 2; ITT Population) 98
Figure 14: Change from Baseline in the MFM32 Total Score at Month 12 by Ascending Values of Age (Years) and by SMA Type (Type 2 or Type 3) (Placebo Controlled Period) (Part 2; ITT Population)..... 99
Figure 15: Change from Baseline in the RULM Total Score at Month12 by Ascending Values of Age (Years) and by SMA Type (Type 2 or Type 3) (Placebo Controlled Period) (Part 2; ITT Population)..... 100
Figure 16: Least-Squares Mean Change from Baseline and 95% Confidence Interval in MFM32 Total Score at Each Timepoint up to Month 12 (Placebo-Controlled Period) (Sunfish Part 2; ITT Population)..... 101
Figure 17: Least-Squares Mean Change from Baseline and 95% Confidence Interval on RULM Total Score at Each Timepoint up to Month 12 (Placebo Controlled Period) (Part 2; ITT Population)..... 102
Figure 18: Shift Plot of Blood Creatinine in the Sunfish study..... 119
Figure 19: Shift Plot of Blood Urea in the Sunfish study..... 120
Figure 20: Change from Baseline for Systolic Blood Pressure in the Sunfish Study 121

Reference ID: 4646272

Figure 21: Change from Baseline for Diastolic Blood Pressure in the Sunfish Study 122
Figure 22: Change from Baseline for Heart Rate in the Sunfish Study 123
Figure 23: Change from Baseline for Weight in the Sunfish Study..... 123
Figure 24: Change from Baseline for Head Circumference in the Sunfish Study 124
Figure 25: Change from Baseline for Height in the Sunfish Study..... 124
Figure 26: QTCB in the Sunfish study..... 125
Figure 27: Shift Plot of Blood AST in the Sunfish study. 131
Figure 28: Shift Plot of Blood ALT in the Sunfish study..... 132
Figure 29: Shift Plot of Blood GGT in the Sunfish study..... 133
Figure 30: Shift Plot of Blood Direct Bilirubin in the Sunfish study. 134
Figure 31: Treatment Emergent Adverse Events Description by Age (in years)..... 135
Figure 32: Treatment Emergent Adverse Events Description by Sex 136

Reference ID: 4646272

Glossary

AC	advisory committee
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CCOD	clinical cutoff date
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHOP INTEND	Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSF	cerebrospinal fluid
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GCP	good clinical practice
GRMP	good review management practice
HFMSE	Hammersmith Functional Motor Scale - Expanded
HINE	Hammersmith Infant Neurological Examination
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IMC	Independent Monitoring Committee
IND	Investigational New Drug
ISE	integrated summary of effectiveness

Reference ID: 4646272

ISS	integrated summary of safety
IT	intrathecal
ITT	intent to treat
IxRS	Interactive (voice/web) response system
MedDRA	Medical Dictionary for Regulatory Activities
MEP	Maximal expiratory pressure
MIP	Maximal inspiratory pressure
mITT	modified intent to treat
MUNE	Motor unit number estimation
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PCF	Peak Cough Flow
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SCE	Summary of Clinical Efficacy
SD-OCT	Spectral Domain Optical Coherence Tomography
SGE	special government employee
SMA	Spinal muscular atrophy
SOC	standard of care
SOC	system organ class
TEAE	treatment emergent adverse event
ULMT	Upper Limb Module Test
6MWT	6-minute Walk Test

Reference ID: 4646272

1. Executive Summary

1.1. Product Introduction

Risdiplam (called RO7034067 in clinical trials; EVRYSDI is the proposed proprietary name) is an orally administered small molecule SMN2 (survival motor neuron 2) splicing modifier that promotes the inclusion of exon 7 to generate full-length SMN2 mRNA, thereby increasing the production of functional SMN protein from the SMN2 gene.

Risdiplam is a new molecular entity (NME) containing no previously approved active ingredient (including any ester or salt of the active ingredient).

Note that reviewer commentary throughout the text is presented in *italics*.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The placebo-controlled Sunfish Part 2 study is an adequate and well-controlled efficacy study that can support approval of risdiplam for the treatment of children and adults with Types 2 and 3 SMA. It is a well-designed multicenter study that has provided reliable and statistically significant (p=0.016) evidence of an important clinical benefit, motor function improvement, that is inconsistent with the natural course of the disease.

Additional evidence of efficacy in infants with Type 1 SMA is provided by the Firefish study, an open-label, externally-controlled, multi-center study that showed improvements in multiple clinical functional measures compared to the natural history of SMA, including motor function and developmental milestones as well as survival and ventilation-free survival. Note that the biometrics team review assessed this open-label study as not having a concurrent control and concluded that "the evidence from Firefish, though impressive on face compared to the reported natural history, is not well controlled." However, this reviewer considers the external natural history control as sufficient to describe the Firefish study as "well-controlled" because no Type 1 SMA patients would be expected to achieve sitting without support in the natural history of the disease. Further, the threshold of 5 out of 40 patients sitting for 5 seconds was agreed between the sponsor and the Division in pre-IND meeting minutes from March 4, 2016, prior to the start of the study. The study was rigorously conducted and the study endpoints of sitting unsupported and ventilator-free survival were well-defined with a low potential for bias.

The underlying cause of SMA, a deficiency of survival motor neuron (SMN) protein, is common to patients with all types of SMA (with increasing amounts of SMN corresponding to less severe disease). The two clinical studies, Sunfish in Types 2 and 3 SMA and Firefish in Type 1 SMA, are

Reference ID: 4646272

therefore complementary and support a conclusion of efficacy for SMA in general.

1.3. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4646272

Benefit-Risk Integrated Assessment

Risdiplam (called RO7034067 in clinical trials; EVRYSDI is the proposed proprietary name) is an orally administered small molecule SMN2 (survival motor neuron 2) splicing modifier that promotes the inclusion of exon 7 to generate full-length SMN2 mRNA, thereby increasing the production of functional SMN protein from the SMN2 gene. Risdiplam is intended to treat patients with spinal muscular atrophy (SMA).

Spinal muscular atrophy (SMA) is an autosomal recessive disease with survival motor neuron (SMN) protein deficiency that causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. Type 1 (infantile-onset) SMA is fatal, usually by 2 years of age, due to respiratory failure and infection. It is the most common genetic cause of infant mortality, with a global incidence of 8.5 to 10.3 per 100,000 live births.

Medical care focuses on respiratory support, nutritional support, the management of resulting respiratory infections with antibiotics, and the management of resulting tendon contractures and scoliosis through bracing, physical therapy, and surgery. Although the lifespan of the most severely affected SMA patients can be increased through invasive mechanical ventilation, the quality of such a life is poor and most patients eventually succumb to respiratory infection.

There are two FDA-approved drugs for the treatment of SMA. Nusinersen (Spinraza), an intrathecally administered SMN2-targeting antisense oligonucleotide, was approved for the treatment of SMA in pediatric and adult patients in 2016. Onasemnogene abeparvovec (Zolgensma), a gene-replacement therapy that uses a non-replicating adeno-associated virus (AAV) capsid to deliver a functional copy of the SMN gene by intravenous infusion, was approved by the FDA in 2019 for patients with SMA <2 years of age. There remains a significant unmet clinical need for effective treatments for SMA patients because not all SMA patients are able to receive, tolerate, or adequately benefit from the two currently approved drugs. Nusinersen must be re-administered intrathecally every 4 months, but is difficult to use in patients with poor spinal access or significant anxiety about repeated spinal injection. Repeated lumbar punctures also carry risks of headache, hemorrhage, and infection. The duration of benefit from Zolgensma has not yet been established and it cannot be administered more than a single time because of AAV antibody development. Further, the proportion of patients with pre-existing AAV antibodies preventing Zolgensma treatment increases from ~2% in infants up to 30% in adults.

A 12-month placebo-controlled multicenter study of risdiplam in Type 2 and 3 SMA children and adults (120 risdiplam, 60 placebo) has provided reliable and statistically strong evidence that risdiplam can help these patients achieve motor function improvement that they would otherwise not achieve due to the disease. The study also showed improvement in upper limb function compared to placebo, as well as nominal

Reference ID: 4646272

improvements in patient and caregiver-reported outcomes.

Further evidence of the benefit of risdiplam in treating infants with Type 1 SMA was provided by an open-label, historically controlled, multi-center study that showed improvements in multiple clinical functional measures compared to the natural history of SMA, including motor function and developmental milestones as well as survival and ventilation-free survival.

The underlying cause of SMA, a deficiency of survival motor neuron (SMN) protein, is common to patients with all types of SMA. The two clinical studies are therefore complementary and support a conclusion of efficacy for SMA in general.

The following common adverse events occurred in the 12-month placebo-controlled multicenter study of risdiplam in children and adults with SMA: upper respiratory tract infection (32%), pyrexia (21%), headache (20%), diarrhea (17%), rash (13%), nausea (9%), constipation (8%), pneumonia (8%), urinary tract infection (5%), and arthralgia (5%). Although nonclinical studies found a risk of retinal damage in monkeys, ophthalmological monitoring and adverse events analysis of the risdiplam clinical studies found no evidence of retinal injury in humans.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Spinal muscular atrophy (SMA) is a genetic disease that causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. • There are different types of SMA (types 0, 1, 2, 3 and 4). Classification into SMA types used to be based only on the age when symptoms began and the kinds of movements patients could achieve. Today we also have genetic testing to help classify the different types of SMA. • In general, the more copies of the survival motor neuron 2 gene (SMN2) that a patient has, the better the prognosis is. • Affected infants have impaired motor milestone development. For	• Type 1 (infantile-onset) SMA is fatal, usually by 2 years of age, due to weakening of the muscles needed for breathing and infections that occur when babies become too weak to cough and clear their lungs. • Genetic testing alone can't always tell one exactly which type of SMA will develop in all patients. • Different patients with the same SMN2 gene copy number can have different severities of symptoms.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	example, they remain unable to lift the head, sit, stand, or walk. Following the initial weakness and impaired motor development, there is a long-term decline or a plateau in strength and movement ability. • Type 1 (infantile-onset) SMA is the most common genetic cause of infant mortality, with a global incidence of 8.5 to 10.3 per 100,000 live births.	
Current Treatment Options	• Medical care focuses on respiratory support, nutritional support, the management of resulting respiratory infections with antibiotics, and the management of resulting tendon contractures and scoliosis through bracing, physical therapy, and surgery. Although the lifespan of the most severely affected SMA patients can be increased through invasive mechanical ventilation, the quality of such a life is poor and most patients eventually succumb to respiratory infection. • There are two FDA-approved drugs for the treatment of SMA. Nusinersen (Spinraza), an intrathecally administered SMN2-targeting antisense oligonucleotide, was approved for the treatment of SMA in pediatric and adult patients in 2016. Onasemnogene abeparvovec (Zolgensma), a gene-replacement therapy that uses a non-replicating adeno-associated virus (AAV) capsid to deliver a functional copy of the SMN gene by intravenous infusion, was approved by the FDA in 2019 for patients with SMA <2 years of age.	• Although the lifespan of the most severely affected SMA patients can be increased through permanent mechanical ventilation, the quality of such a life is poor and most patients eventually succumb to respiratory infection. • There remains a significant unmet clinical need for effective treatments for SMA patients because not all SMA patients are able to receive, tolerate, or adequately benefit from the two currently approved drugs. Nusinersen must be re-administered intrathecally every 4 months, but is difficult to use in patients with poor spinal access or significant anxiety about repeated spinal injection. Repeated lumbar punctures also carry risks of headache, hemorrhage, and infection. The duration of benefit from Zolgensma has not yet been established and it cannot be

Reference ID: 4646272

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		administered more than a single time because of AAV antibody development. Further, the proportion of patients with pre-existing AAV antibodies preventing Zolgensma treatment increases from ~2% in infants up to 30% in adults.
Benefit	• In the 12-month placebo-controlled multicenter study of risdiplam in Type 2 and 3 SMA children and adults (120 risdiplam, 60 placebo) there was a mean increase in MFM32 score, a measure of motor function, in the risdiplam-treated group (1.4) compared to a mean decrease (-0.2) in the placebo group (p=0.016). • Upper limb function, measured by the mean RULM score change from baseline at Month 12, showed a 1.6 point improvement in the risdiplam-treated group compared to no change in the placebo group (p=0.047). • Patient, parent/caregiver, and clinician-reported outcome measures gave nominal support for the efficacy of risdiplam as measured by the SMAIS and CGI-C scales (SMAIS: +1.7 caregiver-reported for risdiplam; -0.9 caregiver-reported for placebo; +1 patient-reported for risdiplam; -0.4 patient-reported for placebo; CGI-C: 48% for risdiplam; 40% for placebo). • 41% of the higher dose subjects in a 12-month open-label study achieved sitting without support compared to the normal course of Type 1 SMA, in which no patients would be expected to achieve sitting without support. • Of the higher dose subjects in the open-label study, 88% achieved an increase of at least 4 points in their CHOP-INTEND score, a measure of	The 12-month placebo-controlled study of risdiplam has provided reliable and statistically strong evidence that risdiplam can help Type 2 and 3 SMA patients achieve motor function improvement that they would otherwise not achieve due to the disease. Further evidence of the benefit of risdiplam in treating infants with Type 1 SMA was provided by an open-label, historically controlled, multi-center study that showed improvements in multiple clinical functional measures compared to the natural history of SMA. This study provides evidence of reduced mortality and permanent ventilation in the risdiplam group compared to the natural history of Type 1 SMA.

Reference ID: 4646272

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	motor function, from baseline at Month 12 compared to 0% in natural history studies of SMA • Of the higher dose subjects in the open-label study, 94% were alive without permanent ventilation at Month 12 of the study. At the time of this review, 81% of patients were alive without permanent ventilation, were older than 28 months of age, and had at least 24 months of treatment with risdiplam. In natural history studies of Type 1 SMA, survival at age 18 months ranged from 9% to 51%.	
Risk and Risk Management	• The most commonly observed (10% or greater) adverse events associated with the use of risdiplam in the 12-month placebo-controlled study were upper respiratory tract infection (32%), pyrexia (21%), headache (20%), diarrhea (17%), and rash (13%). • There were no withdrawals from the placebo-controlled or open-label studies due to adverse events. • There were 6 deaths (~10% of the study population) in the open-label study of infants with Type 1 SMA. All deaths were caused by respiratory complications that are common in Type 1 SMA patients. There were no deaths in the placebo-controlled study of Types 2 and 3 SMA children and adults. • Serious adverse events of pneumonia, bacteremia, and influenza occurred more frequently in the risdiplam group (8%, 2%, 2%, respectively) than the placebo group (2%, 0%, 0%, respectively). • Four serious adverse events in 4 patients (3%) in the risdiplam arm (gastroenteritis, constipation, pyrexia, aspiration) and 2 events in 2 patients (3%) in the placebo arm (sleep apnea syndrome, appendicitis) led to dose interruption. • Infections and infestations occurred in 75% of the risdiplam group and	• The safety profile of risdiplam is acceptable to support an approval. • The difference in serious adverse events of pneumonia, bacteremia, and influenza between the risdiplam and placebo groups is difficult to interpret because of the small numbers of subjects affected and the common occurrence of respiratory infections in SMA patients with disease-related weakening of respiratory muscles. • Analysis of overall infection rates and lung infection rates does not suggest a clinically significant difference in infection rates between the risdiplam and placebo groups. • Although nonclinical studies found a risk of retinal damage in monkeys, ophthalmological monitoring and adverse events analysis of the risdiplam clinical studies found no evidence of retinal injury

Reference ID: 4646272

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	80% of the placebo group. • Lower respiratory tract and lung infections occurred in 17% of the risdiplam group and 22% of the placebo group.	in humans.

Reference ID: 4646272

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	6.1.2, 6.2.2, 7.1.2
		X	Observer reported outcome (ObsRO)	6.1.2, 6.2.2, 7.1.2
		X	Clinician reported outcome (ClinRO)	6.1.2, 6.2.2, 7.1.2
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	X	Natural history studies		6.2.2., 7.1.2
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

Reference ID: 4646272

2. Therapeutic Context

2.1. Analysis of Condition

Spinal muscular atrophy (SMA) is an autosomal recessive disease with survival motor neuron (SMN) protein deficiency that causes motor neuron loss in the brainstem and spinal cord, leading to weakness and muscle atrophy. Type 1 (infantile-onset) SMA is fatal, usually by 2 years of age, due to respiratory failure and infection. It is the most common genetic cause of infant mortality, with a global incidence of 8.5 to 10.3 per 100,000 live births (Arkblad 2009; Jedrzejowska 2010; Prior 2010; Sugarman 2012).

There are multiple types of SMA (0-4), as shown in the following table. Classification into SMA types has historically been based on the age of symptom onset and the maximal achieved motor abilities (Finkel 2015). In general, the severity of symptoms decreases and the age of onset is delayed with increasing survival motor neuron 2 gene (SMN2) copy number and correspondingly increasing amounts of SMN protein (Arnold, 2015), although different patients with the same SMN2 copy number can have different clinical phenotypes.

Table 1: Classification of Spinal Muscular Atrophy. Source: Mercuri et al., 2012

	Age of onset	Maximum function achieved	Prognosis	Proposed subclassification	*SMN* copy number
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	..	..
Type 1 (severe)	0–6 months	Never sits	If untreated, life expectancy <2 years	1A, head control never achieved, signs in the neonatal period; 1B, head control never achieved, onset after neonatal period; 1C, head control achieved, onset after neonatal period	One or two copies of *SMN2* in 80% of patients
Type 2 (intermediate)	7–18 months	Sits but never stands	Survival into adulthood	Decimal classification according to functional level, from 2·1 to 2·9	Three copies of *SMN2* in >80% of patients
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	3A, onset of weakness before 3 years; 3B, onset of weakness after 3 years	Three or four copies of *SMN2* in 96% of patients
Type 4 (adult)	10–30 years	Stands and walks	Survival into adulthood	..	Four or more copies of *SMN2*

Affected infants have impaired motor milestone development, e.g., lift the head, sit, stand, or walk. Following the initial acute weakness and impaired motor development, there is a chronic decline or plateau in functional capabilities (Crawford 2004; Swoboda et al. 2007).

Reference ID: 4646272

2.2. Analysis of Current Treatment Options

Medical care focuses on respiratory support, nutritional support, the management of resulting respiratory infections with antibiotics, and the management of resulting tendon contractures and scoliosis through bracing, physical therapy, and surgery. Although the lifespan of the most severely affected SMA patients can be increased through invasive mechanical ventilation, the quality of such a life is poor and most patients eventually succumb to respiratory infection.

There are two FDA-approved drugs for the treatment of SMA. Nusinersen (Spinraza), an intrathecally administered SMN2-targeting antisense oligonucleotide, was approved for the treatment of SMA in pediatric and adult patients in 2016. Onasemnogene abeparvovec (Zolgensma), a gene-replacement therapy that uses a non-replicating adeno-associated virus (AAV) capsid to deliver a functional copy of the SMN gene by intravenous infusion, was approved by the FDA in 2019 for patients with SMA <2 years of age.

There remains a significant unmet clinical need for effective treatments for SMA patients because not all SMA patients are able to receive, tolerate, or adequately benefit from the two currently approved drugs. Nusinersen must be re-administered intrathecally every 4 months but is difficult to use in patients with poor spinal access or significant anxiety about repeated spinal injection. Recurrent lumbar punctures also carry risks of infection, hemorrhage, and pain. The duration of benefit from Zolgensma has not yet been established and it cannot be administered more than a single time because of AAV antibody development. Further, the proportion of patients with pre-existing AAV antibodies preventing Zolgensma treatment increases from ~2% in infants up to 30% in adults.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Risdiplam is a new molecular entity (NME) that is not currently marketed in the United States or in any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 128972 for risdiplam was allowed to proceed on November 10, 2016.

The FDA clinical review from 11/9/2016 noted that “nonclinical studies have identified a number of issues of potential concern at lower exposures to the drug, consisting primarily of retinal toxicity, but also including testicular cell degeneration. No relevant findings were

Reference ID: 4646272

observed in the completed Phase 1 SAD study in 25 healthy multi-ethnic adults, and that study revealed adverse events of only mild intensity and without safety signal clustering. Several subjects in that study had elevated LFTs and alterations in lipid and phosphate levels."

In written responses from a pre-IND meeting dated 3/4/2016, the Agency made recommendations for ophthalmological monitoring and stated that "it is unlikely that the occurrence of irreversible retinal injury can necessarily be prevented; however, considering the potential benefits of a successful therapy, the risks are recommended to be monitored."

Regarding the design of the confirmatory Part 2 of Study BP39055 (Sunfish), the Agency stated that "The MFM is acceptable as the primary endpoint; however, it is unclear why the inclusion of domain D1 (standing position and transfer) is warranted for your non-ambulant trial population. We also note that, based on the publications provided in your briefing package, the mean annual decline of this patient population appears to be < 1 point/year, and your trial is powered to detect a 3-point difference after a 12-month treatment. However, if the placebo group in the trial declines by about 1 point as anticipated, the drug would need to produce a 2-point improvement above baseline to achieve a 3-point difference in favor of the drug. Therefore, to increase the likelihood of demonstrating a treatment effect, we recommend that you consider a longer trial duration (e.g., 24 months) with an interim analysis at 12 months.

The Agency made the following comments regarding the design of Study BP39056 (Firefish). "We continue to believe that a placebo-controlled trial would be most informative for this trial in infants with SMA Type 1. The effect of treatment in the single arm trial in SMA type 1 may be very difficult to interpret, due to the many possible sources of bias with such a design (and small sample size), such as lack of a concurrent control, differences in study populations, change in standard of care, etc. However, the design of your proposed trial in patients with Type I SMA is potentially acceptable, pending a review of the full study protocol. We also have the following specific responses to your questions: a) Your choice of primary endpoint, the proportion of patients able to sit without support at Month 12 for at least 5 seconds as assessed by the Gross Motor Scale of the BSID-III, is potentially acceptable based on your criteria that at least 5 subjects out of 40 would need to meet this endpoint for the trial to be considered positive. However, you should clarify whether children will be able to use their own hands for support and still be considered to be sitting unsupported. The acceptability of this endpoint in an open-label efficacy trial is also dependent upon your ability to provide data that supports the assertion that untreated children essentially never would be expected to reach this milestone as defined by the protocol."

In meeting minutes from a Type C meeting on 1/23/18, the Agency stated that "given the seriousness of the indication, the 2-year carcinogenicity study in rat may be conducted post approval, provided the available data support such a strategy. Deferral of the carcinogenicity

Reference ID: 4646272

study would not be based on a lack of concern regarding the carcinogenic potential of RO7034067."

The Agency further commented on the applicant's ophthalmological monitoring plan, stating that "the sponsor's proposed changes in the ophthalmologic safety assessment schedule, beyond the acceptable modifications described in the Agency's preliminary meeting comments, represent an unacceptable risk to subjects. The Agency also explained that there is an insufficient safety database at present [redacted] (b) (4) considering the toxicity observed in the nonclinical studies."

Regarding study design, the Agency stated "As indicated in the March 4, 2016, pre-IND meeting responses, we continue to believe that a placebo-controlled trial in your proposed patient population would be most informative. As noted in those responses, in the context of a historical-control trial, data would be required to demonstrate that any observed effects in Study BP39056 would not have occurred in the natural history of the disease in patients enrolled in the trial (consistent with the principles discussed in ICH E10)."

The Agency stated that the "proposed ECG monitoring plan is acceptable. You will not need to conduct a TQT study to support the filing of any future NDA for RO7034067 for the treatment of SMA."

[redacted] (b) (4)

Therefore, the Agency reiterated that efficacy would need to be established based on the demonstration of a positive treatment effect on an endpoint(s) that directly assesses a clinically meaningful benefit(s) to patients.

At a Type C meeting on 12/18/19, the sponsor provided preliminary clinical data from FIREFISH Part 1 that was suggestive of efficacy.The Agency stated that "the data from FIREFISH trial Part 1 in infantile-onset patients with at least 12 months of treatment may be adequate to support an NDA submission if there is an acceptable proportion of patients who achieve the primary endpoint of sitting unassisted, and the findings are supported by the secondary endpoints and by changes on relevant biomarkers. For such an approach to be acceptable, any planned NDA would need to include an adequate evidence-based justification for the assertion that this milestone would not occur in these patients in the absence of treatment…. It appears that the available risdiplam safety data from currently ongoing and planned studies may constitute an adequate safety database for an NDA submission for risdiplam, provided that there are no concerning safety findings… We continue to recommend sd-OCT [spectral domain - optical coherence tomography] monitoring and visual acuity testing every three months, and visual field testing and fundus photography assessments every six months."

Reference ID: 4646272

In meeting minutes from a Pre-NDA meeting dated 7/10/2019, the Agency stated that an NDA application may be fileable based on the results of the primary endpoint analysis from FIREFISH Part 1; however,"as the natural history of the proposed motor functional endpoints (e.g., CHOP-INTEND, HINE) is not as well-characterized in the infantile-onset SMA population, subject-level natural history data would be needed to serve as an external comparator for the potential inclusion of a detailed description of the motor functional endpoints from FIREFISH Part 1 in any approved label. Additionally, as survival is well-characterized in the infantile-onset SMA population, the Division is open to a description of survival outcomes from FIREFISH Part 1 compared to the established natural history of survival in the disease." The sponsor also proposed to submit efficacy and safety data from SUNFISH Part 1 with Type 1 and 3 SMA (at least 12 months of treatment with risdiplam) compared to a natural history control.

The FDA granted risdiplam Fast Track (04/05/2017), Orphan Drug (01/04/2017), Priority review, and Rolling submission (05/30/2019) designations.

The applicant submitted additional data from the completed placebo-controlled Sunfish Part 2 study during the review of this application. This submission constituted a major amendment and the review time was extended.

3.3. Foreign Regulatory Actions and Marketing History

Risdiplam has not been marketed previously in any country.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Foreign site inspections have been cancelled as a result of the worldwide Covid-19 pandemic.

4.2. Product Quality

Risdiplam, a light yellow powder, is administered as an oral solution with purified water. A total of 7 different variants of oral solution formulations, including the market formulation, were used in clinical studies. The to-be-marketed formulation is identical to the formulation used in the open-label extension phases in Part 1 and Part 2 of Studies BP39055 (SUNFISH) and BP39056 (FIREFISH), and in Study BP39054 (JEWELFISH). The excipients of the formulation used in Part 1 of Studies BP39055 (SUNFISH) and BP39056 (FIREFISH) were the same as in the Part 2 formulation, except for isomalt, as seen in the table copied from the submission below. To support the later clinical studies (BP39055 Part 2, BP39056 Part 2, and BP39054) and the

Reference ID: 4646272

market, a 1-bottle formulation of risdiplam powder for oral solution was developed. The 1-bottle formulation was presented in two strengths, 0.25 mg/mL and 0.75 mg/mL.

Analysis and discussion of the acceptability of product quality is deferred to the chemistry, manufacturing, and controls (CMC) reviewer.

Table 2: Composition of Risdiplam Powder for Oral Solution 0.75 mg/mL

Components	Reference to Standards	Function	Amount Bottle (mg/bottle)	Concentration in Solution per Bottle (mg/mL)
Risdiplam	In-house	Active ingredient	60.00	0.75
Mannitol[a]	USP, Ph. Eur., JP	(b) (4)		
Isomalt	USP/NF, Ph. Eur., JP			
Strawberry Flavor[b,c]	In-house			
Tartaric Acid	USP/NF, Ph. Eur., JP			
Sodium Benzoate	USP/NF, Ph. Eur., JP			
(b) (4) Polyethylene Glycol 6000	USP/NF, Ph. Eur., JP			
Sucralose	USP/NF, Ph. Eur.,JPE			
Ascorbic Acid	USP, Ph. Eur.			
Disodium Edetate Dihydrate	USP, Ph. Eur., JP			
Target Weight	—			
Target Volume[d]	—			

(b) (4)

Reference ID: 4646272

4.3. Clinical Microbiology

The drug product is a nonsterile powder to be constituted with purified water or sterile water for injection (WFI). The in-use period after constitution is up to 64 days for solution stored at 2°C – 8°C. Sodium benzoate is added [redacted] (b) (4) The reader is referred to the separate Quality Team Review for analysis and discussion.

4.4. Nonclinical Pharmacology/Toxicology

The applicant reports the following results of nonclinical studies. *The reader is referred to the separate nonclinical review for further details and analysis.*

4.4.1. In vitro Findings Relevant to Mechanism of Action Using Human-Derived Products

RO7034067 corrected the dysfunctional splicing of the human SMN2 pre-mRNA in cultured cells by shifting the balance of the alternative splicing reaction completely towards the inclusion of SMN2 exon 7 and the production of the full-length mRNA and functional SMN protein. Increased SMN protein was shown in fibroblasts and motor neurons derived from patients with SMA. Splicing events of a total 11 genes, including FOXM1 and MADD, were affected at the highest concentration. FOXM1 and MADD have been described as being involved in cell cycle regulation and apoptosis, respectively.

4.4.2. Pharmacological Proof-of-Mechanism in Mouse Models

SMAΔ7 mice have decreased survival relative to unaffected littermates and they exhibit aberrant motor behaviors similar to features observed in human SMA. SMAΔ7 mice were treated from postnatal day 3 to postnatal day 23 once daily with vehicle or risdiplam. Drug-treated mice had improved survival that matched that of unaffected littermates, and they also exhibited improved motor behavior (righting reflex).

4.4.3. Toxicology Studies

Repeat-dose toxicity studies have included studies in rabbits, mice, rats, and juvenile cynomolgus monkeys (up to 39 weeks, NOEL = 1.5 mg/kg/day, retinal findings).

Findings of note include:

- Apoptosis in GI epithelia in 13-week juvenile rat (NOAEL AUC 0-24hr of 7160 ng.hr/mL [conservatively lowest value from males) and in 39-week prepubertal monkey (NOAEL AUC 0-24hr of 5580 ng.hr/mL [conservative value from males]).
- Hyperplasia and degeneration of skin, tongue, and larynx in prepubertal monkey

Reference ID: 4646272

(NOAEL AUC 0-24hr of 4850 ng.hr/mL [conservative value from females]).

- Testicular germ cell degeneration in juvenile prepubertal monkeys and rat (observed in rat at AUC 0-24hr of 744 ng.hr/mL; NOAEL not provided, and interpretable values unavailable for monkey).
- "***Multifocal peripheral retina degeneration in the photoreceptor layer and microcystic spaces in the inner retinal layers in monkeys as detected by OCT***." This was associated with depressed scotopic (rod) B-wave and somewhat less affected photopic (cone) B-wave in the ERG. OCT and ERG evaluation was initiated in week 20 (subsequent to reporting of retinal changes for RO6885247 at the end of the chronic monkey toxicity study with that molecule) and continued until week 35 of the study. These findings were confirmed by histopathology. The NOEL of the retinal finding with 39 weeks of treatment is 1870/2060 ng.h/mL (AUC 0-24h in M/F) with effects seen by OCT and histology at an exposure of 4880/4850 ng.h/mL (AUC 0-24h in M/F). Depressed ERG and microcystic spaces in the inner nuclear layer were only seen in high dose animals with an exposure of 5880/6470 ng.h/mL (AUC 0-24h in M/F) [IB, section 4.3.3]."
    - This finding may have an underlying basis from *in vitro* studies that demonstrated evidence of high binding of the drug to melanin with tissue retention in the retina, and with impairment of lysosomal function and autophagosomal accumulation in retinal pigmented epithelial cells.

4.4.4. Genotoxicity Studies

The drug produced no bacterial mutagenicity (Ames test). The drug produced a positive mouse micronucleus test with a statistically calculated No-Genotoxic Effect Level (NOGEL) AUC 0-24 hrs of at least 3000ng.hr/mL.

4.4.5. Carcinogenicity Studies

A carcinogenicity study using rasH2 transgenic mice with 6 months duration of treatment did not generate any evidence for a tumorigenic potential of risdiplam. A two-year carcinogenicity study in rats is planned to be conducted as a post-approval commitment.

4.4.6. Reproductive and Developmental Toxicity

Studies to assess reproductive and developmental toxicity have been conducted in rats and rabbits. The findings of testicular germ cell degeneration in the 4-week juvenile rat toxicology study and in the 13-week prepubertal monkey study suggest the potential for reproductive toxicity in males. In rats there was no reduction in fertility when previously treated males were paired with non-treated females.

Risdiplam caused maternal and embryofetal toxicity without signs of malformations in

Reference ID: 4646272

rats. In rabbits, risdiplam was teratogenic at the high dose level of 12 mg/kg/day, which also induced severe maternal toxicity.

4.4.7. Safety Pharmacology

No significant reduction of hERG channel current (CHO cells) was observed through the highest dose tested (5 uM). A dog telemetry study revealed no effects on vital signs or on ECG conduction intervals. No effects on CNS function were observed in rats (modified Irwin test). No effects on respiratory function were observed in rats (whole body plethysmography).

4.5. Clinical Pharmacology

The key outcomes of the clinical pharmacology studies are summarized below.
The reader is referred to the full review of the Office of Clinical Pharmacology (OCP) for further details and analysis.

- Risdiplam was well tolerated at single oral doses up to 18 mg in healthy subjects (mean AUC0-24h 1290 ng.h/mL; mean Cmax 93.2 ng/mL).
- Risdiplam PK is approximately linear at 0.6-18 mg given as single dose and at 0.02-0.25 mg/kg up to 5 mg multiple dose once daily administration.
- An exploratory assessment of the effect of food on the PK of risdiplam has been performed in the single ascending dose Study BP29840 in 3 subjects each, after administration in fed and fasted condition. Food had no clinically significant effect on the PK of risdiplam.
- The clinical study dose levels have been selected in order to target an at least 2-fold increase in SMN protein at an exposure of ≤2000 ng.h/mL which corresponds to the no-observed-adverse-effect-level (NOAEL) in animal toxicology studies.
- Parent drug was the major component found in plasma, accounting for 83% of drug-related material in circulation. Approximately 53% of the dose (14% unchanged risdiplam) was excreted in feces and about 28% (8% unchanged risdiplam) in urine. The pharmacologically inactive metabolite M1 (N-oxidation of risdiplam) was identified as the major circulating metabolite. Plasma M1 levels were approximately 30% of the parent risdiplam in SMA patients.
- Risdiplam is primarily metabolized by flavin monooxygenase 1 and 3 (FMO1 and 3), and also by CYPs 1A1, 2J2, 3A4 and 3A7. The strong CYP3A inhibitor itraconazole had no clinically relevant effect on risdiplam exposure. Therefore, risdiplam may be co-administered with CYP3A inhibitors.
- Treatment with risdiplam led to a >2-fold median increase in SMN protein versus baseline in all studies in SMA patients within 4 weeks after start of treatment with

Reference ID: 4646272

risdiplam. This obtained SMN protein increase was maintained over the entire treatment duration, with follow-up available to date for more than 1 year.

4.6. Devices and Companion Diagnostic Issues

Not applicable to this application.

4.7. Consumer Study Reviews

Not applicable to this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The studies submitted to support the safety and efficacy of patisiran are summarized in the tables below. This NDA submission includes the placebo-controlled Study BP39055 (SUNFISH) in pediatric and adult patients with later-onset SMA and the open-label Study BP39056 (FIREFISH) in pediatric patients with infantile-onset SMA. Additional supportive safety data is provided from the ongoing open-label Study BP39054 (JEWELFISH) in infantile-onset and later-onset SMA patients who have previously participated in clinical trials other than risdiplam trials and/or received currently approved therapies for SMA.

Note that the original NDA submission included only data from Part 1 of the Sunfish and Firefish studies. The applicant later submitted additional data for Part 2 of the Sunfish study during the course of this NDA review. The applicant submitted topline efficacy results for Part 2 of the Firefish study during the NDA review, although the data were not submitted or reviewed for this NDA.

Reference ID: 4646272

Table 3: Overview of Risdiplam Clinical Development Program. Source: Clinical Overview, p. 13

Study Number	Study Design and Objectives	Population	Number of Patients and Data Contributing to NDA
BP39056 (FIREFISH), an ongoing pivotal Phase 2/3 study	Open-label, two-part operationally seamless, multicenter study. Part 1 objectives: Safety, tolerability, PK and PD, dose selection for Part 2 Part 2 objectives: Efficacy, safety and tolerability, PK and PD	Infants with Type 1 SMA aged 1–7 months at enrollment	Part 1: 21 patients (efficacy, safety, PK, PD) Part 2: 41 patients (safety, PK, PD)
BP39055 (SUNFISH), an ongoing pivotal Phase 2/3 study	Two-part operationally seamless randomized, multicenter, placebo-controlled, double-blind study. Part 1 objectives: Safety, tolerability, PK and PD, dose selection for Part 2 Part 2 objectives: Efficacy, safety and tolerability, PK and PD	Patients with Type 2 and 3 SMA aged 2–25 years	Part 1: 51 patients (efficacy, safety, PK, PD) Part 2: 180 patients (blinded safety data)
BP39054 (JEWELFISH), an ongoing supportive Phase 2 study	Multicenter, open label, non-comparative, single-arm, exploratory study in SMA patients previously enrolled in BP29420 (MOONFISH) or previously treated with nusinersen, onasemnogene abeparvovec or olesoxime. Objectives: Safety, tolerability, PK and PD	Type 1, 2, or 3 SMA patients aged 6 months–60 years	Up to 180 patients planned N=12 at CCOD (age 13–52 years) (safety, PK, PD)

CCOD=clinical cutoff date; NDA=New Drug Application; PD=pharmacodynamics; PK=pharmacokinetics.

Reference ID: 4646272

Table 4: Listing of Placebo-Controlled Clinical Trials Relevant to this NDA

Protocol No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BP39055 **(SUNFISH)**	**Part 1: Safety**, tolerability, PK and PD, dose selection for Part 2	Multicenter, two-part study as follows: **Part 1**: A double-blind, placebo controlled, randomized, **exploratory dose finding** study in patients with Type 2 and Type 3 SMA (ambulant and non-ambulant) to select the dose for Part 2.	Oral, OD administration **Part 1** Age 12-25 years: 3 mg or 5 mg Age 2-11 years: 0.02, 0.05, 0.15 or 0.25 mg/kg Minimum of 12-weeks placebo-controlled treatment, after which patients on placebo switched to risdiplam at the dose tested in their cohort. After the dose selection for Part 2, all patients switched to the pivotal dose.	**Part 1**: 51 patients in 2 age groups, 2 – 11 years (n = 31) and 12 – 25 years (n = 20)	SMA **Type 2 and 3** patients 44 sites, 15 countries (Belgium, Italy, Croatia, Canada, Spain, USA, France, Poland, Germany, Serbia, Brasil, Russia, Japan, Turkey, China)	At least 5 years. Thereafter, treatment will continue until the drug is available commercially in the patient's country.	*Ongoing*; Full, CCOD 9 Jan 2019 (Part 1 efficacy and safety data and blinded Part 2 safety data)

Reference ID: 4646272

Protocol No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
	Part 2: Efficacy, safety and tolerability, PK and PD	**Part 2:** A double-blind, randomized, placebo controlled, parallel design study to investigate the **efficacy**, safety, and tolerability of risdiplam in patients with Type 2 and non-ambulant Type 3 SMA.	**Part 2** Pivotal dose: 5 mg once daily for patients with a BW ≥ 20 kg and 0.25 mg/kg once daily for patients with a BW <20 kg 24-month treatment period (patients on placebo will be switched to active treatment in a blinded manner after 12 months). Following 24 months of treatment in each part, patients can enter an OLE phase.	**Part 2**: 180 patients aged 2 – 25 years			

Reference ID: 4646272

Table 5: Listing of Uncontrolled Clinical Trials Relevant to this NDA

Protocol No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage regimen; Route of Admin.	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BP39056 (**FIREFISH**)	**Part 1: Safety,** tolerability, PK and PD, dose selection for Part 2 **(Part 2: Efficacy**, safety and tolerability, PK and PD. Planned, but data not submitted for this NDA.)	Multicenter, two-part study in SMA Type 1 infants aged 1 to 7 months at the time of enrollment: **Part 1: Open-label** dose-escalation study to select the dose for Part 2. **Part 2: Open-label** study to assess the efficacy, safety,	OD oral administration **Part 1** Starting dose for first infant: 0.00106 mg/kg single dose. Once daily treatment with 0.0106, 0.04, 0.08, 0.2, 0.25 mg/kg. After selection of the starting dose for **Part 2** the protocol was amended to switch all patients to the dose of 0.2	**Part 1**: 21 infants **Part 2**: 41 infants	SMA **Type 1** Patients. Part 1: 7 sites, 5 countries (Belgium, France, Italy, Switzerland, US)	4 years or until drug is available commercially in the patient's country.	*Ongoing*; Full, CCOD 27 Feb 2019 (Part 1 efficacy and safety data; Part 2 safety data)

Reference ID: 4646272

		and tolerability of risdiplam.	mg/kg. Minimum of 4 weeks treatment for dose selection after which all patients continue to receive risdiplam until Month 24. Part 2 starting dose Infants >1 month and <3 months at enrollment: 0.04 mg/kg Infants ≥3 to <5 months: 0.08 mg/kg Infants ≥ 5 months: 0.2 mg/kg. The dose for all infants <2 years has been adjusted to 0.2 mg/kg. Infants ≥2 years: 0.25 mg/kg. Following 24 months of treatment in each part, patients can **enter an OLE.**				
BP39054 (**JEWELFISH**)	**Safety**, tolerability, PK, PD	Multi-center, **open-label**, single-arm study in SMA patients previously	OD oral administration Initial dose was 3 mg (patients 12–60 years). Dosing was	180 patients planned (aged 6 months to 60 years**).**	SMA patients	At least 5 years. Thereafter, treatment will continue until the drug	*Ongoing*; Full, CCOD 1 Dec 2018

Reference ID: 4646272

		enrolled in Study BP29420 (MOONFISH) with the splicing modifier RO6885247 or previously treated with nusinersen, onasemnogene abeparvovec, or olesoxime	amended in line with the pivotal dose selection in Studies BP39055 and BP39056 Age 2–60 years: 5 mg for patients with BW ≥ 20 kg; 0.25 mg/kg for patients with BW < 20 kg Age 6 months to < 2 years: 0.2 mg/kg 24-month treatment period.	N=12 at time of NDA submission.		is available commercially in the patient's country.	

Reference ID: 4646272

5.2. Review Strategy

An efficacy determination was made by evaluating the results from Part 2 of the placebo-controlled Study BP39055 (SUNFISH) in pediatric and adult patients with later-onset SMA and the Part 1 results of the historically controlled Study BP39056 (FIREFISH) in infants with Type 1 SMA. . Safety was assessed by evaluating the results of the Sunfish and Firefish studies, with a small amount of additional safety data from the Jewelfish study (BP39054).

The effectiveness assessment focused on the clinical interpretability of the trial endpoints and the applicant's reported results. Confirmation of the efficacy analyses themselves was provided by the biometrics reviewer for this application. The safety assessment was based on the applicant's reports and clinical reviewer analysis of the submitted data.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study BP39055, SUNFISH:

A Two-Part Seamless, Multi-Center Randomized, Placebo-controlled, Double-blind Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam in Type 2 and 3 Spinal Muscular Atrophy Patients

6.1.1. Study Design

Overview and Objective

The Sunfish study was a Phase 2/3, multinational, randomized, double-blind, placebo-controlled, two-part study of risdiplam in subjects with Type 2 and 3 Spinal Muscular Atrophy.

Part 1

- The primary objective of Part 1 was to evaluate the safety, tolerability, PK and PD of risdiplam and to select the dose for Part 2 of the study.
- To investigate the PK/PD relationship of risdiplam by PK/PD modeling
- To explore the effect of risdiplam on motor function, respiratory function, and pre-specified adverse events (in terms of proportion of patients experiencing them) and patient-reported QOL measures.

Reference ID: 4646272

Part 2

- Part 2 of Study BP39055 investigated the efficacy and safety of risdiplam at the selected dose from Part 1 over a 24-month treatment period, in patients with Type 2 and Type 3 SMA (non-ambulant only) of 2 to 25 years of age.
- To evaluate efficacy of risdiplam compared to placebo in terms of motor function in Type 2 and non-ambulant Type 3 SMA patients, as assessed by the change from baseline in the total score of the motor function measure (MFM) at 12 months.

Secondary objectives for Part 2 are as follows:

- To investigate the PK/PD relationship of risdiplam by PK/PD modeling (PD to include SMN2 mRNA and survival of motor neuron [SMN] protein).
- To investigate the efficacy of 12-month treatment with risdiplam in terms of motor function as assessed by the Hammersmith functional motor scale expanded (HFMSE), the revised upper limb module (RULM) and responder analyses of the MFM.
- To investigate the efficacy of 12-month treatment with risdiplam in terms of respiratory function as assessed by sniff nasal inspiratory pressure (SNIP) and, in patients aged 6 years and older, by maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1) and peak cough flow (PCF).
- To investigate the proportion of patients who experience a pre-specified disease-related adverse event by Month 12.
- To investigate the efficacy of 12-month treatment with risdiplam in terms of global health status as assessed by the Clinical Global Impression of Change (CGI-C).
- To investigate the efficacy of 12-month treatment with risdiplam in terms of patient-reported and caregiver-reported independence, as measured by the SMA Independence Scale (SMAIS).
- To investigate the safety and tolerability of risdiplam treatment.

Trial Design

- **Basic study design:**

This was a multicenter (44 study centers), multinational (15 countries), randomized, double-blind, placebo-controlled, Phase 2/3 study. The planned study size was N=36 in Part 1 and N=168 in Part 2; the actual number randomized in this study was N=51 (35 initially to risdiplam; 16 to placebo; 5 dose cohorts) for Part 1 and N=180 (120 to risdiplam, 60 to placebo) for Part 2.

Part 1 was a double-blinded, placebo-controlled, randomized (2:1 risdiplam: placebo), exploratory dose-finding study in Type 2 and Type 3 (ambulant and non-ambulant) SMA patients. The dose determined from Part 1 was then used in Part 2, a double-blinded, placebo-controlled, randomized (2:1 risdiplam: placebo) efficacy and safety study in Type 2 and 3 (non-

Reference ID: 4646272

ambulant only) SMA patients of 2 to 25 years of age.

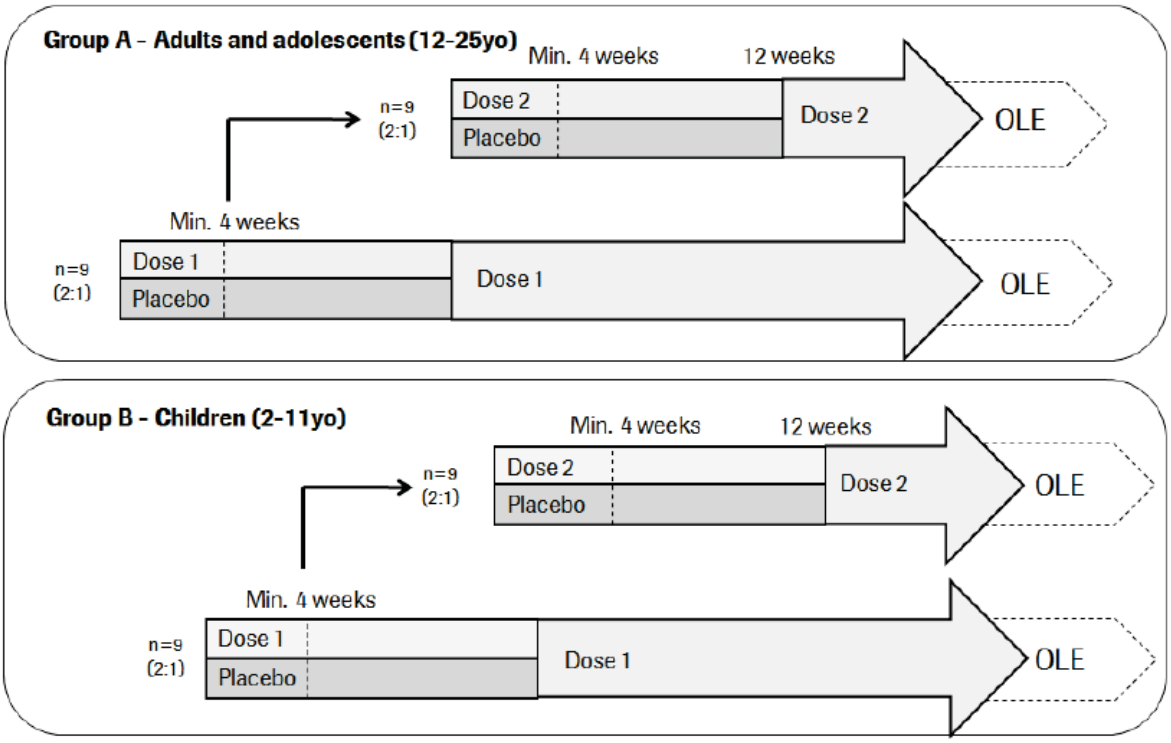
The duration of patient participation in this study was at least 12 months in Part 1. Part 2 was planned with a 24-month treatment period. The median duration of exposure to risdiplam during the all exposure to risdiplam period was 410 days (min-max: 1.0-673 days). The cumulative exposure to risdiplam was 163 PY.

After patients in Part 1 completed the minimum 12-week double-blind treatment period, patients on placebo were switched to risdiplam at the dose tested in their cohort until the Independent Monitoring Committee selected the dose for Part 2 (triggered by data availability from the last cohort enrolled). Patients from Part 1 were not included in Part 2. For Part 2, patients receiving placebo were switched to risdiplam in a blinded manner after the first 12-month treatment period (i.e., at their Week 52 visit). All patients are continuing on risdiplam until Month 24. The primary analysis was conducted once the last patient completed the 12-month randomized, double-blind, treatment period (i.e., before all patients completed the 24-month treatment period).

The study designs of Parts 1 and 2 are shown in the following figures, copied from the submission.

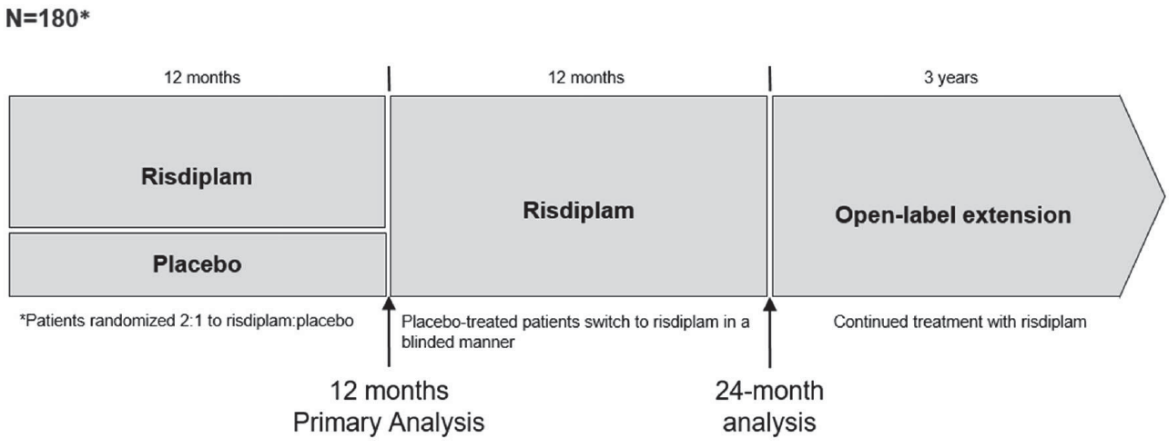
Reference ID: 4646272

Figure 1: Sunfish Study Design of Part 1 Exploratory Dose-Finding



Minimum of 4-week data from all patients in the cohort is required before selecting the next dose.
OLE = open-label extension

Figure 2: Sunfish Study Design of Placebo-controlled Part 2



- **Diagnostic criteria:**

SMA diagnosis was based on genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the SMN1 gene and clinical symptoms attributable to Type 2 or

Reference ID: 4646272

Note that SMA was historically diagnosed based on clinical phenotype prior to the availability of genetic testing, as described in the following table. There may be phenotypic overlap between patients with different SMN2 copy number, and patients with the same SMN2 copy number may have more or less severe phenotypes. It is therefore possible that some patients who would historically have been classified as type 3 SMA based solely on phenotype could initially be called type 2 given current genetic testing capability.

Table 6: Classification of Spinal Muscular Atrophy. Source: Mercuri et al., 2012

	Age of onset	Maximum function achieved	Prognosis	Proposed subclassification	SMN copy number
Type 0 (very severe)	Neonatal with prenatal signs	Never sits	If untreated, no survival beyond the first months after birth	..	..
Type 1 (severe)	0–6 months	Never sits	If untreated, life expectancy <2 years	1A, head control never achieved, signs in the neonatal period; 1B, head control never achieved, onset after neonatal period; 1C, head control achieved, onset after neonatal period	One or two copies of *SMN2* in 80% of patients
Type 2 (intermediate)	7–18 months	Sits but never stands	Survival into adulthood	Decimal classification according to functional level, from 2·1 to 2·9	Three copies of *SMN2* in >80% of patients
Type 3 (mild)	>18 months	Stands and walks	Survival into adulthood	3A, onset of weakness before 3 years; 3B, onset of weakness after 3 years	Three or four copies of *SMN2* in 96% of patients
Type 4 (adult)	10–30 years	Stands and walks	Survival into adulthood	..	Four or more copies of *SMN2*

- **Key inclusion/exclusion criteria:**

The criteria listed below from the submitted protocol appear adequate to enroll patients with SMA representative of the U.S. population.

Key Inclusion Criteria

To participate in this study, candidates were required to meet the following eligibility criteria at Screening:

1. Males and females 2 to 25 years of age inclusive (at screening).
2. For Part 1: Type 2 or 3 SMA ambulant or non-ambulant.
   For Part 2: Type 2 or 3 SMA non-ambulant. Non-ambulant is defined as not having the ability to walk unassisted (i.e., without braces, assisted devices such as canes, crutches or calipers, or person/hand-held assistance) for 10 m or more.
3. Confirmed diagnosis of 5q-autosomal recessive SMA, including:
   a. Genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the SMN1 gene.
   b. Clinical symptoms attributable to Type 2 or Type 3 SMA.

Reference ID: 4646272

4. For non-ambulant patients in Part 2 (at screening):
    a. Revised upper limb module (RULM) entry item A (Brooke score) >= 2 (i.e., "Can raise 1 or 2 hands to the mouth, but cannot raise a 200 g weight in it to the mouth").
    b. Ability to sit independently (i.e., scores >= 1 on item 9 of the MFM 32 "with support of one or both upper limbs maintains the seated position for 5 seconds").

Key Exclusion Criteria
Subjects meeting any of the following criteria were not eligible for the study:

1. Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening, or 5 half-lives of the drug, whichever is longer.
2. Concomitant or previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy either in a clinical study or as part of medical care.
3. Any history of cell therapy.
4. Hospitalization for a pulmonary event within the last 2 months or planned at time of screening.
5. Surgery for scoliosis or hip fixation in the one year preceding screening or planned within the next 18 months.
6. Recent history (less than one year) of ophthalmological diseases
7. Patients requiring invasive ventilation or tracheostomy
8. Clinically significant abnormalities in laboratory test results
9. Any major illness within one month before the screening examination

- **Dose selection:**
  Part 1: A total of 51 patients were enrolled in five cohorts and randomized in a 2:1 ratio to active treatment or placebo. Patients were initially assigned to the following dose levels:

  3 mg and 5 mg daily in patients aged 12-25 years-old (Group A Cohort 1 and Cohort 2, respectively), and 0.02 mg/kg, 0.05 mg/kg and 0.25 mg/kg in patients aged 2-11 years old (Group B Cohort 1, Cohort 2 and Cohort 3, respectively). As recommended by the Independent Monitoring Committee, the dose given to Group B Cohort 1 and Cohort 2 was then increased to 0.15 mg/kg (in 2 steps for Group B Cohort 1, in 1 step for Group B Cohort 2).

  Part 2: Based on the results of Part 1, a dosing regimen of 5 mg daily for patients with a body weight ≥20 kg and 0.25 mg/kg daily for patients with a body weight <20 kg was selected for Part 2 of this study.

- **Study treatments:**
  Risdiplam clinical formulation for Part 1 was a powder and solvent for constitution to an

Reference ID: 4646272

oral solution. Matching-placebo oral solutions for the 0.25 mg and 1.5 mg/mL risdiplam drug products were prepared [redacted] (b) (4), and the same excipients as for the study drug (except for ascorbic acid and disodium edetate) but containing no active drug substance. The excipient blend used for constitution of the drug substance consisted of mannitol, tartaric acid, sodium benzoate, ascorbic acid, polyethylene glycol 6000, disodium edetate, sucralose and strawberry flavor.

Risdiplam clinical formulation for Part 2 was a powder for constitution to an oral solution. The powder was constituted with purified water to yield an oral solution containing 0.25 mg/mL or 0.75 mg/mL of risdiplam, respectively. Matching-placebo oral solutions for the 0.25 mg and 0.75 mg/mL Part 2 risdiplam drug products were prepared [redacted] (b) (4) and the same excipients as for the study drug (except for ascorbic acid and disodium edetate) but containing no active drug substance.

Please refer to the Office of Pharmaceutical Quality (OPQ) review for discussion of the product formulation used for the active study arm.

- **Assignment to treatment:**
  Randomization was performed using an Interactive (voice/web) Response System (IxRS). Separate randomization lists were generated for the exploratory dose-finding Part 1 and the confirmatory Part 2 of the study. In the exploratory Part 1 of the study, patients were randomized to risdiplam or placebo in a 2:1 ratio for each cohort. In the confirmatory Part 2 of the study, patients were randomized to the selected dose of risdiplam from Part 1 or placebo in a 2:1 ratio. The randomization in Part 2 was stratified by age group (2 to 5, 6 to 11, 12 to 17, 18 to 25 years at randomization).

- **Blinding:**
  The following methods were used for blinding. These methods appear adequate.

  In Part 1 of the study the patients and the investigators were blinded to the treatment assignment within each cohort until the Internal Monitoring Committee (IMC) decided to close the placebo-controlled period of that cohort and begin the risdiplam open-label treatment. All individuals in direct contact with the patient at the investigative site were blinded until this point, except for the Pharmacist handling the study drug.

  Part 1 patients were not included in the Part 2 confirmatory analysis and new patients were randomized into Part 2 of the study. In Part 2 of the study the study patients and the investigators were blinded to the initial treatment assignment until the last patient in Part 2 completed the 24-month assessments. All individuals in direct contact with the patient at the investigative site were blinded until this point, except for the unblinded Pharmacist

Reference ID: 4646272

handling the study drug.

- **Administrative structure:**

Fifteen countries (Belgium, Italy, Croatia, Canada, Spain, USA, France, Poland, Germany, Serbia, Brasil, Russia, Japan, Turkey, China) and 44 sites randomized patients in this study.

An Independent Monitoring Committee (IMC) was responsible for reviewing safety, pharmacokinetic and pharmacodynamic data and for dose-escalation decisions in Part 1 and the dose-selection for Part 2. An Independent Data Monitoring Committee reviewed all available data from Part 1 to confirm the dose-decision taken by the IMC, and reviewed safety, efficacy, pharmacokinetic and pharmacodynamic data for Part 2.

An interactive (voice/web) response system (IxRS) was used to register the screening/screening failures, enrollment, randomization, drug allocation, withdrawal, discontinuation, and termination of patients.

A contract research organization was responsible for study management, monitoring, and in some cases, vendor oversight.

An ophthalmological monitoring vendor was responsible for central review of optic assessments, and for help support activities associated with training local readers and procuring equipment.

- **Procedures and schedule:**
  The schedule of key assessments for Part 2 of the Sunfish study is presented in the following two tables, based on the submitted protocol. The second table lists the schedule of ophthalmology assessments.

Reference ID: 4646272

Table 7: Sunfish Study Part 2 Schedule of Key Assessments

Assessment	Schedule
Physical Examination	Screening, Weeks 1, 2, 4, 8, 17, 26, 35, 52, 70, 78, 87, 104
Neurological Examination	Screening, Weeks 17, 35, 52, 78, 104
Vital Signs	Screening, Weeks 1, 2, 4, 8, 17, 26, 35, 52, 70, 87, 104
ECG-12 lead	Screening, Weeks 1, 2, 4, 8, 17, 26, 35, 52, 70, 87, 104
Hematology	Screening, Weeks 1, 4, 8, 17, 35, 52, 70, 87, 104
Blood Chemistry	Screening, Weeks 1, 4, 8, 17, 35, 52, 70, 87, 104
Coagulation	Screening, Weeks 1, 4, 17, 35, 52, 70, 87, 104
Urinalysis	Screening, Weeks 1, 4, 17, 35, 52, 104
Ophthalmological Exam	Screening, Weeks 8, 17, 26, 35, 52, 70, 78, 87, 96, 104
MFM	Screening, Weeks 1, 17, 35, 52, 78, 104
Pulmonary testing	Screening, Weeks 1, 17, 35, 52, 78, 104
RULM/HMFSE	Screening, Weeks 17, 35, 52, 78, 104
EQ-5D	Weeks 1, 17, 35, 52, 78, 104
Administration of Study Medication	Weeks 1 through 104

Reference ID: 4646272

Table 8: Sunfish Study Schedule of Ophthalmology Assessments

Assessment	Schedule
Adults & Cooperative Children	
Best corrected visual acuity	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
Sloan low contrast	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
Threshold Perimetry	Screening, Weeks 17, 35, 52, 70, 87, 104
Slit Lamp and fundus examination	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
Intraocular pressure	Screening, Weeks 17, 35, 52, 70, 87, 104
Color fundus photography	Screening, Weeks 26, 52, 78, 104
SD-OCT	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
Fundus autofluorescence	Screening, Weeks 17, 35, 52, 70, 87, 104
Dark adaption	Screening, Weeks 17, 35, 52, 70, 87, 104
Children	
Visual testing	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
Intraocular pressure	Screening, Weeks 52, 104
Slit Lamp and fundus examination	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
Color Fundus photography	Screening, Weeks 26, 52, 78, 104
SD-OCT	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104

- **Dietary restrictions/instructions:**
  Not applicable to this application.

- **Concurrent medications:**
  Use of the following medications/treatments was prohibited during study participation.
  1. Any administration of nusinersen (Spinraza) either in a clinical study or for medical care at any time prior to or during the study was prohibited.
  2. Prohibited for 2 weeks prior to dosing and throughout the study:
     Any OCT-2 and MATE substrates, e.g., amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine.
  3. Prohibited during the study and for at least 90 days prior to randomization:

Reference ID: 4646272

Riluzole, Valproic acid, Hydroxyurea, Sodium phenylbutyrate, Butyrate derivatives, Creatine, Carnitine, Growth hormone, Anabolic steroids, Probenecid, Chronic oral or parenteral use of corticosteroids (inhaled corticosteroid use is allowed), Oral or topical retinoids, amiodarone, phenothiazines, minocycline.

4. Patients should not have received the following drugs previously. These were also prohibited during the study: Quinolines (chloroquine and hydroxychloroquine), thioridazine, retigabin and vigabatrin.
5. Use of the following therapies was prohibited during the study and for at least 1 year prior to randomization: Desferoxamine, topiramate, latanoprost, niacin, rosiglitazone, tamoxifen, canthaxanthine, sildenafil, interferon or any other drugs known to cause retinal toxicity, including chronic use of minocycline.

- **Treatment compliance:**

The qualified individual responsible for dispensing the study drug prepared the dose according to the randomization schedule. This individual wrote the date dispensed and patient number and initials on the study drug vial label and on the Drug Accountability Record. This individual recorded the MEDNO/ study drug batch number received by each patient during the study. A patient diary was required to capture information related to drug administration for all doses throughout the study.

If a patient, or parent/caregiver, did not administer the dose at the regular time, but realized prior to 12:00 (noon) local time, they were instructed to administer the regular dose at that time. If a parent or caregiver realized a missed administration only after 12:00 (noon) local time, this was considered a missed dose and they were instructed to not administer study drug for that day. They were to give the regular amount at the next scheduled time on the subsequent day, but not double-up the dose, and report the event in the medication diary.

Allowing occasional missed doses is acceptable. A dose delay beyond the effective half-life (40-69 hours) could allow drug concentrations to drop below therapeutic levels and might diminish efficacy.

- **Rescue medication:**
  There were no applicable rescue medications for this trial.

- **Subject completion, discontinuation, or withdrawal:**
  Patients who completed the study or discontinued from the study early were asked to return to the clinic for a follow-up visit.

  The Investigator had the right to discontinue a patient's treatment or withdraw a patient from the study at any time. In addition, patients had the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study included, but were not

Reference ID: 4646272

limited to, the following:

- Patient withdrawal of consent at any time.
- Any medical condition that the Investigator or Sponsor determines may jeopardize
- the patient's safety if he or she continues in the study.
- Investigator or Sponsor determines if it is in the best interest of the patient.
- Patient non-compliance (including study drug administration as recorded in the patient's diary).

Patients were required to discontinue study drug if they experienced any of the following:

- Pregnancy
- Ophthalmological or other events, as described in Section 5.2.4.1
- Unable to continue to comply with study requirements.

Patients withdrawing from the study for safety reasons were not replaced. Patients withdrawing from the study for other reasons were not replaced in Part 2, but could be replaced in Part 1.

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint for Part 2 of the Sunfish study is the change from baseline in the Motor Function Measure 32(MFM32) total score at Month 12. The MFM32 is an ordinal scale constructed for use in patients with neuromuscular disorders (Bérard et al. 2005). The validation study included 303 patients, aged 6–62 years, including various muscular dystrophies and 35 patients with spinal muscular atrophy.

The scale comprises 32 items that evaluate physical function in three dimensions:

- D1 (13 items, total score range 0-39) evaluates function related to standing and transfer.
- D2 (12 items, total score range 0-36) evaluates axial and proximal function in supine and sitting position on mat and chair (3/12 items evaluate arm function with the patient seated on a chair).
- D3 (7 items, total score range 0-21) evaluates distal motor function.

The scoring of each task uses a 4-point Likert scale based on the patient's maximal abilities without assistance:

- 0: cannot initiate the task or maintain the starting position
- 1: performs the task partially
- 2: performs the task incompletely or imperfectly (with compensatory/uncontrolled movements or slowness)
- 3: performs the task fully and "normally."

Reference ID: 4646272

The 32 scores are summed and then transformed onto a 0-100 scale to yield a total score expressed as the percentage of the maximum possible score (the one obtained with no physical impairment: the sum of the 32 item scores divided by 96 and multiplied by 100); the lower the total score, the more severe the impairment.

The 32 items of the MFM32 are listed in the following table, copied from Bérard et al. 2005.

Reference ID: 4646272

Table 9: List of the 32 items of the Motor Function Measure with the starting position and exercises required. Source: Bérard et al. 2005

No.	Starting position	Exercise required and conditions for obtaining maximum score
1	Supine	Head in the axis: maintains the head in the axis and turns it completely to one side and then to the other
2		Raises the head and maintains the raised position
3		Flexes the hip and the knee more than 90 degrees by raising the foot from the mat
4		Lower limb supported by examiner: from the position in plantar flexion, raises the foot in dorsal flexion of 90 degrees in relation to the leg
5		Raises one hand from the mat and moves it to the opposite shoulder
6		Lower limbs half-flexed, patella facing up and feet resting on the mat: raises the pelvis, lumbar spine, pelvis and thighs aligned and feet slightly apart
7		Rolls to prone and frees the upper limbs
8		Without support of upper limbs, sits up on the mat
9	Seated on the mat	Without support of upper limbs, maintains the sitting position and is then capable of maintaining contact between the two hands
10		The tennis ball placed in front of the subject: without support of upper limbs, leans forward, touches the ball and sits up again
11		Without support of upper limbs, stands up
12	Standing	Without support of upper limbs, sits down on the chair, feet slightly apart
13	Seated on the chair	Without support of upper limbs or leaning against the back of the chair, maintains the sitting position, head and trunk in the axis
14	Seated on the chair or in their wheelchair	Head in flexion: from the fully flexed position, raises the head and maintains the raised position, head in the axis during the movement and when maintained
15		Forearms on the table but not elbows: raises both hands to the top of the head at the same time, head and trunk in the axis
16		The pencil on the table: reaches the pencil with one hand, elbow in complete extension at the end of the movement
17		10 coins placed on the table: successively picks up and holds 10 coins in one hand within 20 s
18		One finger placed in the center of the fixed CD: traces the complete border of the disk with one finger without support of the hand
19		The pencil on the table: picks up the pencil placed next to their hand and draws a continuous series of loops of 1 cm height in the 4-cm-long frame
20		Holding the sheet of paper: tears the paper folded in 4, beginning at the fold
21		The tennis ball on the table: picks up the ball, raises it off the table and turns over the hand holding onto the ball
22		A finger placed in the center of the fixed square: raises the finger and places it successively in the center of the 8 squares of the diagram without touching the lines
23		Upper limbs along the trunk: places the two forearms and/or hands on the table at the same time
24	Seated on the chair	Without support of upper limbs, stands up, feet slightly apart
25	Standing with support of upper limbs on equipment	Lets go of the support and maintains the standing position, feet slightly apart, head, trunk and limbs in the axis
26		Without support of upper limbs, raises one foot for 10 s
27	Standing	Without support, lowers theirself, touches the floor with one hand and stands up again
28	Standing without support	Walks forward 10 steps on both heels
29		Walks forward 10 steps on a straight line
30		Runs 10 m
31		On one foot: hops 10 times in place on one foot
32		Without support of upper limbs, attains the squatting position and gets up twice in a row

The Agency made the following comments about the MFM32 as a primary endpoint at a pre-IND meeting on 3/4/2016.

"The MFM is acceptable as the primary endpoint; however, it is unclear why the inclusion of domain D1 (standing position and transfer) is warranted for your non-ambulant trial

Reference ID: 4646272

population. We also note that, based on the publications provided in your briefing package, the mean annual decline of this patient population appears to be < 1 point/year, and your trial is powered to detect a 3-point difference after a 12- month treatment. However, if the placebo group in the trial declines by about 1 point as anticipated, the drug would need to produce a 2-point improvement above baseline to achieve a 3-point difference in favor of the drug. Therefore, to increase the likelihood of demonstrating a treatment effect, we recommend that you consider a longer trial duration (e.g., 24 months) with an interim analysis at 12 months."

This reviewer agrees that the standing position and transfer items of the MFM32 would not be relevant to the non-ambulant population of Part 2 of the Sunfish study. The effect of including these items in the analysis would most likely be to dilute any efficacy signal and reduce the ability of the study to detect a positive drug effect, unless the drug were able to restore ambulation to this study population. The fact that the study achieved a positive result despite this dilution effect further supports the positive efficacy finding. See Section 6.1.2 for a discussion of the results for individual MFM32 domains.

Key Secondary Efficacy Endpoints

Part 2 of the Sunfish study evaluated the difference between the study arms in the following key secondary efficacy outcome measures at 12 months. They are listed in the statistical hierarchical testing order, discussed further in the Statistical Analysis Plan section below.

- Change from baseline in the Total score of the revised upper limb module (RULM) at Month 12. The RULM is a tool used to assess motor performance of the upper limb in SMA patients. It consists of 20 items that test proximal and distal motor functions of the arm. The total score ranges from 0, if all the items cannot be performed, to 37, if all the activities are achieved fully without any compensatory maneuvers (Mazzone et al., 2017; Pera et al. 2019).

- Change from baseline in Total score of Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 12. The HFMSE is a tool used to assess motor function in children that has been validated for use in SMA (Glanzman 2011). The maximum score for this test is 66; higher scores indicate better motor function.

Reviewer Comment: The Agency recommended this secondary endpoint to the applicant in the pre-IND meeting of 3/4/2016. "We recommend that your protocol also assess the Hammersmith Functional Motor Scale, given the significant longitudinal experience with this measure in patients with SMA."

- Change from baseline in Forced Vital Capacity (FVC) at Month 12.

- Change from baseline in the Total Score of the caregiver-reported SMA independence Scale (SMAIS) at Month 12.

Reference ID: 4646272

- Proportion of patients rated by clinicians as no change or improved in the Clinical Global Impression of Change (CGI-C) Scale at Month 12. The CGI-C is a single item measure of change in global health, using seven response options: "Very much improved", "Much improved", "Minimally improved", "No change", "Minimally worse", "Much worse", "Very much worse".

Additional secondary endpoints are listed below.

- Proportion of patients who achieve stabilization or improvement (i.e., a change from baseline >= 0) on the total MFM score at Month 12.
- Proportion of patients who achieve an improvement of at least one standard error of measurement (SEM calculated at baseline) on the total MFM score at Month 12.
- Change from baseline in the MFM domain scores of D1, D2, D3 and the total combined score of (D1 + D2) at Month 12.
- Proportion of patients rated by clinicians as improved in the Clinical Global Impression of Change (CGI-C) Scale at Month 12.
- Change from baseline in the best SNIP (expressed as a percentage of the predicted value) at Month 12. The Sniff Nasal Inspiratory Pressure (SNIP) test is a volitional, non-invasive test of inspiratory muscle strength

  In the pre-IND meeting of 3/4/2016, the Agency commented that "Although we do not object to the assessment of Sniff Nasal Inspiratory Pressure (SNIP) as an exploratory endpoint, the clinical relevance of this measure is uncertain."

  In patients aged 6 to 25 years only:

- Change from baseline in the best Maximal Inspiratory Pressure (MIP) at Month 12.
- Change from baseline in the best Maximal Expiratory Pressure (MEP) at Month 12.
- Change from baseline in Forced Expiratory Volume in 1 second (FEV1) at Month 12.
- Change from baseline in Forced Vital Capacity (FVC) at Month 12.
- Change from baseline in the Peak Cough Flow (PCF) at Month 12.

Disease-Related Adverse Events

- Proportion of patients who experience at least one disease-related adverse event by

Reference ID: 4646272

Month 12.

- Number of disease-related adverse events per patient-year at Month 12.

  Reviewer comment: Limiting this endpoint to "disease-related" adverse events introduces an element of subjectivity and potential bias.

Patient/Caregiver-Reported Outcomes

- Change from baseline in the Total Score of the caregiver-reported SMA independence Scale (SMAIS) at Month 12.

<u>In patients aged 12 to 25 years only</u>:

- Change from baseline in the Total score of the patient-reported SMA independence scale (SMAIS) at Month 12. The SMAIS contains 29 items, assessing the amount of assistance required from another individual to perform daily activities such as eating, or transferring to/from their wheelchair. Each item is scored on a 0-4 scale (with an additional option to indicate that an item is non-applicable). Item scores are summed to create the total score. Lower scores indicate greater dependence on another individual.

Safety Endpoints

The safety endpoints for Part 2 of the Sunfish study are as follows:

- Incidence and severity of adverse events.
- Incidence and severity of serious adverse events.
- Incidence of treatment discontinuations due to adverse events.
- Incidence of abnormal laboratory values.
- Incidence of abnormal ECG values.
- Incidence of abnormal vital signs (body temperature, systolic and diastolic blood pressure, heart rate, respiratory rate).
- Physical examination including examination of the skin, mouth, pharynx and larynx
- Neurological examination
- Height, weight and head circumference.

Reference ID: 4646272

- Incidence of emergence or worsening of items of the Columbia-Suicide Severity Rating Scale (C-SSRS: adult version for adults and adolescents, pediatric version for patients aged 6-11 years).

- Ophthalmological examination:

    - For adults, adolescents and cooperative children (>= 10 year old): Ophthalmological examination including best corrected visual acuity (ETDRS) and Sloan low contrast, intra-ocular pressure (IOP), slit lamp examination of the anterior and posterior segment including the cornea, anterior chamber, funduscopy (with indirect ophthalmoscopy and eye dilation as needed), visual field-threshold perimetry testing, wide-field optical coherence tomography (SD-OCT), FAF and fundus photography (7-field), dark adaptation measurement.

    - For children younger than 10 years of age: Bruckner test, fix and follow test, cover-uncover test, visual acuity simple field test, slit lamp examination fundus photography and SD-OCT.

- For patients aged 9-17 years old at screening, physical examination at baseline and Month 24 will include formal Tanner staging for pubertal status.

Statistical Analysis Plan

Reviewer Comment: Please refer to the statistical review for detailed evaluation of the applicant's planned statistical analysis. Note that the applicant initially had not completed Part 2 of the Sunfish study and submitted only Part 1 data with an analysis of those data using the method intended for Part 2. The applicant later submitted the results of the placebo-controlled Part 2. As controlled data became available, the Division determined that this would form the primary basis for the review's efficacy assessment instead of the Part 1 data.

The analyses of the Sunfish study are structured into two parts; exploratory (Part 1) to select the dose and confirmatory (Part 2) to evaluate the treatment effect of risdiplam. The confirmatory analysis only includes the patients randomized into Part 2 of the study; it does not include the Part 1 patients who are analyzed to select the dose.

The primary analysis and the analysis of the secondary endpoints in Part 2 only includes data up to the 12-month time-point for each individual. All available efficacy data post Month 12 in Part 2 are reported for the exploratory efficacy endpoints. All available safety data in both parts of the study are also reported.

The approach to multiple comparisons used by the applicant is as follows. To control the Type I error rate due to multiple testing of risdiplam versus placebo for the primary and the six key

Reference ID: 4646272

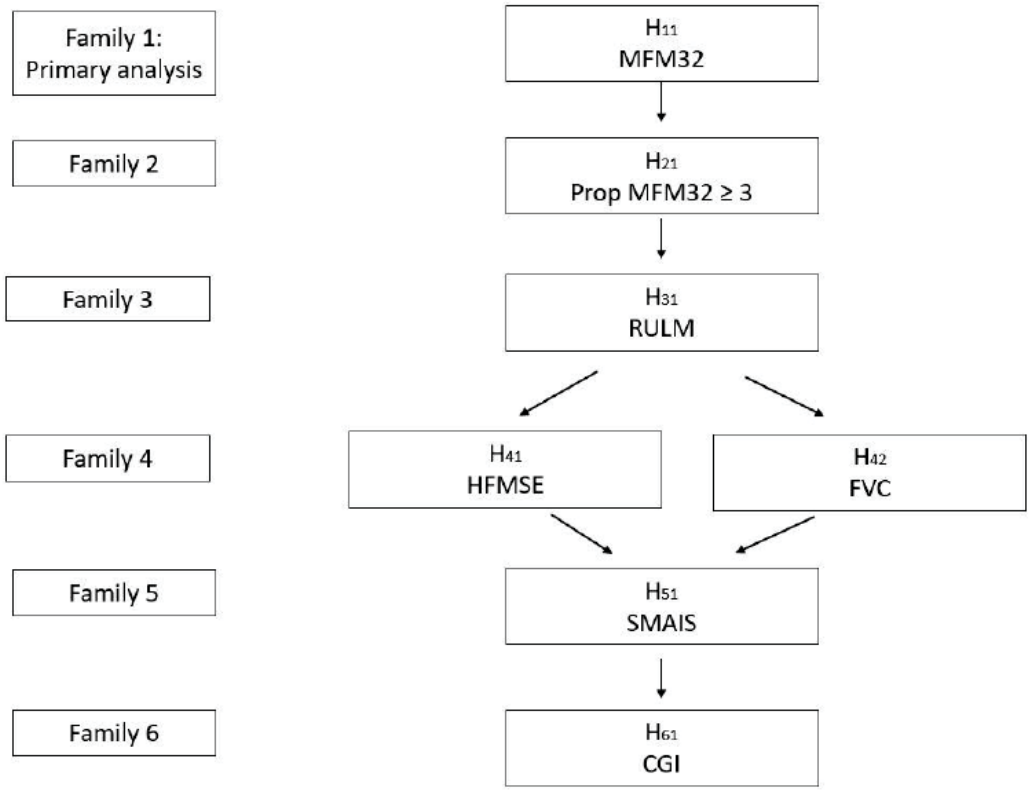
secondary efficacy endpoints in the ITT population of Part 2 of the study, a gatekeeping approach was applied to the seven null hypotheses which were grouped into six families. Hypotheses to be tested were ordered hierarchically and the truncated Hochberg procedure was used in the family which contained more than one hypothesis. The following table and figure show the seven null hypotheses, the six families of the testing for Part 2, and the decision tree. If both hypotheses H41 and H42 in Family 4 were rejected, the hypothesis H51 in Family 5 was to be tested at 0.05 level. If only one of the hypotheses of H41 or H42 in Family 4 was rejected, the hypothesis H51 was to be tested at 0.00125 level.

Table 10: The seven null hypotheses and the six families of the testing for Sunfish study Part 2. Source: Sunfish CSR

Testing Family	Null Hypothesis No difference in the following:
1	primary endpoint: change from baseline total MFM32 score at Month 12 comparing risdiplam versus placebo: H_{11} (MFM32)
2	proportion of patients who achieve a change from baseline >=3 on the total MFM32 score at Month 12 comparing risdiplam versus placebo: H_{21} (Prop. MFM32 >=3)
3	change from baseline total score of RULM at Month 12 comparing risdiplam versus placebo: H_{31} (RULM)
4	a) change from baseline total score of HFMSE at Month 12 comparing risdiplam versus placebo: H_{41} (HFMSE) b) change from baseline best percentage predicted value in FVC at Month 12 comparing risdiplam versus placebo: H_{42} (FVC)
5	change from baseline in total score of caregiver/parent reported SMAIS at Month 12 comparing risdiplam versus placebo: H_{51} (SMAIS)
6	proportion of patients rated by clinician as "Improved" in the CGI-C scale at Month 12 comparing risdiplam versus placebo: H_{61} (CGI)

Reference ID: 4646272

Figure 3: Decision Tree for Part 2 Key Efficacy Endpoints for Hierarchical Testing. Source: Sunfish CSR



CGI= Clinical Global Impression; FVC=forced vital capacity; HFMSE=Hammersmith Functional Motor Scale Expanded; MFM=Motor Function Measure; RULM=Revised Upper Limb Module; SMAIS=Patient Reported and Parent/Caregiver reported SMA Independence Scale.

Protocol Amendments

The original study Protocol BP39055 (Version 1) was released on 3 May 2016. As of the CCOD, Protocol BP39055 had been amended 3 times. These amendments were largely administrative in nature, were reviewed, and found to be reasonable.

6.1.2. Study Results

Compliance with Good Clinical Practices

All clinical studies were conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and local requirements, and in consideration of applicable regulatory

Reference ID: 4646272

Financial Disclosure

The applicant has adequately disclosed financial interests/ arrangements with clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators.

Patient Disposition

Patient disposition is described in the following table, copied from the applicant. *The lack of discontinuations due to adverse events is supportive of the safety of risdiplam.*

Table 11: Patient disposition (placebo-controlled period)

	Risdiplam (N=120)	**Placebo (N=60)**
Safety population	120 (100%)	60 (100%)
ITT population	120 (100%)	60 (100%)
No. completed placebo-controlled period	117 (97.5%)	59 (98.3%)
No. discontinued early from placebo-controlled period	3 (2.5%)	1 (1.7%)
Reason for early discontinuation#		
Access to Spinraza	0	1 (1.7%)
Changed to other treatment	1 (0.8%)	0
Move to Spinraza treatment	1 (0.8%)	0
The patient's family requested discontinuation of the study to initiate the use of nusinersen	1 (0.8%)	0

Protocol Violations/Deviations

A summary of major protocol deviations is in the following table, copied from the applicant. There were no protocol deviations leading to study discontinuation. There is no meaningful difference in the proportion of subjects with deviations between the placebo (23%) and risdiplam (20%) groups. *These deviations do not compromise the efficacy and safety results of the study.*

Reference ID: 4646272

Table 12: Summaries of major protocol deviations that occurred during the placebo-controlled period of the Sunfish study.

Protocol Deviation	Risdiplam (N=120)	Placebo (N=60)
Total number of major protocol deviations	31	17
Total number of patients with at least one major protocol deviation	24 (20%)	14 (23%)
Exclusion criteria		
Clinically significant abnormal laboratory tests	0	1 (1.7%)
Ophthalmology report not received at time of enrolment.	1 (0.8%)	1 (1.7%)
Inclusion criteria		
No signed written informed consent to join the study	2 (1.7%)	1 (1.7%)
Medication		
Consistant non-compliance with daily use of study medication	0	1 (1.7%)
Medication - other	0	1 (1.7%)
Received incorrect doseage of study medication for = or > 1 week	4 (3.3%)	2 (3.3%)
Procedural		
Failure to comply with contraceptive requirements	1 (0.8%)	0
MFM-20 performed instead of MFM-32	0	1 (1.7%)
More than 3 consecutive pregnancy tests not done	1 (0.8%)	0
No subsequent reconsent	2 (1.7%)	1 (1.7%)
OCT obtained by non-certified person by AEBC	3 (2.5%)	1 (1.7%)
Ophthalmology test not performed as per protocol	1 (0.8%)	0
Procedural - other	2 (1.7%)	1 (1.7%)
Safety laboratory assessments missed in 2 consecutive visits	2 (1.7%)	0

Reference ID: 4646272

Serious Adverse Event not reported within 24 hours	4 (3.3%)	1 (1.7%)

Table of Demographic Characteristics

Demographics for the placebo-controlled Sunfish Part 2 study are described in the following tables, based on the submitted data. The Sunfish Part 2 study enrolled 180 patients (128 [71%] with Type 2, and 52 [29%] with Type 3 SMA). Ninety-one patients (51%) were female. At screening, the median age of all patients was 9 years (range: 2-25 years); 68 patients (38%) were 12 years or older. 67% of patients were white/Caucasian, 1% were black/African American, and 19% were Asian. 18% of patients were from Poland, 12% from France, 12% from Spain, 10% from Canada, and 2% from the United States. *Overall, there appears to be an acceptable balance of demographic characteristics between the control and treatment groups that adequately represents the demographics of the intended patient population. The statistical reviewer indicated that the positive study results were dependent on the data from the sites in Poland.*

Table 13: Demographics of Sunfish Study Part 2. Source: Submitted data

Subject Population by Treatment

Description of Actual Arm	Count	% of Total
PART 2 - RO7034067	120	66.7%
PART 2 - PLACEBO	60	33.3%
All	180	100.0%

Reference ID: 4646272

Subject Population by Age

		Description of Actual Arm		
		PART 2 - RO7034067	PART 2 - PLACEBO	All
Age	N	120	60	180
	Mean	9.88	10.28	10.01
	Std Dev	5.78	6.05	5.85
	Min	2	2	2
	Quantiles25	5	5	5
	Median	9	9	9
	Quantiles75	14	14	14
	Max	25	24	25

Subject Population by Sex

	Description of Actual Arm					
	PART 2 - RO7034067		PART 2 - PLACEBO			
Sex	Count	Column %	Count	Column %	Count	% of Total
F	61	50.8%	30	50.0%	91	50.56%
M	59	49.2%	30	50.0%	89	49.44%
All	120	100.0%	60	100.0%	180	100.00%

Subject Population by Race

	Description of Actual Arm					
	PART 2 - RO7034067		PART 2 - PLACEBO			
Race	Count	Column %	Count	Column %	Count	% of Total
ASIAN	23	19.2%	12	20.0%	35	19.44%
BLACK OR AFRICAN AMERICAN	2	1.7%	0	0.0%	2	1.11%
MULTIPLE	1	0.8%	0	0.0%	1	0.56%
UNKNOWN	14	11.7%	7	11.7%	21	11.67%
WHITE	80	66.7%	41	68.3%	121	67.22%
All	120	100.0%	60	100.0%	180	100.00%

Reference ID: 4646272

Subject Population by Ethnicity

	Description of Actual Arm					
	PART 2 - RO7034067		PART 2 - PLACEBO			
Ethnicity	Count	Column %	Count	Column %	Count	% of Total
HISPANIC OR LATINO	5	4.2%	2	3.3%	7	3.89%
NOT HISPANIC OR LATINO	114	95.0%	57	95.0%	171	95.00%
NOT REPORTED	0	0.0%	1	1.7%	1	0.56%
UNKNOWN	1	0.8%	0	0.0%	1	0.56%
All	120	100.0%	60	100.0%	180	100.00%

Reference ID: 4646272

Subject Population by Study Site

		Description of Actual Arm					
		PART 2 - RO7034067		PART 2 - PLACEBO			
Country	Study Site Identifier	Count	Column %	Count	Column %	Count	% of Total
BEL	21818	7	5.8%	1	1.7%	8	4.44%
	41339	2	1.7%	3	5.0%	5	2.78%
	96838	2	1.7%	1	1.7%	3	1.67%
	All	11	9.2%	5	8.3%	16	8.89%
BRA	45324	1	0.8%	1	1.7%	2	1.11%
	All	1	0.8%	1	1.7%	2	1.11%
CAN	109916	5	4.2%	2	3.3%	7	3.89%
	111756	4	3.3%	1	1.7%	5	2.78%
	113204	4	3.3%	2	3.3%	6	3.33%
	All	13	10.8%	5	8.3%	18	10.00%
CHN	94105	5	4.2%	3	5.0%	8	4.44%
	119348	6	5.0%	2	3.3%	8	4.44%
	All	11	9.2%	5	8.3%	16	8.89%
ESP	34744	1	0.8%	1	1.7%	2	1.11%
	43830	6	5.0%	4	6.7%	10	5.56%
	91658	2	1.7%	2	3.3%	4	2.22%
	119497	3	2.5%	2	3.3%	5	2.78%
	All	12	10.0%	9	15.0%	21	11.67%
FRA	54061	7	5.8%	4	6.7%	11	6.11%
	65435	1	0.8%	0	0.0%	1	0.56%
	102419	1	0.8%	0	0.0%	1	0.56%
	109229	3	2.5%	2	3.3%	5	2.78%
	119482	2	1.7%	1	1.7%	3	1.67%
	All	14	11.7%	7	11.7%	21	11.67%
HRV	119476	10	8.3%	1	1.7%	11	6.11%
	All	10	8.3%	1	1.7%	11	6.11%
ITA	105090	0	0.0%	1	1.7%	1	0.56%
	107431	0	0.0%	1	1.7%	1	0.56%
	111203	0	0.0%	2	3.3%	2	1.11%
	113484	3	2.5%	1	1.7%	4	2.22%
	113485	2	1.7%	1	1.7%	3	1.67%
	All	5	4.2%	6	10.0%	11	6.11%
JPN	55965	3	2.5%	0	0.0%	3	1.67%
	94326	1	0.8%	2	3.3%	3	1.67%
	94348	0	0.0%	1	1.7%	1	0.56%
	96007	0	0.0%	1	1.7%	1	0.56%
	112922	1	0.8%	0	0.0%	1	0.56%
	116969	0	0.0%	1	1.7%	1	0.56%
	116970	1	0.8%	0	0.0%	1	0.56%
	116971	1	0.8%	0	0.0%	1	0.56%
	116974	2	1.7%	0	0.0%	2	1.11%
	117424	1	0.8%	0	0.0%	1	0.56%
	All	10	8.3%	5	8.3%	15	8.33%
POL	113502	10	8.3%	3	5.0%	13	7.22%
	118492	10	8.3%	1	1.7%	11	6.11%
	118493	4	3.3%	4	6.7%	8	4.44%
	All	24	20.0%	8	13.3%	32	17.78%
RUS	119495	1	0.8%	3	5.0%	4	2.22%
	All	1	0.8%	3	5.0%	4	2.22%
SRB	119862	4	3.3%	4	6.7%	8	4.44%
	All	4	3.3%	4	6.7%	8	4.44%
TUR	107710	1	0.8%	0	0.0%	1	0.56%
	All	1	0.8%	0	0.0%	1	0.56%
USA	47566	2	1.7%	1	1.7%	3	1.67%
	48342	1	0.8%	0	0.0%	1	0.56%
	All	3	2.5%	1	1.7%	4	2.22%

Reference ID: 4646272

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Part 1 of the study enrolled patients with Type 2 and Type 3 (ambulant and non-ambulant) SMA. Part 2 recruited patients with Type 2 and non-ambulant Type 3 SMA.

Patients enrolled in Study BP39055 Part 2 included patients with both Type 2 and non-ambulant Type 3 SMA, with different numbers of SMN2 copies, and with varied baseline disease characteristics including severe scoliosis.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Rates of treatment non-compliance are listed in the table of protocol deviations above. Placebo non-compliance occurred in 1.7% of the placebo group and 0% of the risdiplam group in Part 2 of the Sunfish study.

113 patients (94%) in the risdiplam arm and 57 patients (95%) in the placebo arm received concomitant medications, including budesonide, tropicamide, cyclopentolate, salbutamol, amoxicillin, paracetamol, ibuprofen, and sodium chloride supplementation. *Overall concomitant medication use was similar between the patisiran and placebo groups.*

There were no applicable rescue medications for this trial.

Efficacy Results – Primary Endpoint

The table below, derived from the submission, illustrates the outcomes for the primary and key secondary endpoints. The change from baseline in MFM32 total score, MFM responders, and RULM total score had a statistically significant difference between the risdiplam group compared with the placebo group, based on the multiplicity adjustment procedures defined in the SAP and discussed in Section 6.1.1. *The primary endpoint result, change from baseline at month 12 in the MFM32 total score, indicates an improvement of motor function in the risdiplam group and a worsening in the placebo group. The observed improvement of motor function as evidenced by the increase in MFM32 score is not consistent with the natural history of SMA and supports the efficacy of risdiplam.*

Reference ID: 4646272

Table 14: Summary of Key Efficacy Results – ITT Population.

Endpoint	Risdiplam (N=120)	Placebo (N=60)	Treatment Comparison
MFM32 Total Score			
Baseline, n Mean (SD)	115 45.5 (12.1)	59 47.4 (10.1)	
Change from baseline at month 12, LS Mean (95% CI) P-value (nominal, adjusted)	1.36 (0.61, 2.11)	-0.19 (-1.22, 0.84)	**Mean (95% CI)** 1.55 (0.30, 2.81) p=0.0156, p=0.0156
Proportion of patients (95% CI) who achieve improvement (i.e., change from baseline at month 12 of ≥ 3) P-value (nominal, adjusted)	38.3% (28.9%, 47.6%)	23.7% (12.0%, 35.4%)	**Odds Ratio (95% CI)** 2.35 (1.01, 5.44) p=0.0469, p=0.0469
RULM Total Score			
Baseline, n Mean (SD)	119 19.7 (7.2)	58 20.9 (6.4)	
Change from baseline at Month 12, LS Mean (95% CI) P-value (nominal, adjusted)	1.59 (0.98, 2.20)	0.02 (-0.83, 0.88)	**Mean (95% CI)** 1.59 (0.53, 2.62) p=0.0028, p=0.0469
Hammersmith Functional Motor Scale Expanded (HFMSE): Change from baseline at month 12, Mean (SE) P-value (nominal, adjusted)	0.95 (0.33)	0.37 (0.46)	0.58 p=0.3015; p=0.3902
Forced vital capacity (FVC): Change from baseline in best percentage predicted value at month 12, Mean (SE) P-value (nominal, adjusted)	-5.16% (1.40%)	-3.11% (1.94%)	-2.05%; p=0.3804; p=0.3902

Reference ID: 4646272

Endpoint	Risdiplam (N=120)	Placebo (N=60)	Treatment Comparison
Patient Reported and Parent/Caregiver reported SMA Independence Scale (SMAIS): Change from baseline in the total score at month 12, Lsmean (SE) P-value (nominal, adjusted)	Caregiver reported: 1.65 (0.50) Patient reported: 1.04 (0.65)	Caregiver reported: -0.91 (0.67) Patient reported: -0.40 (0.86)	Caregiver reported: 2.55; p=0.0022; p=0.3902 Patient reported: 1.45; p=0.1778
Clinical Global Impression of Change (CGI-C): Proportion of patients rated by clinicians as no change or improved (i.e., rated as "no change", "minimally improved", "much improved" or "very much improved") at month 12 P-value (nominal, adjusted)	47.5%	40.0%	1.38; p=0.3544, p=0.3902

Data Quality and Integrity

The Roche Clinical Quality Assurance group or designee conducted audits at one site for each of the pivotal studies, BP39055 (SUNFISH) and BP39056 (FIREFISH), as well as one study audit (BP39055). In addition, the Roche alliance partner/co-development partner Chugai performed one further investigator audit for Study BP39055 (SUNFISH). No critical findings were observed for Study BP39055 (SUNFISH).

No data inconsistencies or discrepancies were found during the course of this review.

Due to the Covid-19 pandemic, OSI inspections of study sites could not be conducted. Although the statistical review indicated that the positive SUNFISH study results were dependent on the data from the sites in Poland, the strength of the positive results of the FIREFISH study in Type 1 SMA patients, which were not driven by particular sites, and the shared pathophysiology of the disease across SMA subtypes, support the efficacy of risdiplam in the SMA Type 2 and 3 SUNFISH population. These findings support a recommendation for approval without site inspections.

Reference ID: 4646272

Efficacy Results – Secondary and other relevant endpoints

The next family of endpoints in the statistical analysis hierarchy defined in the SAP (Family 4 - HFMSE scale and FVC) did not achieve statistical significance, therefore, these and other subsequent secondary endpoints in the rest of the families of the hierarchy (SMAIS and CGI-C) are considered exploratory.

There was no statistically significant difference for either HFMSE (mean treatment difference [95% CI]: 0.59 [-0.52, 1.69]; nominal p=0.2949, adjusted p=0.3902) or FVC % predicted (mean treatment difference [95% CI]: -2.05 [-6.67, 2.56]; nominal p=0.3804, adjusted p=0.3902). Both the risdiplam and placebo groups had increases in HFMSE scores at 12 months, with a nominally greater increase in the risdiplam group. Higher HFMSE scores indicate better motor function. Although the mean increases of 0.95 and 0.37 (maximum possible score = 66) in the risdiplam and placebo groups, respectively, do not represent clinically significant differences, *this finding does not contradict the positive finding for the primary endpoint.*

Both the risdiplam and placebo groups had mean worsening of forced vital capacity (FVC), with best percentage predicted value at month 12 change from baseline of -5.2% for the risdiplam and -3.1% for the placebo groups, respectively. *This finding indicates that any improvement in muscle function shown by the improvement in the primary endpoint, MFM32, was not reflected in improved respiratory function. Note that respiratory infections, common in SMA patients, occurred in both the risdiplam and placebo groups as discussed in Section 8. These respiratory illnesses may have masked any small potential improvements in respiratory muscle function.*

The SMAIS showed nominal improvement (1.7 caregiver, 1.0 patient) in the risdiplam group and worsening (-0.9 caregiver, -0.4 patient) in the placebo group. *This finding is consistent with the positive results for the primary endpoint.*

The CGI-C had a nominal 7.5% difference favoring the risdiplam group. *This finding is consistent with the positive results for the primary endpoint.*

Additional Analyses Conducted on the Individual Trial

The applicant conducted an analysis of individual MFM32 domain scores: D1 (standing and transfer), D2 (axial and proximal function), and D3 (distal function). In an MMRM analysis of the change from baseline in the individual MFM32 domains, the MMRM difference (95% CI) from placebo with risdiplam treatment was 0.64 (-0.20, 1.47) for D1, 1.97 (-0.40, 4.34) for D2, and 2.34 (0.05, 4.62) for D3. *The relatively smaller positive difference between the placebo and risdiplam groups in D1 (standing and transfer) is likely related to the fact that only non-ambulant patients were enrolled in the Sunfish study Part 2.*

Reference ID: 4646272

The applicant conducted a planned age sub-group analysis both for MFM32 and RULM, shown in the following table copied from the submission. *This analysis suggests that the greatest efficacy is seen in the youngest age group, consistent with the pathophysiology of SMA in which motor neurons are progressively lost with time.*

Table 15: Subgroup Analysis of Change from Baseline in MFM32 and RULM at Month 12 by Age Group

Age Group	Mean Treatment Difference (95% CI)	
	MFM32	RULM
2-5 years (N=55)	3.03 (0.71, 5.35)	3.41 (1.55, 5.26)
6-11 years (N=57)	1.58 (-0.58, 3.74)	1.07 (-0.81, 2.94)
12-17 years (N=46)	1.04 (-1.31, 3.39)	0.06 (-1.93, 2.04)
18-25 years (N=22)	-0.65 (-4.04, 2.74)	1.74 (-1.06, 4.53)

The applicant conducted a planned region sub-group analysis for MFM32, shown in the following table copied from the submission. *The mean treatment difference favors risdiplam in Europe and North America with the largest numbers of subjects (N=146 total), but the placebo group had a better response in Japan and China (N=31 total).*

Reference ID: 4646272

Table 16: Subgroup Analysis of Change from Baseline in MFM32 at Month 12 by Region

Region	Mean Treatment Difference (95% CI)
Europe (N=124)	2.35 (0.95, 3.74)
North America (N=22)	2.51 (-1.16, 6.19)
Japan (N=15)	-3.54 (-7.53, 0.46)
China (N=16)	-1.78 (-5.70, 2.14)
Rest of World (N=3)	3.48 (-6.21, 13.17)

6.2. Study BP39056, FIREFISH

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

6.2.1. Study Design

Overview and Objective

Note that the NDA submission included only efficacy data from the dose-finding Part 1 of the Firefish study, upon Agency agreement (see Section 3. Regulatory Background). Some safety data from Part 2 were submitted and are reviewed in Section 8. The applicant applied the efficacy analysis originally intended for Part 2 to the data from Part 1.

Open-label studies are difficult to interpret unless there is a large effect on a well-defined endpoint that is clearly outside of the natural variability of the disease, because of the intrinsic limitations of the study design, such as the lack of placebo control groups and the potential for observer bias in some endpoints.

The Firefish study was a Phase 2/3, multicenter, multinational, open-label, single-arm, two-part study of risdiplam in subjects with Type 1 Spinal Muscular Atrophy.

The primary objectives of the study are described by the applicant as follows:

Reference ID: 4646272

Part 1

- The primary objective of Part 1 was to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of risdiplam in infants with Type 1 SMA, and to select the dose for Part 2.

Part 2

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

Secondary objectives for Part 2 are as follows:

- To assess the safety and tolerability of oral treatment with risdiplam.
- To assess the pharmacokinetics of risdiplam.
- To assess the pharmacodynamic effects of risdiplam (*SMN2* mRNA, SMN protein).
- To evaluate at 12 months of treatment with risdiplam the effect on motor development milestones, such as head control and rolling, as measured in the BSID-III gross motor scale.
- To evaluate at 24 months of treatment with risdiplam the effect on sitting without support for 5 seconds and further motor development milestones, such as sitting without support for 30 seconds, crawling, standing alone, and walking, as measured in the BSID-III gross motor scale.
- To assess the achievement of motor milestones at 12 and 24 months of treatment with risdiplam, as measured by the Hammersmith Infant Neurological Examination Module 2 (HINE-2).
- To evaluate the proportion of infants who achieve a score of 40 or higher in the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) at 12 months of treatment.
- To evaluate the proportion of infants who achieve an increase of at least 4 points on their CHOP-INTEND score from baseline at 8 and 12 months of treatment.
- To evaluate the proportion of infants who achieve head control at 8, 12, and 24 months of treatment (defined as a score of 3 or higher for item 12 of the CHOP-INTEND).
- To assess the change from baseline in the total raw score of the BSID-III gross motor scale at 12 and 24 months of treatment.
- To assess the proportion of infants who achieve a reduction of at least 30 degrees in phase angle at 12 months of treatment measured by respiratory plethysmography (RP).
- To evaluate the proportion of infants who do not require invasive or non-invasive respiratory (e.g., bilevel positive airway pressure [BiPAP]) support at 12 and 24 months of treatment.
- To assess at 12 and 24 months of treatment the proportion of infants who are alive

Reference ID: 4646272

without permanent ventilation, as defined by >=16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy.

- To assess the impact of treatment with risdiplam on time to event (death, permanent ventilation).
- To evaluate the proportion of infants with the ability to feed orally at 12 and 24 months of treatment.

Trial Design

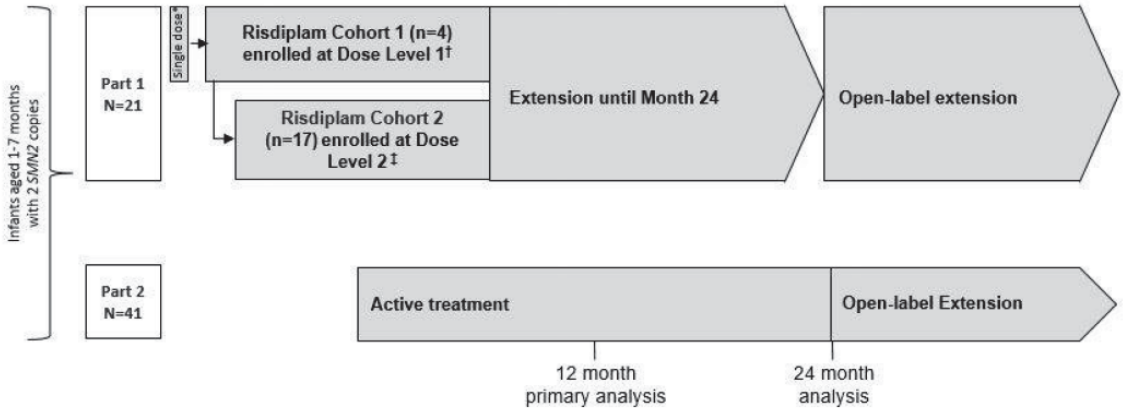
- **Basic study design:**

This was a multicenter (7 sites for Part 1 and 14 sites for Part 2), multinational (12 countries), open-label, single-arm Phase 2/3 study. The planned study size was N=8-24 in Part 1 and N=40 in Part 2; the actual number randomized in this study was N=21 for Part 1 and N=41 for Part 2.

Part 1 was an open-label exploratory dose-escalation study in infants with Type 1 SMA aged 1 to 7 months at the time of enrollment. The dose determined from Part 1 was then used in Part 2, an on-going open-label, single-arm study in patients with Type 1 SMA aged 1 to 7 months at the time of enrollment to assess the efficacy of risdiplam over a 24-month treatment period, with the primary endpoint analyzed at 12 months of treatment

The Firefish study design is shown in the following figure, copied from the submission.

Figure 4: Firefish Study Design



Reference ID: 4646272

- **Key inclusion/exclusion criteria:**
  The criteria listed below from the submitted protocol appear adequate to enroll patients with Type 1 SMA representative of the U.S. population.

  Key Inclusion Criteria
  To participate in this study, candidates were required to meet the following eligibility criteria at Screening:

  1. Males and females aged between 28 days (1 month) of life and 210 days (7 months) (inclusive) at enrollment. For the first 3 patients enrolled in Part 1, age was between 150 days (5 months) and 210 days (7 months) inclusive and a minimum body weight of 7 kg was required for the first patient only. Enrollment was defined as the moment when a patient had their dosing number assigned.
  2. Confirmed diagnosis of 5q-autosomal recessive SMA, including:
     - Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of the SMN1 gene.
     - Clinical history, signs or symptoms attributable to Type 1 SMA, i.e., hypotonia, absent deep tendon reflex and/or tongue fasciculations with onset after the age of 28 days, but prior to the age of 3 months (inclusive), and inability to sit independently (without support) at the time of screening.
  3. Patient had two SMN2 gene copies, as confirmed by central testing.

  Key Exclusion Criteria
  Subjects meeting any of the following criteria were not eligible for the study:

  1. Concomitant or previous participation in any investigational drug or device study within 90 days prior to screening or 5 half-lives, whichever was longer.
  2. Concomitant or previous administration of a SMN2-targeting antisense oligonucleotide, SMN2 splicing modifier or gene therapy either in a clinical study or as part of medical care.
  3. Any history of cell therapy.
  4. Hospitalization for a pulmonary event within the last 2 months, or planned at the time of screening.
  5. Required invasive ventilation or tracheostomy.
  6. Required awake non-invasive ventilation or with awake hypoxemia (SaO2 <95%) with or without ventilator support.
  7. A history of respiratory failure or severe pneumonia, and had not fully recovered their pulmonary function at the time of screening.
  8. Recent history (less than 6 months) of ophthalmic diseases
  9. Any inhibitor of CYP3A4 taken within 2 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing

Reference ID: 4646272

10. Any inducer of CYP3A4 taken within 4 weeks (or within 5 times the elimination half-life, whichever is longer) prior to dosing
11. Any organic cation transporter-2 (OCT-2) and multidrug and toxin extrusion (MATE) substrates
12. Presence of non-SMA-related concurrent syndromes or diseases

- **Dose selection:**
  Part 1: During the dose-selection phase of the study, risdiplam dose levels were investigated in a staggered, dose-escalation manner. The first patient enrolled (aged 5 to 7 months) received a single starting dose of 0.00106 mg/kg risdiplam to assess safety and tolerability and pharmacokinetics. This dose was selected based on the most conservative PBPK modelling scenario, plus an additionally applied safety factor of 10. Once this single dose was shown to be safe and well tolerated, and after the pharmacokinetics had been evaluated, this patient continued in the study and, approximately 6 weeks later, started administration of once daily risdiplam at a dose that was selected based on the PK data obtained from the first single dose, targeting an exposure of area under the curve from time 0 to 24 hours at steady state [$AUC_{0\text{-}24h,ss}$] of 700 ng x h/mL. This exposure, called Dose Level 1, was predicted to result in a doubling of SMN protein levels (i.e., a 2-fold increase versus the patient's baseline). Dose Level 2 was a target exposure of mean $AUC_{0\text{-}24h,ss}$ <=2000 ng x h/mL; which remained below the no observed adverse effect level (NOAEL) from the animal toxicology studies.

  Part 2: The IMC dose selection criteria for Part 2 were the following:

  - A dose that was judged to be well tolerated and without any known safety signal, based on all available data from Part 1 and as confirmed by the external iDMC.
  - A dose that results in a target exposure of mean $AUC_{0\text{-}24h,ss}$ <=2000 ng x h/mL (adjusted for free fraction, if required).

  On the basis of data from Part 1, the following starting dose levels were selected for Part 2:
    - Infants >1 month old and <3 months old at enrollment: 0.04 mg/kg.
    - Infants >=3 months old and <5 months old at enrollment: 0.08 mg/kg.
    - Infants >=5 months old at enrollment: 0.2 mg/kg.

- **Study treatments:**
  Study medication (risdiplam) was taken orally once daily. For patients able to swallow, study drug was administered with a syringe inserted between the baby's gum and cheek. Patients who were unable to swallow the study medication and who had a nasogastric or gastrostomy tube in situ received the study medication by bolus via the tube.

- **Assignment to treatment:** This was an open-label study and all subjects received risdiplam.

Reference ID: 4646272

- **Blinding:** Not applicable. This was an open-label study.

- **Administrative structure:** An IMC was responsible for reviewing safety, PK and PD data and for dose-escalation decisions in Part 1 and the dose-selection for Part 2. An iDMC reviewed all available data from Part 1 to confirm the dose-decision taken by the IMC, and reviewed safety, efficacy, PK and PD for Part 2. The scope and responsibility of these committees was detailed in a specific Charter. An ophthalmological monitoring vendor was responsible for central review of ophthalmological assessments.

- **Procedures and schedule:**
  The schedule of key assessments for Part 1 of the Firefish study is presented in the following two tables, based on the submitted protocol. The second table lists the schedule of ophthalmology assessments.

Table 17: Firefish Study Part 1 Schedule of Key Assessments

Assessment	Schedule
Physical Examination	Screening, Weeks 1, 2, 4, 8, 12, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
Vital Signs	Screening, Weeks 1, 2, 4, 8, 12, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
ECG-12 lead	Screening, Weeks 1, 2, 4, 8, 12, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
Hematology	Screening, Weeks 2, 8, 17, 35, 52, 70, 87, 104
Blood Chemistry	Screening, Weeks 2, 8, 17, 35, 52, 70, 87, 104
Ophthalmological Exam	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
BSID-gross motor score	Screening, Weeks 17, 35, 52, 70, 87, 104
Respiratory Plethysmography	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
HINE-2	Screening, Weeks 17, 35, 52, 70, 87, 96, 104
CHOP-INTEND	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
CMAP	Screening, Weeks 17, 35, 52, 70, 104
Administration of Study Medication	Weeks 1 through 104
Infant Toddler Quality of Life	Screening, Weeks 17, 35, 52, 70, 87, 104
SMN protein	Screening, Weeks 1, 2, 4, 17, 35, 52, 87, 104

Reference ID: 4646272

Table 18: Firefish Study Schedule of Ophthalmology Assessments, Parts 1 & 2

Assessment	Schedule
Ophthalmology examination	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
SD-OCT	Screening, Weeks 8, 17, 26, 35, 43, 52, 61, 70, 78, 87, 96, 104
Color Fundus photography	Screening, Weeks 26, 52, 78, 104

- **Dietary restrictions/instructions:**
  Subjects were to avoid grapefruit juice and Seville orange (juice) starting at least 2 weeks prior to study drug administration.

  Breastfeeding of the patient was allowed if the mother was not consuming any prohibited medications. Breastfeeding was not permitted for 1 hour after study drug administration in order to avoid direct contact between the mother's skin and the drug product immediately after administration.

- **Concurrent medications:**
  Use of the following medications/treatments was prohibited for patients and the mother if breastfeeding the patient during study participation.

  - Any inhibitor of CYP3A4, including but not limited to: ketoconazole, miconazole, itraconazole, fluconazole, erythromycin, clarithromycin, ranitidine, cimetidine.
  - Any inducer of CYP3A4, including but not limited to: rifampicin, rifabutin, glucocorticoids, carbamazepine, phenytoin, phenobarbital, St. John's wort.
  - Any OCT-2 and MATE substrates were to be avoided, including but not limited to: amantadine, cimetidine, memantine, amiloride, famotidine, metformin, pindolol, ranitidine, procainamide, varenicline, acyclovir, ganciclovir, oxaliplatin, cephalexin, cephradine, fexofenadine.
  - Any known FMO1 or FMO3 inhibitors or substrates.
  - Oral or topical retinoids, amiodarone, phenothiazines, and chronic use of minocycline

Use of the following therapies was prohibited for at least 90 days prior to enrollment because they had the potential to confound treatment efficacy: Riluzole, Valproic acid, Hydroxyurea, Sodium phenylbutyrate, Butyrate derivatives, Creatine, Carnitine, Growth hormone, Anabolic steroids, Probenecid, Bortezomin, Quercetin, chronic oral or parenteral use of corticosteroids. Any prior use of nusinersen or any other SMN2-targeting antisense oligonucleotide, SMN2-splicing modifier, or gene therapy was prohibited.

Reference ID: 4646272

- **Treatment compliance:**
  Records of all investigational medicinal product by study site were recorded on the Drug Inventory Log. A subject diary was used to capture information related to drug administration for all doses throughout the study. All bottles and unused drug and drug supplies were returned to the site during a study visit or collected during a home visit.

- **Rescue medication:**
  There were no applicable rescue medications for this trial.

- **Subject completion, discontinuation, or withdrawal:**
  Patients discontinued study drug if they experienced any of the following:
  - Ophthalmological or other events as described in the following table, copied from the submission.
  - Unable to continue to comply with study requirements.

Table 19: Guidelines for Managing Specific Adverse Events

Event	Action to take
Symptoms or signs of oropharyngitis	Examine, treat symptomatically and document resolution and outcome. Consult otolaryngology specialist in case of unusual findings.
Grade ≥ 2 skin toxicity reaction Grade ≥ 2 larynx toxicity reaction	Discontinue study treatment immediately. Contact promptly the Study Investigator, consult as quickly as possible a dermatologist / otolaryngology specialist.
Ophthalmological event	Consult an Ophthalmologist as quickly as possible for ophthalmic examination and provide a copy of the ICF and contact promptly the study Investigator. If findings are unusual, discontinue study treatment until the study-trained Ophthalmologist at study site and the study Investigator have been consulted and the results of a full ophthalmic examination have been reviewed.

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

Reference ID: 4646272

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

Study Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint for the Firefish study was the proportion of infants who were sitting without support at 12 months of treatment. The endpoint was defined as sitting without support for 5 seconds as assessed in Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) gross motor scale, shown in the figure below. The testing order of the BSID-III was modified and sitting was evaluated first in order to limit patients' fatigue and to allow the primary endpoint to be assessed consistently.

Figure 5: Item 22 of the Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) (Bayley, N., 2006)

22
26

22 Sits Without Support Series: 5 Seconds

Position	Materials	Trials	Time
Seated	Stopwatch	1	5 seconds
Series items	22 (5 Seconds), 26 (30 Seconds)		

With the child seated, provide pelvic support by placing your hands around the child's lower back. According to the child's ability to sit alone, gradually loosen your hold.

On the Record Form, indicate how long the child was able to maintain the position without support.

1 point: Child sits alone without support for at least 5 seconds.

0 points: Child sits alone for less than 5 seconds before losing balance and falling over. Child uses his or her arms to prop him- or herself up.

The evaluation of the BSID-III gross motor scale, including sitting, was video-recorded in a standardized manner and centrally reviewed by two independent readers in addition to the site clinical evaluator assessment. The assessment of the central readers was used for the primary endpoint analysis after 12 months of treatment with risdiplam.

The Bayley Scales of Infant and Toddler Development – Third Edition (BSID-III) is a measure of infant and toddler development that has been standardized on an American pediatric population. The BSID consists of a core battery of five scales. Three scales (cognitive, motor, language) are administered with child interaction and two scales (social-emotional, adaptive

Reference ID: 4646272

behavior) are conducted with parent questionnaires. The BSID-III also includes a Behavior Observation Inventory, a separate scale for validating examiner and parent perceptions of the child's responses. For the Firefish study only the Gross Motor scale of the BSID-III was used as an outcome measure to assess attainment of motor milestones. The other BSID-III scales were not used.

Reviewer Comment: The natural history of SMA is well understood (Finkel et al. 2014; De Sanctis et al. 2016; Kolb et al. 2017). Type 1 SMA patients never achieve sitting without support. The primary endpoint is acceptable, although the possibility of bias remains because of the open-label nature of the study.

Secondary Efficacy Endpoints

The secondary efficacy endpoints of the Firefish study were as follows:

Motor Function and Development Milestones:

1. Proportion of infants who achieve a score of 40 or higher in the CHOP-INTEND at Month 12;
2. Proportion of infants who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 8 and Month 12;
3. Proportion of infants who achieve head control at Month 8, Month 12, and Month 24 (defined as a score of 3 or higher for item 12 of the CHOP-INTEND);
4. Change from baseline in the total raw score of the BSID-III gross motor scale at Month 12 and Month 24;
5. Proportion of infants who achieve the attainment levels of the motor milestones as assessed in Section 2 of the Hammersmith Infant Neurological Examination (HINE-2) at Month 8 (head control, ability to kick, rolling), Month 12, and Month 24;
6. Proportion of motor milestone responders as assessed by HINE-2 at Month 12 and Month 24;

   The applicant defines a responder as "at least a 2-point increase in ability to kick (or maximal score) or a 1-point increase in head control, rolling, sitting, crawling, standing, or walking. Worsening is similarly defined as a 2-point decrease in ability to kick (or lowest score) or a 1-point decrease in head control, rolling, sitting, crawling, standing, or walking. Voluntary grasp is excluded from the definition. An infant will be classified as a responder if more motor milestones show improvement than show worsening; infants who die or withdraw will be classified as non-responders. Infants with a totally missing HINE-2 assessment at Month 12 or Month 24 will also be classified as non-responders." *This responder definition is reasonable.*

Reference ID: 4646272

7. Highest motor milestone achieved by Month 12 and Month 24;
8. Proportion of infants who are alive and sitting without support for 5 seconds at Month 24 (defined as per the primary endpoint);
9. Proportion of infants who are alive and sitting without support for 30 seconds at Month 24 (defined as "Sits without support for 30 seconds" as assessed in Item 26 of the BSID-III gross motor scale);
10. Proportion of infants who are alive and standing at Month 24 (defined as 'Stands Alone' as assessed in Item 40 of the BSID-III gross motor scale);
11. Proportion of infants who are alive and walking at Month 24 (defined as 'Walks Alone' as assessed in Item 42 of the BSID-III gross motor scale).

Survival and Ventilation-Free Survival:

12. Time to death or permanent ventilation (defined as >=16 hours of non-invasive ventilation per day or intubation for >21 consecutive days in the absence of, or following the resolution of, an acute reversible event or tracheostomy) from enrollment, time to death from enrollment,
13. Proportion of infants who are alive without permanent ventilation at Month 12 and Month 24,
14. Proportion of infants who are alive at Month 12 and Month 24.

Respiratory:

15. Time to permanent ventilation from enrollment,
16. Proportion of infants who are without permanent ventilation at Month 12 and Month 24,
17. Proportion of infants who achieve a reduction of at least 30 degrees in their phase angle from baseline, as measured by RP, at Month 12,
18. Proportion of infants who do not require invasive or non-invasive respiratory support at Month 12 and Month 24.

Nutrition:

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

The Children's Hospital of Philadelphia Infant Test for Neuromuscular Disease (CHOP INTEND) is a validated 16-item, 64-point motor assessment designed to evaluate the motor skills of infants with symptomatic SMA (Glanzman, 2010). The test captures neck, trunk, proximal, and distal limb strength in 14 elicited and 2 observational items.

Reviewer Comment: The CHOP INTEND is an acceptable neuromuscular evaluation for use as a secondary endpoint. See the CHOP INTEND scoring sheet in Appendix 13.3.

Reference ID: 4646272

The HINE (scoring sheet shown in the figure below) evaluates the neuromuscular development of infants in 8 motor milestone categories (head control, sitting, grasping, ability to kick in supine position, rolling, crawling, standing and walking) with 3 to 5 progressively more difficult items for each milestone category, as shown in the figure below. Scoring proceeds from left to right, with 0 meaning inability to perform a task and 3 or 4 (depending on the task) meaning full milestone development. The HINE has been assessed in a retrospective multicentric study of 33 type I SMA infants (De Sanctis et al., 2016). The authors reported that "all [type 1 SMA] patients studied had a score of 0 out of a scale of 4 on items assessing sitting, rolling, crawling, standing or walking. A score of more than 0 was only achieved in three items: head control (n = 13), kicking (n = 15) and hand grasp (n = 18). In these items, the maximal score achieved was 1 out of a scale of 4, indicating only partial achievement of the milestone."

Reference ID: 4646272

Figure 6: Hammersmith Infant Neurological Examination (HINE) Section 2 – Motor Milestones.

Scoring: 0 1 2 3 4

Motor Milestone Category	Milestone Level Progression [age expected in heathy infants*] →				
Voluntary grasp	No grasp	Uses whole hand	Finger and thumb; immature grasp	Pincer grasp	
Ability to kick (in supine)	No kicking	Kicks horizontal; legs do not lift	Upward (vertically) (3 months)	Touches leg (4-5 months)	Touches toes (5-6 months)
Head control	Unable to maintain upright (<3 months)	Wobbles (4 months)	All the time upright (5 months)		
Rolling	No rolling	Rolling to side (4 months)	Prone to supine (6 months)	Supine to prone (7 months)	
Sitting	Cannot sit	Sit with support at hips (4 months)	Props (6 months)	Stable sit (7 months)	Pivots (rotates) (10 months)
Crawling	Does not lift head	On elbow (3 months)	On outstretched hand (4-5 months)	Crawling flat on abdomen (8 months)	On hands and knees (10 months)
Standing	Does not support weight	Supports weight (4-5 months)	Stands with support (8 months)	Stands unaided (12 months)	
Walking	No walking	Bouncing (6 months)	Cruising (holding on) (11 months)	Walking independently (15 months)	

* Values for healthy infants in [Haataja 1999].

Reviewer Comment: Based on the above descriptions of the HINE and the progressive loss of motor milestones in type 1 SMA patients, the choice of motor milestone development as measured by the HINE is an acceptable secondary endpoint.

The safety endpoints include the following:

- Incidence of adverse events (overall, by severity and by relationship to study
- medication).
- Incidence of serious adverse events.
- Incidence of treatment discontinuations due to adverse events.
- Incidence of laboratory abnormalities.
- Incidence of ECG abnormalities.
- Incidence of vital sign abnormalities.
- Incidence of clinically significant findings on ophthalmological examination.

Reference ID: 4646272

- Anthropometric examination including weight, height, head, and chest circumference.

Statistical Analysis Plan

Please refer to the statistical review for detailed evaluation of the applicant's planned statistical analysis.

In the original statistical analysis plan, the confirmatory efficacy analyses were only to have included data from infants enrolled into Part 2 of the study. However, the study is still ongoing and this NDA submission only includes descriptive efficacy analyses based on the exploratory dose-finding Part 1 of the Firefish study using the same methods as for the planned Part 2 analysis.

The pre-defined performance criteria for the proportion of motor milestone responders at Month 12 will be 8%, based on the placebo (sham-procedure) results from the Phase 3 ENDEAR study assessing the clinical efficacy and safety of ISIS 396443 (Nusinersen) in patients with infantile-onset SMA (ClinicalTrials.gov identifier: NCT02193074; Finkel et al., 2017).

Protocol Amendments

The original study Protocol BP39056 (Version 1) was released on 22 June 2016. There were 5 amendments to the protocol. Version 5 was released on 27 January 2019. *These amendments were largely administrative in nature, were reviewed, and found to be reasonable.*

6.2.2. Firefish Study Results

Demographic and Baseline Characteristics

The open-label Firefish study Part 1 enrolled 21 patients with Type 1 (infantile-onset) SMA. Fifteen patients (71%) were female. Seventeen (81%) patients were white/Caucasian and four (19%) were Asian. Eleven (52%) of patients were from Italy, four (19%) from France, and three (14%) from the United States.

The patients in Part 1 of the study (Part 2 data were not included in this NDA submission) had a median age of 2 months (range: 0.9-3 months) at symptom onset and a median disease duration (time between onset of symptoms and first treatment) of 4 months (range: 2-5.8 months). At screening the median age was 4.9 months (range: 1.5-6.7 months). No patients were sitting without support at baseline. Most patients (16/21, 76%) were receiving no pulmonary care at baseline; 3 patients (14%) were receiving non-invasive ventilation (BiPAP)

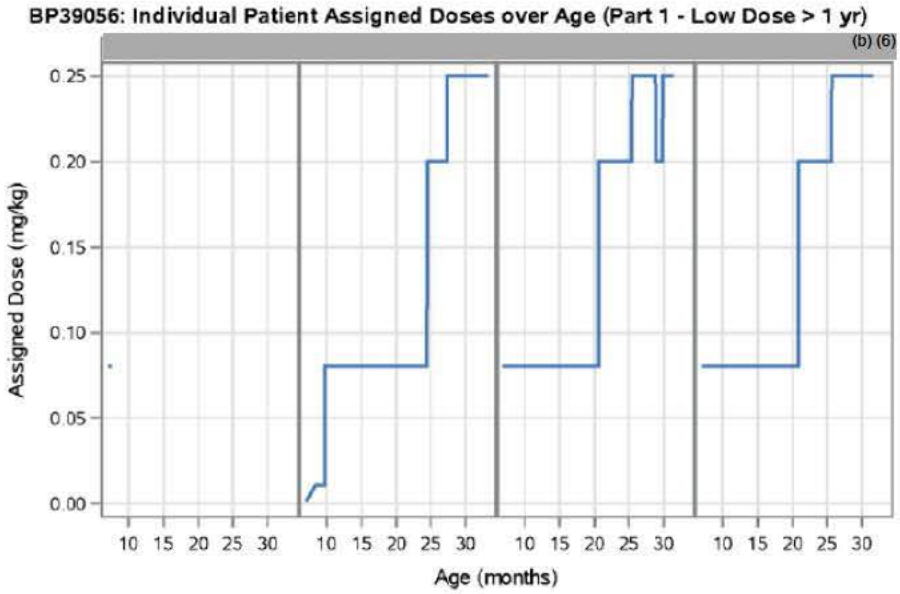
Reference ID: 4646272

support for <16 hours/day, and 1 patient (5%) was receiving cough assistance. At the time of analysis 12 months later the median age was 16.9 months (range 13.5-18.7 months).

The following figures and tables, copied from the submission, summarize the key efficacy results of the open-label Firefish study based on the exploratory dose-finding Part 1. Patients in Cohort 2 received the selected pivotal dose (at a higher target exposure than Cohort 1) of risdiplam. Risdiplam dose levels were investigated in a staggered, dose-escalation manner and several patients had dose changes during the study, as shown in the following figure, copied from the submission.

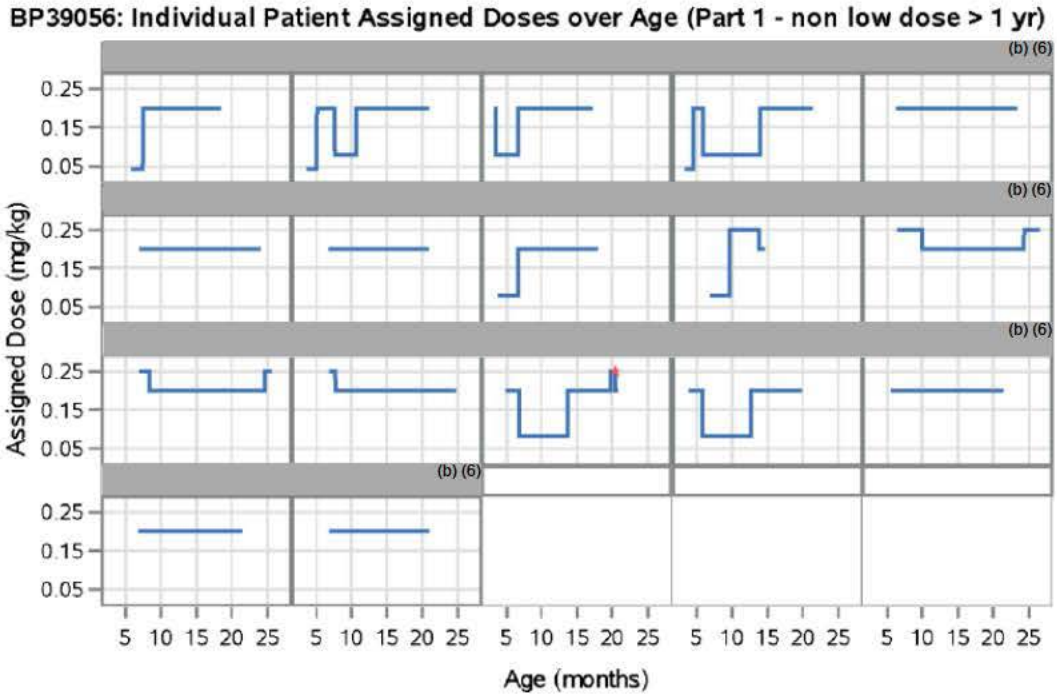
Figure 7: FIREFISH Study Part 1: Assigned Doses for Each Infant

Cohort 1:



Reference ID: 4646272

Cohort 2:



Reference ID: 4646272

Table 20: Summary of Firefish Efficacy Endpoints in Part 1 at Month 12 (ITT Population)

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

Reference ID: 4646272

Table 21: Summary of Additional Firefish Efficacy Endpoints in Part 1 at Month 12 (ITT Population)

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

Primary Endpoint:

1. Proportion of patients sitting without support for 5 seconds (BSID-III) at Month 12: The natural history of SMA is well understood (Finkel et al. 2014; De Sanctis et al. 2016; Kolb et al. 2017). Type 1 SMA patients never achieve sitting without support. *The finding that 41% of the higher dose Cohort 2 patients achieved sitting without support indicates a clinically significant improvement compared to the normal course of the disease. The topline results from Part 2 of the Firefish study have been reported as 29% of all subjects being able to sit without support for 5 seconds after 12 months of treatment. This result appears consistent with the result from Part 1, although the data from Part 2 have not been submitted to this NDA or reviewed.*

Secondary Endpoints:

Note that the Firefish Part 1 study has not completed 24-month assessments so only 12-month results are reported below.

Reference ID: 4646272

Motor Function and Development Milestones:

1. Proportion of patients who achieve a score of 40 or higher in the CHOP-INTEND at Month 12: 10 of 17 (59%) of the higher dose Cohort 2 achieved a score of 40 or higher in the CHOP-INTEND at Month 12. In comparison, in a natural history study of infantile onset SMA (Kolb et al., 2017), 0 out of 7 infants with 2 copies of the SMN2 gene had a score of at least 40 after 12 months of follow-up (mean score= 10, range: 2-28). *This finding indicates an improvement in the risdiplam-treated Type 1 SMA infants compared to the normal course of the disease.*

2. Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12: 15 of 17 (88%) of the higher dose Cohort 2 achieved an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12. The applicant cites a personal communication from the author of Kolb et al. 2017 as well as data from Darras (2016, N=7) that none of the Type 1 SMA infants with 2 copies of the SMN2 gene in the natural history studies had an increase of at least 4 points from baseline in their CHOP-INTEND score after 12 months of follow-up. The Darras (2016) reference was reviewed and found to be consistent with the applicant's statement. *This finding indicates an improvement in the risdiplam-treated Type 1 SMA infants compared to the normal course of the disease.*

3. Proportion of infants who achieve head control at Month 8, Month 12, and Month 24 (defined as a score of 3 or higher for item 12 of the CHOP-INTEND); Proportion of patients who achieve head control assessed by HINE-2 at Month 12: 9 of 17 (53%) of the higher dose Cohort 2 achieved head control (score of 3 or higher for item 12 of the CHOP-INTEND) at Month 8, Month 12, and Month 24. In the HINE-2 assessment, 9 of 17 (53%) achieved head control (maintained upright, Score =2) in the higher dose Cohort 2. In a study of 33 type I SMA infants (De Sanctis et al. 2016) only partial achievement of head control was achieved in 13 infants with a maximum score of 1 out of 2, as assessed by the HINE. *This finding indicates an improvement in the risdiplam-treated Type 1 SMA infants compared to the normal course of the disease.*

4. Proportion of motor milestone responders as assessed by HINE-2 at Month 12 and Month 24: 77% (13 of 17) of the higher dose Cohort 2 was classified as a motor milestone responder at Month 12, as defined in Section 6.2.1. In comparison, 0% (0 of 24) Type 1 SMA infants were motor milestone responders in the natural history study of De Sanctis et al. (2016). "Thirty-three type I SMA infants, who classically do not achieve the ability to sit unsupported, were included in the study. Our results confirmed that all patients had a score of 0 out of a scale of 4 on items assessing sitting, rolling, crawling, standing or walking. A score of more than 0 was only achieved in three items: head

Reference ID: 4646272

control (n = 13), kicking (n = 15) and hand grasp (n = 18). In these items, the maximal score achieved was 1 out of a scale of 4, indicating only partial achievement of the milestone" (De Sanctis et al., 2016). *Motor milestone development is an acceptable functional endpoint based on the known clinical course of type 1 SMA, in which there is progressive loss of motor milestones through the course of the disease. Patients with type 1 SMA never sit, stand, or walk. This result indicates an improvement in the risdiplam-treated Type 1 SMA infants compared to the normal course of the disease.*

Survival and Ventilation-Free Survival:

Proportion of infants who are alive without permanent ventilation at Month 12 and Month 24: Sixteen out of seventeen (94%) of the higher dose Cohort 2 was alive without permanent ventilation at Month 12, and the same 94% was alive at Month 12. Note that at the time of analysis after 12 months of risdiplam the median age was 16.9 months (range 13.5-18.7 months).

The applicant provided updated survival data during the course of this review. At the time of the latest clinical cut-off date (3 March 2020) seventeen out of twenty-one (81%) patients were alive without permanent ventilation. The median age for all patients alive was 32.3 months (range: 28.4 to 45.1 months) with a median treatment duration of 26.9 months (range 23.8 to 37.0 months). All alive patients were older than 28.4 months of age and had at least 23.8 months of treatment with risdiplam.

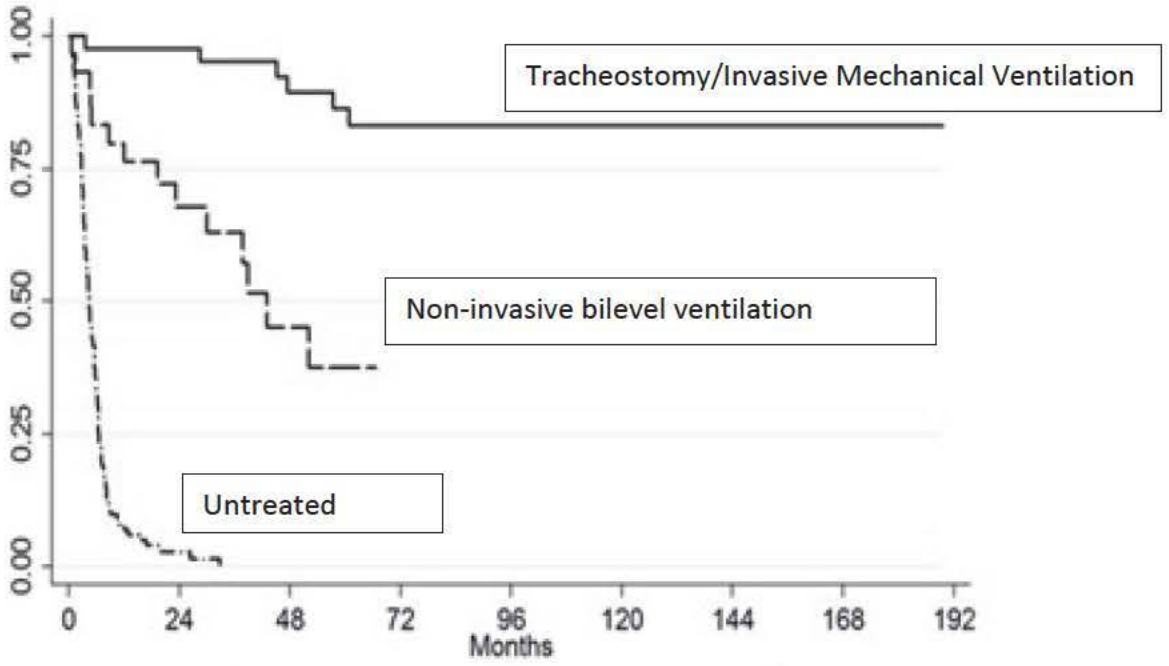
In five natural history studies of Type 1 SMA (CARNI-VAL Type I, PNCR Network, NeuroNEXT SMA Infant Biomarker Study, Oskoui et al. 2007, Rudnik-Schoeneborn et al. 2009), the rates of ventilation-free survival ranged from 9% to 51% at 18 months of age. At 12 months of age, Rudnik-Schoeneborn et al. (2009) reported survival of approximately 15-40% depending on variables such as nutritional and respiratory support and respiratory infections. Of four patients with only a single copy of SMN2, the "life span did not exceed a few months." For 57 patients with two SMN2 copies, the median/mean age at death was 6.1/6.7 months (range 0.5-19 months). Five patients with three SMN2 copies were alive throughout the study up to 55 months. Oskoui et al. (2007) reported a survival range of 37% (birth years 1980-1994) to 79% (birth years 1995-2006) at 12 months in Type 1 SMA patients. Kolb et al. (2017, NeuroNEXT) reported a median age of 8 months at death in sixteen Type 1 SMA infants with 2 copies of SMN2 (95% confidence interval, 6, 17). Finkel et al. (2014) reported that the median age at reaching the combined endpoint of death or requiring at least 16 hours/day of ventilation support was 13.5 months (interquartile range 8.1–22.0 months) in 27 Type 1 SMA subjects.

Survival as an endpoint in Type 1 SMA can be difficult to interpret because it can be strongly affected by the type and quality of respiratory support provided to SMA infants, as shown in the figure below comparing survival with no respiratory support, non-invasive ventilation, and invasive ventilation/tracheostomy (Gregoretti et al., 2013). Therefore, it is important that the

Reference ID: 4646272

endpoint for this study specified that infants are alive without permanent ventilation. The statistical analysis plan for the Firefish study stated that "the date of permanent ventilation will be the first of the >21 days of non-invasive ventilation support or intubation required for the endpoint to be confirmed, or the date of tracheostomy… The pre-defined performance criteria for the proportion of infants who are alive without permanent ventilation at Month 12 will be 42% based on the results from the NeuroNEXT SMA infant biomarker study (Kolb et al., 2017)."
The Firefish Part 1 study result indicates reduced mortality and permanent ventilation in the risdiplam group compared to the natural history of Type 1 SMA.

Figure 8: Kaplan-Meier survival curves in type 1 SMA infants as a function of type of respiratory support. Patients with Tracheostomy/Invasive Mechanical Ventilation (top, n=42); Non-invasive bilevel ventilation and mechanically assisted coughing (middle; n=31); Untreated (bottom, n=121). Source: Gregoretti et al., 2013



Reference ID: 4646272

Respiratory:

5. Proportion of infants who achieve a reduction of at least 30 degrees in their phase angle from baseline, as measured by Respiratory Inductance Plethysmography (RP), at Month 12: 29% (5 of 17) of the higher dose Cohort 2 achieved a reduction of at least 30 degrees in their phase angle from baseline. There is limited data available to compare RP assessments in Type 1 SMA patients. In Finkel et al. (2014a), one Type 1 SMA infant had an assessment approximately 12 months after the first visit with an RP increase of approximately 140 degrees from baseline. Phase angle reduction would indicate improved respiration. *The Firefish Part 1 study results suggest a trend of RP phase angle reduction, although there is not an adequate natural history control group for comparison.*

6. Proportion of infants who do not require invasive or non-invasive respiratory support at Month 12: 18% (3 of 17) of the higher dose Cohort 2 did not require invasive or non-invasive respiratory support at Month 12. De Sanctis et al. (2018) reported that 12 of 20 (60%) Type 1 SMA infants did not require any respiratory support at 12 months of age. By 18 months of age, the number had fallen to 4 of 20 (20%) alive without the need for respiratory support. In the observational Type 1 SMA study of Mannaa et al. (2009), 3 of 13 (23%) Type 1 SMA patients did not require mechanical ventilation. Park et al. (2010) found that 6 of 14 (43%) Type 1 SMA patients did not require respiratory support. Sproule et al. (2012) found that 5 of 28 (18%) Type 1 SMA patients did not require respiratory support. These natural history studies show great variability in the rates of respiratory support which is likely due to variability in disease severity of the different clinical subtypes of Type 1 SMA (Type 1A most severe, Type 1C least severe, Mercuri et al., 2012). De Sanctis et al. (2018) divided their 20 Type 1 subjects into severe, typical, and moderate. All 8 severe patients had died by age 18 months. Of the typical patients, 3 of 8 (38%) did not require respiratory support at 18 months of age. Of the 4 moderate patients, 1 in 4 (25%) did not require respiratory support. *Because of the variability and limitations of the available longitudinal natural history data, no clear conclusion can be drawn about the clinical meaningfulness of the 18% rate of not requiring respiratory support at Month 12 in Cohort 2 of the Firefish Part 1 study.*

Nutrition:

7. Proportion of infants with the ability to feed orally at Month 12: 88% (15 of 17) of the higher dose Cohort 2 had the ability to feed orally at Month 12 and no patient had lost the ability to swallow at the time of analysis, as determined by parent interview and clinical evaluation. This result includes patients who were fed exclusively orally (15 patients overall) and those who were fed orally in combination with a feeding tube (3 patients overall) at Month 12. *Thirteen of 17 subjects (77%) in the higher dose Cohort 2*

Reference ID: 4646272

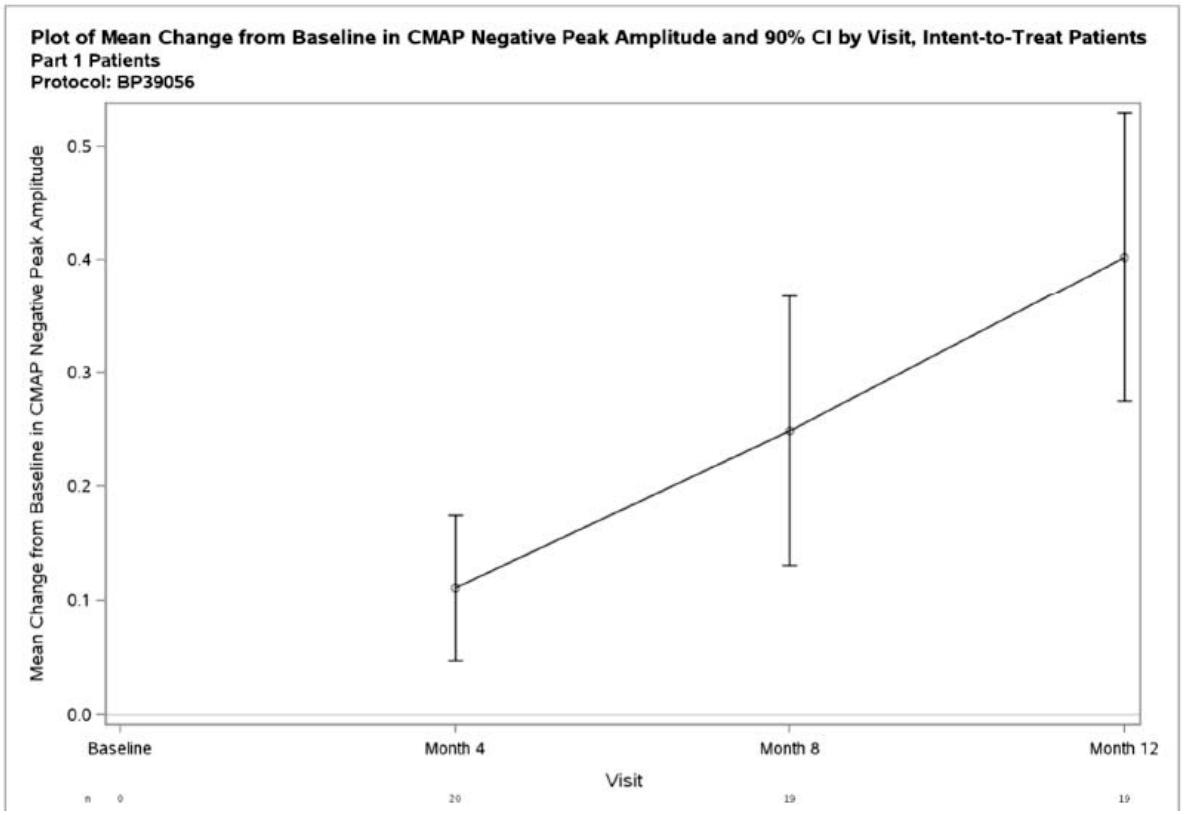
were fed exclusively orally without any tube feeding at Month 12. In contrast, De Sanctis et al. (2018) reported that 7 of 20 (35%) Type 1 SMA subjects did not require nutritional support at age 12 months. At 18 months of age the number had fallen to 5 of 20 (25%). Mannaa et al. (2009) reported that 0 of 13 (0%) Type 1 SMA patients did not require gastrostomy tube placement. Park et al. (2010) found that 6 of 14 (43%) Type 1 SMA patients did not require artificial feeding. Rudnik-Schoeneborn et al. 2009 reported that feeding and swallowing difficulties did not occur in 6 of 66 (9%) Type 1 SMA patients and were not treated with nasogastric tubes or gastrostomy in 15 of 66 (23%) patients. *This finding suggests a trend of improved oral feeding in the risdiplam-treated Type 1 SMA infants compared to the normal course of the disease.*

Muscle Electrophysiology

8. Proportion of patients with an increase of >=0.3mV from baseline in CMAP negative peak amplitude at Month 12: Maximum ulnar compound muscle action potential (CMAP) amplitude and area were obtained by recording from the abductor digiti minimi muscle following ulnar supramaximal nerve stimulation at the wrist. Thirteen of 17 (76%) of the higher dose Cohort 2 had an increase of at least 0.3 mV from baseline in the CMAP negative peak amplitude after 12 months of treatment. The following figure, copied from the submission, shows the mean change from baseline in CMAP amplitude for the Firefish Part 1 study.

Reference ID: 4646272

Figure 9: Mean Change from Baseline in CMAP Negative Peak Amplitude (ITT Population, Firefish Part 1 Patients)



Review of the medical literature supports the use of CMAP to monitor disease progression in type 1 SMA patients. In SMA, studies have shown that CMAP measurements correlate with disease severity, functional status, SMN2 copy number, and age (Swoboda et al. 2005; Lewelt et al 2010; Finkel 2013; Kolb et al. 2016, 2017). Swoboda et al. 2005 reported a rapid and sustained age-dependent decline in the CMAP amplitudes of SMA1 and SMA2 patients. The natural history study of 26 SMA infants and 27 healthy controls by Kolb et al. (2017) found that ulnar CMAP amplitude and area rapidly fell and were lower in the SMA cohort (excluding SMN2 >2 participants) than in controls at all time points and were often not detectable. SMA infants with SMN2 copy number =2 (Type 1) had a rapid decline in CMAP amplitude within 6 months of age, and patients with 2 SMN2 copies who were older than 6 months did not achieve amplitudes higher than 0.6 mV. In contrast, the healthy control group had an average peak CMAP of 6 mV at 6 months and 6.9 mV at 24 months. Note that the mean and median baseline CMAP amplitude in the Firefish Part 1 study was 0.2 mV.

Although the clinical significance of the observed CMAP improvements is unclear, the results indicate a positive trend of CMAP improvement which is not consistent with the

Reference ID: 4646272

natural history of Type 1 SMA.

Healthcare Utilization

9. Number of hospitalizations per patient-year at Month 12: Hospitalizations include all hospital admissions which spanned at least two days. There was an average of 1 hospitalization per patient-year at Month 12 in the higher dose Cohort 2.

10. Proportion of patients with no hospitalizations at Month 12: Eight of 17 (47%) subjects in the higher dose Cohort 2 had no hospitalizations at Month 12.

    The above two descriptive results are difficult to interpret without a placebo control group or adequate natural history comparison, may be subject to regional differences in care availability, and do not differentiate by severity of the conditions leading to hospitalization.

Patient/Caregiver Reported Outcomes

11. Infant/Toddler Quality of Life Questionnaire - Short Form 47-Item Version (ITQOL-SF47) patient overall health item score: median (range) change from baseline to Month 12: At baseline the median parent/caregiver-reported overall health score was 60.0 (range: 0.0-100.0; higher scores are better). There was no change in the median parent/caregiver-reported patient overall health score from baseline to Month 12. At the individual patient level, parent/caregiver reports of overall health showed that 5 patients improved from baseline to Month 12, 10 stayed the same, and 4 declined. The ITQOL-SF47 is a parent-completed measure that was developed to assess health status and health-related quality of life (HRQoL) of children between 2 months and 5 years of age as well as of the parents (Landgraf et al. 2013).

    This result is of unclear clinical significance and is difficult to interpret without a placebo control group or adequate historical control.

Data Quality and Integrity

The Roche Clinical Quality Assurance group or designee conducted audits and identified a critical audit finding in Study BP39056 (FIREFISH) at a site in Milano, Italy (313742) which was related to the absence of a well-defined process for international 'cross border' patients

Reference ID: 4646272

included in the trial, between the time of patient identification and prior to screening. The independent ethics committees were notified of the identified deficiencies and the 'cross border' patient process document and data privacy consent form was updated.

No data inconsistencies or discrepancies were found during the course of this review.

Due to the Covid-19 pandemic, OSI inspections of study sites cannot be conducted for this review.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The results of the open-label Firefish Part 1 study are generally consistent with the positive results of the placebo-controlled Sunfish Part 2 study.

7.1.1. Primary Endpoints

The primary efficacy endpoint for the placebo-controlled Part 2 of the Sunfish study in children and adults with Types 2 and 3 SMA was the change from baseline in the Motor Function Measure 32(MFM32) total score at Month 12. As discussed in Section 6.1.1, the MFM is acceptable as the primary endpoint. Part 2 of the Sunfish study found that there was a statistically significant difference (p=0.016) between the risdiplam group and the placebo group, with a mean increase in the score of 1.4 points in the risdiplam group and a mean decrease of -0.2 points in the placebo group on the 100-point MFM32 scale. Thirty-eight percent of the risdiplam group had an MFM32 score improvement of at least 3 points, compared to 24% of the placebo group (p=0.047). *The observed improvement of motor function as evidenced by the mean increase in MFM32 score in the risdiplam-treated group is not consistent with the natural history of SMA and supports the efficacy of risdiplam.*

The primary efficacy endpoint for the open-label Firefish study in infants with Type 1 SMA was the proportion of subjects sitting without support for 5 seconds (BSID-III) at Month 12. Type 1 SMA infants never achieve sitting without support. The finding that 41% of the higher dose Cohort 2 subjects achieved sitting without support *indicates a clinically significant improvement compared to the normal course of the disease. The results of the open-label Firefish Part 1 study are generally consistent with the positive results of the placebo-controlled Sunfish Part 2 study.*

Reference ID: 4646272

7.1.2. Secondary and Other Endpoints

Part 2 of the Sunfish study evaluated the difference between the study arms in the following key secondary efficacy outcome measures at 12 months, summarized in Table 12 in Section 6.1.2:

- Change from baseline in the Total score of the revised upper limb module (RULM) at Month 12.
- Change from baseline in Total score of Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 12.
- Change from baseline in Forced Vital Capacity (FVC) at Month 12.
- Change from baseline in the Total Score of the caregiver-reported SMA independence Scale (SMAIS) at Month 12.
- Proportion of patients rated by clinicians as no change or improved in the Clinical Global Impression of Change (CGI-C) Scale at Month 12.

The mean change from baseline in RULM total score, used to assess motor performance of the upper limb in SMA patients, had a statistically significant difference between the risdiplam group and the placebo group (p=0.047). There was a mean increase of 1.6 points in the risdiplam group and a mean increase of 0.02 in the placebo group out of a maximum possible score of 37.

There was no statistically significant difference between risdiplam and placebo groups in the change from baseline in HFMSE scale (treatment difference: 0.58; p=0.39) and FVC (treatment difference: -2.1%; p=0.39). Both the risdiplam and placebo groups had increases in HFMSE scores at 12 months (0.95 and 0.37, respectively; maximum possible score = 66), with a nominally greater increase in the risdiplam group. These small increases are not clinically significant. Both the risdiplam and placebo groups had mean worsening of forced vital capacity (FVC), with best percentage predicted value at month 12 change from baseline of -5.2% for the risdiplam and -3.1% for the placebo groups, respectively. Worsening respiratory function with recurrent infections is part of the natural history of Type 1 SMA.

The SMAIS showed nominal improvement (1.7 caregiver, 1.0 patient) in the risdiplam group and worsening (-0.9 caregiver, -0.4 patient) in the placebo group. The CGI-C had a nominal 7.5% difference favoring the risdiplam group.

In the Firefish open-label study of Type 1 SMA infants, 88% of the higher dose Cohort 2 achieved an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12, an improvement never seen in natural history studies of Type 1 SMA infants (Kolb et al. 2017; Darras 2016).

In the CHOP-INTEND and HINE-2 assessments, 53% of the higher dose Cohort 2 achieved head control, an improvement never seen in natural history studies of Type 1 SMA infants (De Sanctis

Reference ID: 4646272

et al. 2016). 77% of the higher dose Cohort 2 was classified as a motor milestone responder at Month 12, as defined in Section 6.2.1. In comparison, 0% of Type 1 SMA infants were motor milestone responders in the natural history study of De Sanctis et al. (2016).

Ninety-four percent of the higher dose Cohort 2 was alive without permanent ventilation at Month 12, and the same 94% was alive at Month 12. In five natural history studies of Type 1 SMA (CARNI-VAL Type I, PNCR Network, NeuroNEXT SMA Infant Biomarker Study, Oskoui et al. 2007, Rudnik-Schoeneborn et al. 2009), the rates of ventilation-free survival ranged from 9% to 51% at 18 months of age. At the time of the latest clinical cut-off date (3 March 2020) seventeen out of twenty-one (81%) patients were alive without permanent ventilation. All alive patients were older than 28.4 months of age and had at least 23.8 months of treatment with risdiplam. *The Firefish Part 1 study result indicates reduced mortality and permanent ventilation in the risdiplam group compared to the natural history of Type 1 SMA.* Twenty-nine percent of the higher dose Cohort 2 achieved a reduction of at least 30 degrees in their phase angle from baseline, as measured by Respiratory Inductance Plethysmography (RP), at Month 12. Phase angle reduction would indicate improved respiration. *The Firefish Part 1 study results suggest a trend of RP phase angle reduction, although there is not an adequate natural history control group for comparison.*

Eighteen percent of the higher dose Cohort 2 did not require invasive or non-invasive respiratory support at Month 12. *Because of the variability and limitations of the available longitudinal natural history data, no clear conclusion can be drawn about the clinical meaningfulness of this result.*

Eighty-eight percent of the higher dose Cohort 2 had the ability to feed orally at Month 12 and no patient had lost the ability to swallow at the time of analysis. *This finding suggests a trend of improved oral feeding in the risdiplam-treated Type 1 SMA infants compared to the normal course of the disease.*

Seventy-six percent of the higher dose Cohort 2 had an increase of at least 0.3 mV from baseline in the CMAP negative peak amplitude after 12 months of treatment. *Although the clinical significance of the observed CMAP improvements is unclear, the results indicate a positive trend of CMAP improvement which is not consistent with the natural history of Type 1 SMA.*

There was an average of 1 hospitalization per patient-year at Month 12 in the higher dose Cohort 2. Forty-seven percent of subjects in the higher dose Cohort 2 had no hospitalizations at Month 12. *These two descriptive results are difficult to interpret without a placebo control group or adequate natural history comparison, may be subject to regional differences in care availability, and do not differentiate by severity of the conditions leading to hospitalization.* There was no change in the median parent/caregiver-reported patient overall health score from baseline to Month 12 (Infant/Toddler Quality of Life Questionnaire - Short Form 47-Item

Reference ID: 4646272

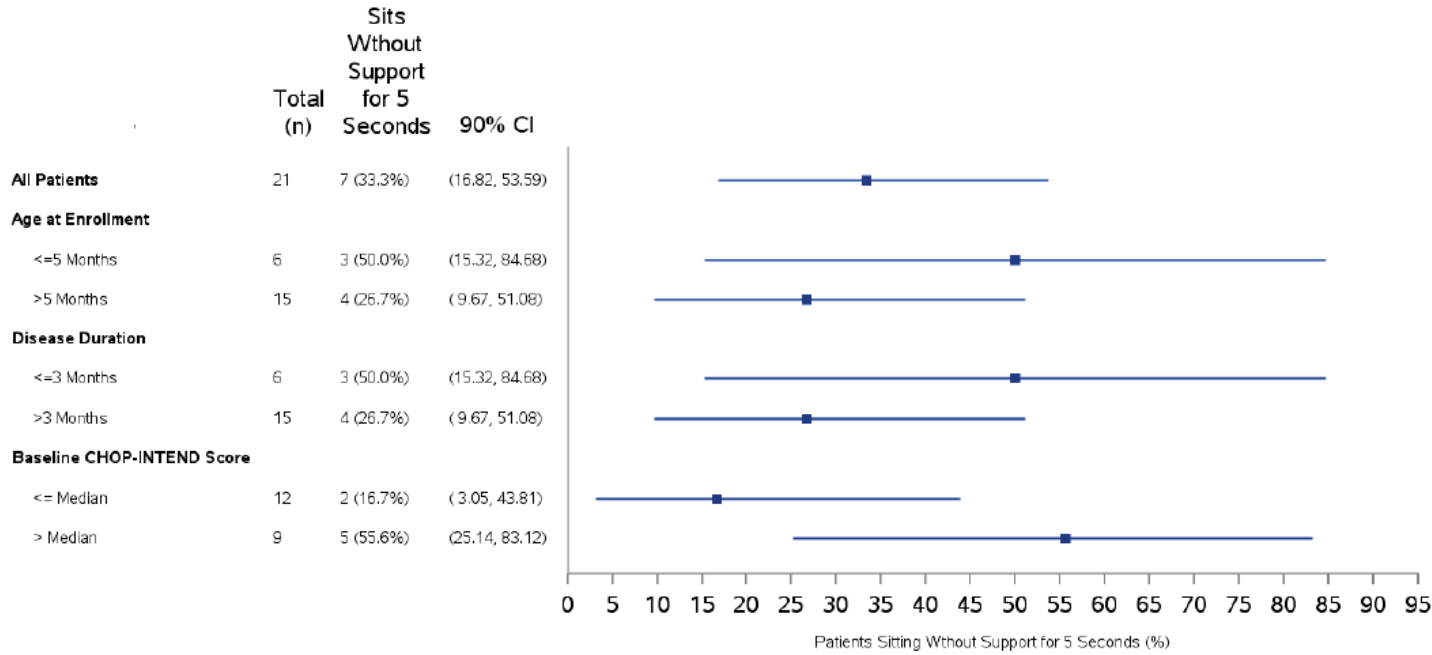
Version). *This result is of unclear clinical significance and is difficult to interpret without a placebo control group or adequate historical control.*

Overall, the results of the secondary and other endpoints across all studies support the positive efficacy results of the primary endpoints of both the Firefish and Sunfish studies.

7.1.3. Subpopulations

The following two figures, copied from the submission, show a trend for subjects in the Firefish study who were younger at enrollment to be more likely to sit without support for 5 seconds by Month 12 and to have higher CHOP-INTEND scores. A similar trend was observed in the Sunfish study for the primary endpoint, change from baseline in the MFM32 total score at month 12, and key secondary endpoint RULM, as seen in the following figures that were copied from the submission.

Figure 10: Forest Plot of Patients Sitting without Support for 5 seconds at Month 12 by Subgroup (ITT Patients; Part 1 Patients)



Reference ID: 4646272

Figure 11: Forest Plot of Patients who Achieved a CHOP-INTEND Score of 40 or Higher at Month 12 by Subgroup (ITT Population; Part 1 Patients)

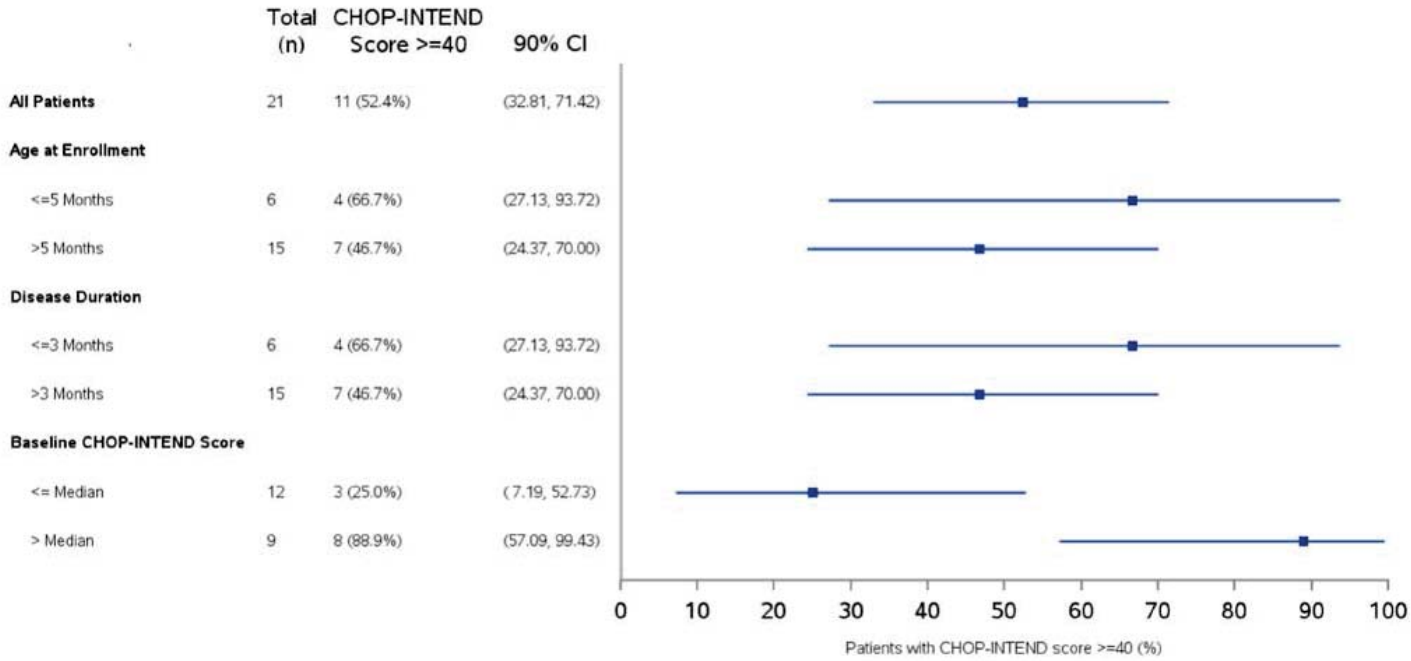
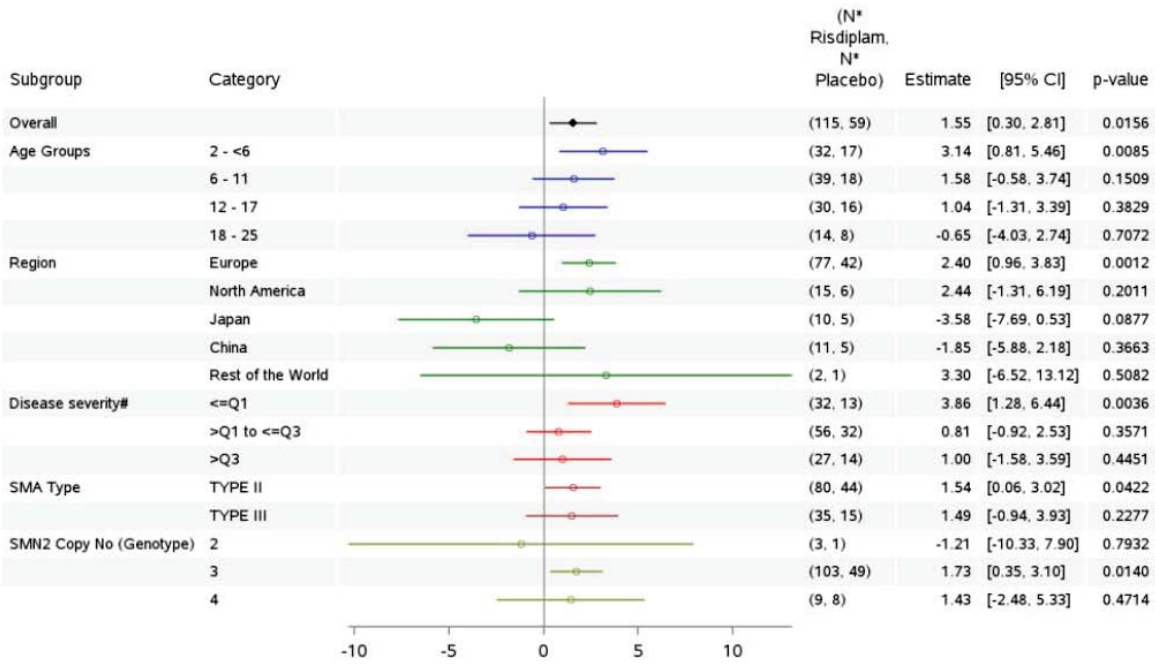
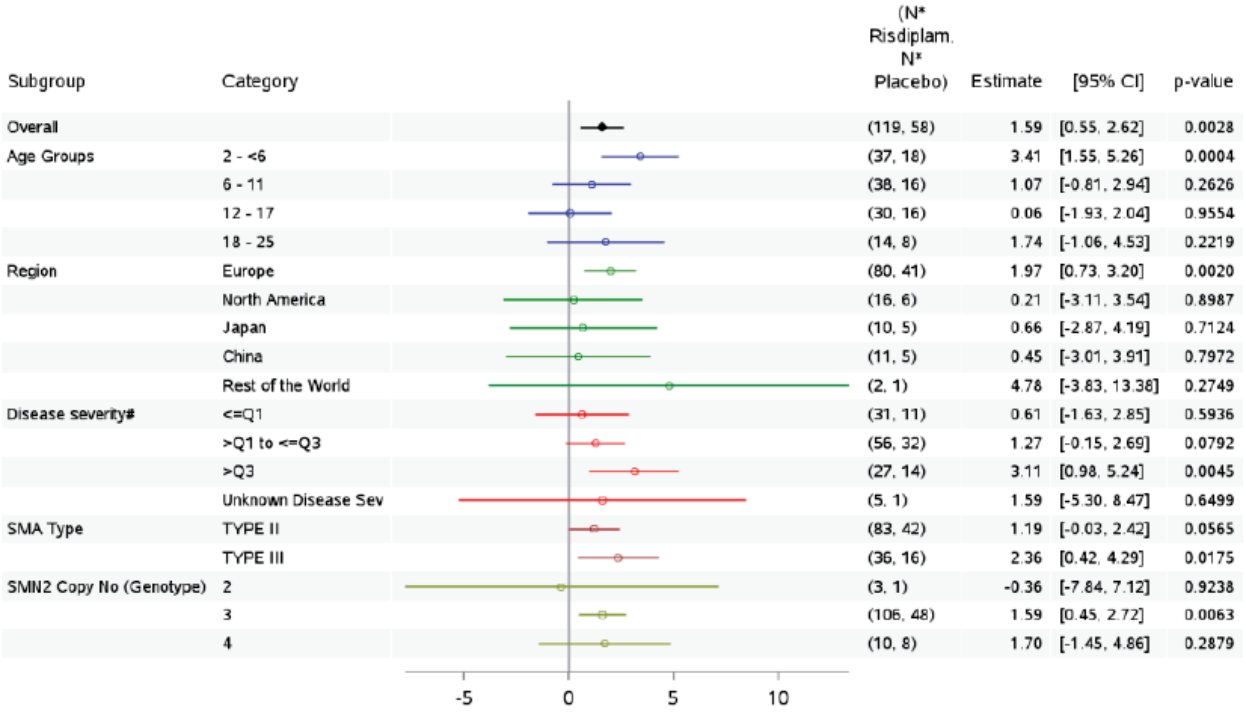


Figure 12: Forest Plot of MMRM Analysis on the Change from Baseline in MFM32 Total Score at Month 12 by Subgroups (Placebo Controlled Period) (Part 2; ITT Population). Source: Sunfish CSR



Reference ID: 4646272

Figure 13: Forest Plot of MMRM Analysis on the Change from Baseline in RULM Total Score at Month 12 by Subgroups (Placebo Controlled Period) (Part 2; ITT Population)



Subgroup	Category	(N* Risdiplam, N* Placebo)	Estimate	[95% CI]	p-value
Overall		(119, 58)	1.59	[0.55, 2.62]	0.0028
Age Groups	2 - <6	(37, 18)	3.41	[1.55, 5.26]	0.0004
	6 - 11	(38, 16)	1.07	[-0.81, 2.94]	0.2626
	12 - 17	(30, 16)	0.06	[-1.93, 2.04]	0.9554
	18 - 25	(14, 8)	1.74	[-1.06, 4.53]	0.2219
Region	Europe	(80, 41)	1.97	[0.73, 3.20]	0.0020
	North America	(16, 6)	0.21	[-3.11, 3.54]	0.8987
	Japan	(10, 5)	0.66	[-2.87, 4.19]	0.7124
	China	(11, 5)	0.45	[-3.01, 3.91]	0.7972
	Rest of the World	(2, 1)	4.78	[-3.83, 13.38]	0.2749
Disease severity#	<=Q1	(31, 11)	0.61	[-1.63, 2.85]	0.5936
	>Q1 to <=Q3	(56, 32)	1.27	[-0.15, 2.69]	0.0792
	>Q3	(27, 14)	3.11	[0.98, 5.24]	0.0045
	Unknown Disease Sev	(5, 1)	1.59	[-5.30, 8.47]	0.6499
SMA Type	TYPE II	(83, 42)	1.19	[-0.03, 2.42]	0.0565
	TYPE III	(36, 16)	2.36	[0.42, 4.29]	0.0175
SMN2 Copy No (Genotype)	2	(3, 1)	-0.36	[-7.84, 7.12]	0.9238
	3	(106, 48)	1.59	[0.45, 2.72]	0.0063
	4	(10, 8)	1.70	[-1.45, 4.86]	0.2879

In the applicant's MMRM analyses of the MFM32 total score at Month 12 by age group in the Sunfish Part 2 study, the greatest improvement from baseline with risdiplam compared to placebo was observed in the youngest patients aged 2 to <6 years (mean treatment difference [95% CI]: 3.14 [0.81, 5.46]), followed by those aged 6 to 11 years (mean treatment difference [95% CI]: 1.58 [-0.58, 3.74]), and those aged 12 to 17 (mean treatment difference [95% CI]: 1.04 [-1.31, 3.39]). No improvement from baseline in MFM32 was observed in the oldest patients aged 18 to 25 (mean treatment difference [95% CI]: -0.65 [-4.03, 2.74]). This diminution in effect as a function of age is also seen in the following scatter plot of the individual patient change from baseline in the MFM32 total score at Month 12 by age and SMA type (Type 2 or Type 3) and treatment (risdiplam or placebo), copied from the submission.

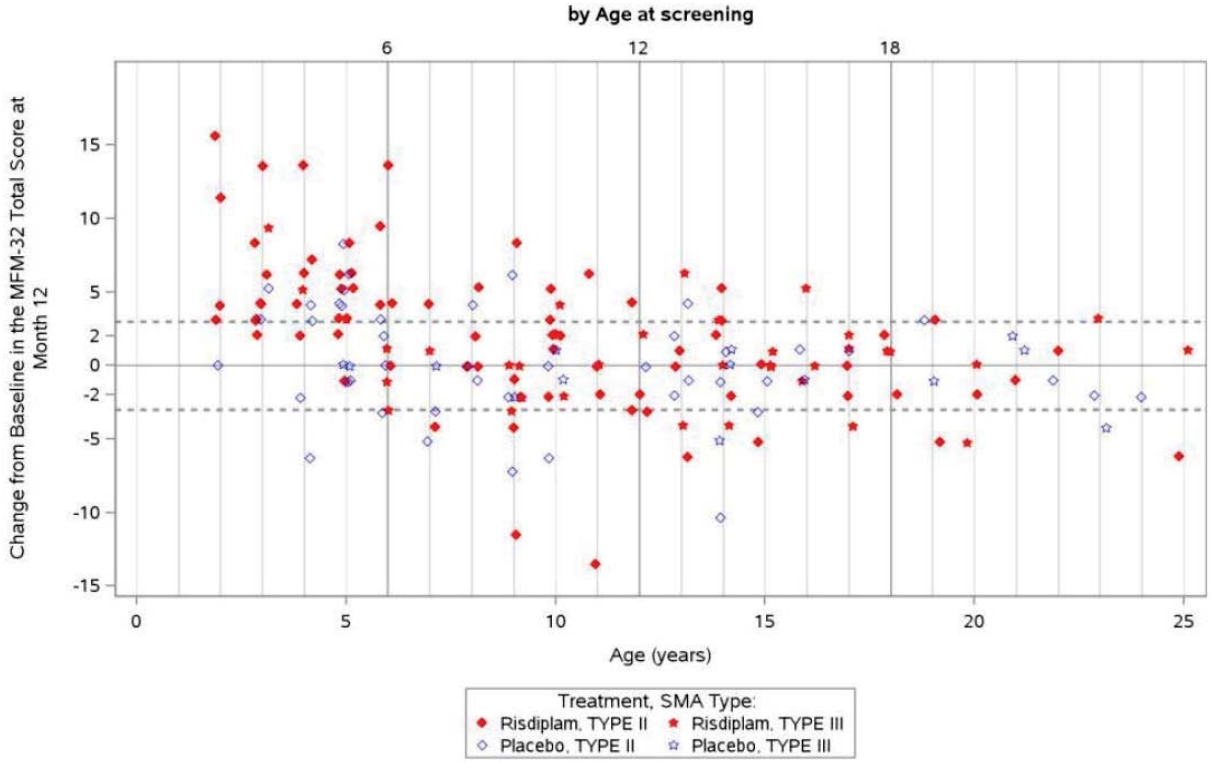
For the RULM a similar pattern was observed with the largest effect observed in the youngest age group (2 to <6 years) with a mean treatment difference [95% CI] of 3.41 [1.55, 5.26]. In contrast to the MFM32 result, the oldest age group (aged 18-25 years) did show a positive mean treatment difference [95% CI] of 1.74 [-1.06, 4.53], whereas no treatment difference in RULM was observed in patients aged 12 to 17 years (mean treatment difference [95% CI]: 0.06 [-1.93, 2.04]).

This observation of diminishing efficacy with increasing subject age is consistent with the mechanism of the disease, in which there is progressive motor neuronal loss over time. Once

Reference ID: 4646272

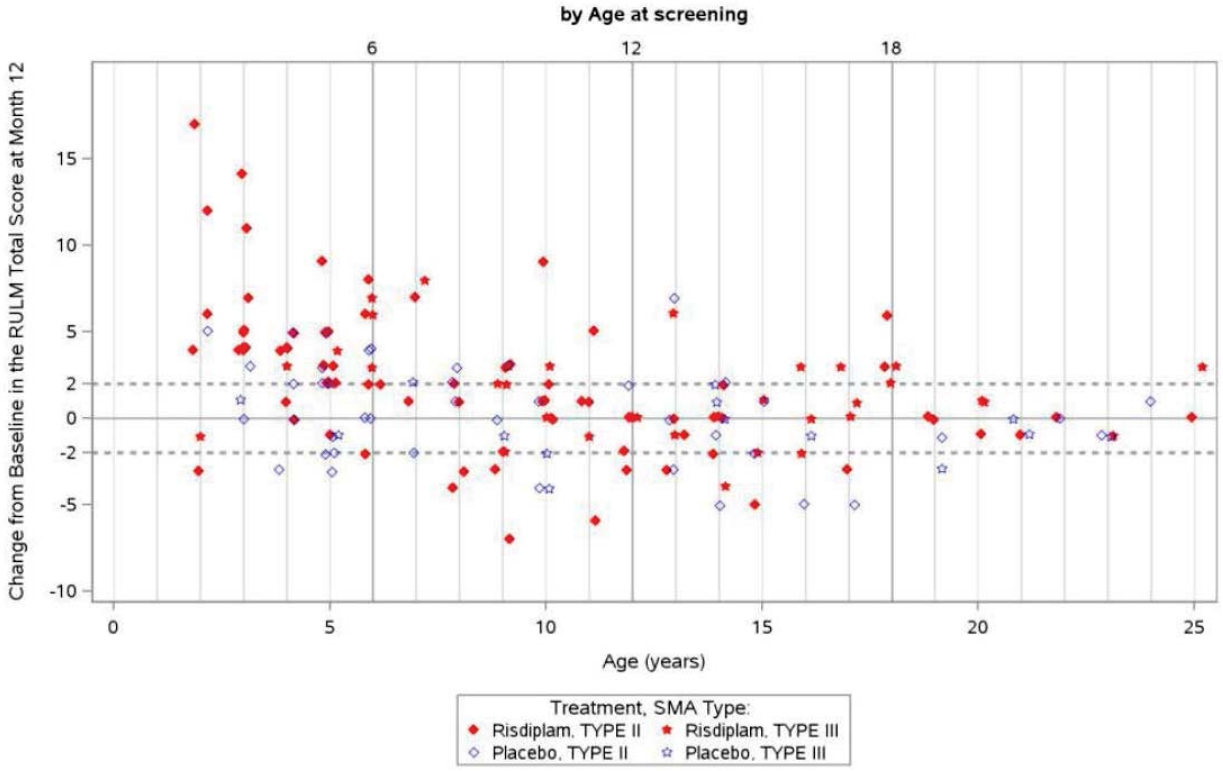
the motor neurons have been lost in older subjects, increasing SMN protein levels will not replace them. The effect of increasing SMN protein levels would only be expected to prevent the motor neuron loss if treatment is given before the motor neurons have died. Therefore, treatment should be initiated as early as possible.

Figure 14: Change from Baseline in the MFM32 Total Score at Month 12 by Ascending Values of Age (Years) and by SMA Type (Type 2 or Type 3) (Placebo Controlled Period) (Part 2; ITT Population)



Reference ID: 4646272

Figure 15: Change from Baseline in the RULM Total Score at Month12 by Ascending Values of Age (Years) and by SMA Type (Type 2 or Type 3) (Placebo Controlled Period) (Part 2; ITT Population)



7.1.4. Dose and Dose-Response

In the Sunfish Part 1 study doses ranged from 3 mg and 5 mg daily in patients aged 12-25 years-old and 0.02 mg/kg, 0.05 mg/kg and 0.25 mg/kg in patients aged 2-11 years old. A dose-related increase in SMN protein was observed across all dose levels and age groups upon treatment with risdiplam, with a median SMN protein increase of 151% (range 49% - 251%) versus baseline at 5 mg in the age group of 12-25 years, and a 96% (range 17% - 150%) increase at 0.25 mg/kg in the age group of 2-11 years.

Increasing SMN protein levels directly addresses the underlying SMN protein deficiency that causes SMA.

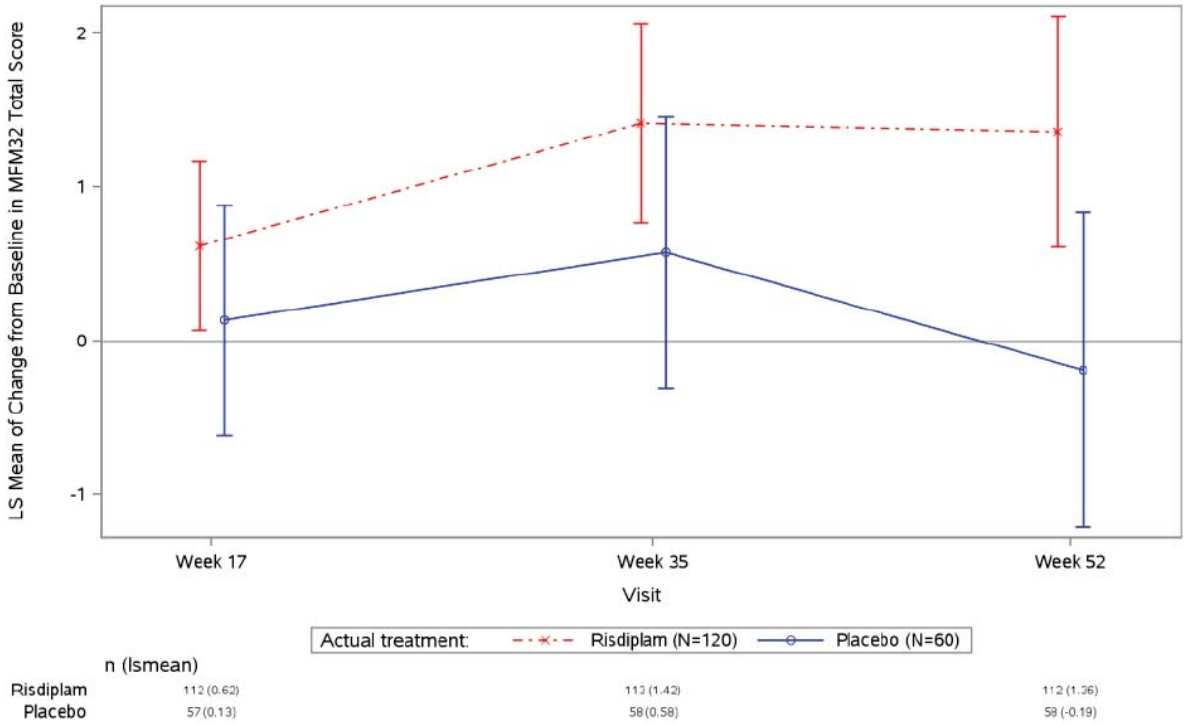
7.1.5. Onset, Duration, and Durability of Efficacy Effects

In the Sunfish Part 2 study the baseline MFM32 scores were 45 and 47 and the baseline RULM scores were 20 and 21 for the risdiplam and placebo groups, respectively. *A trend toward greater improvement in both scores in the risdiplam group was seen by the Week 17 assessment, which continued through to the Month 12 placebo-controlled period completion* as

Reference ID: 4646272

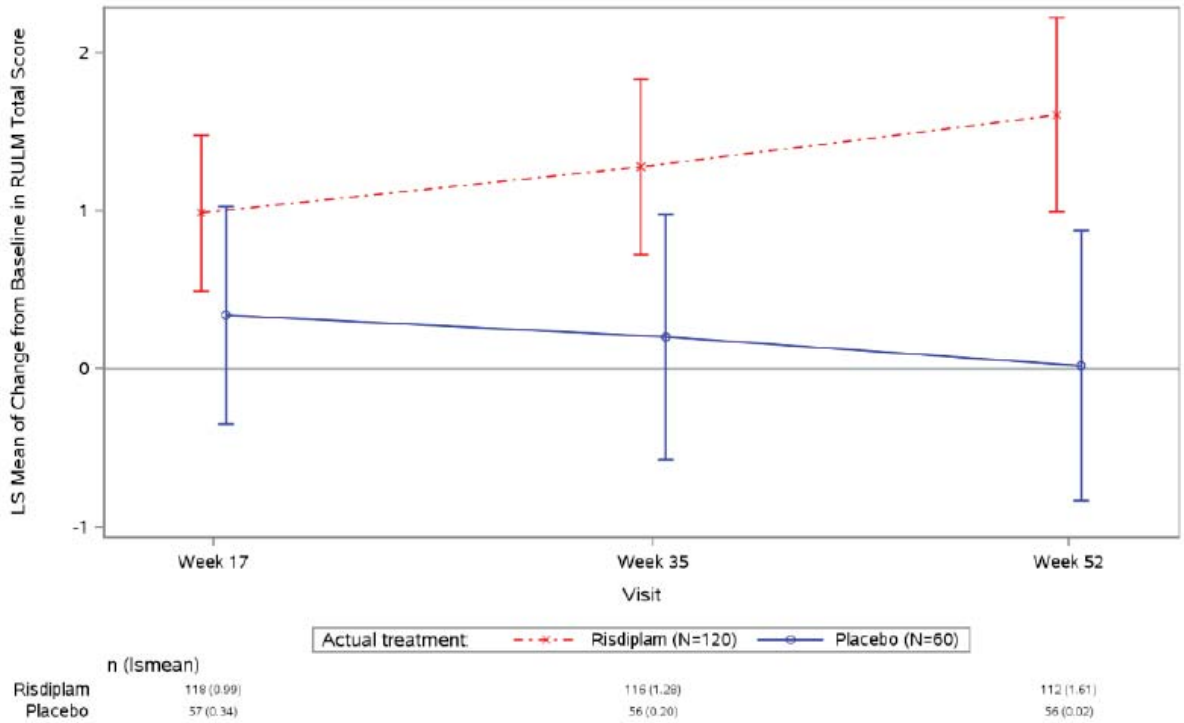
seen in the following figures, copied from the submission. The 3-year open-label extension phase of the Sunfish study is ongoing with no data for review at this time.

Figure 16: Least-Squares Mean Change from Baseline and 95% Confidence Interval in MFM32 Total Score at Each Timepoint up to Month 12 (Placebo-Controlled Period) (Sunfish Part 2; ITT Population)



Reference ID: 4646272

Figure 17: Least-Squares Mean Change from Baseline and 95% Confidence Interval on RULM Total Score at Each Timepoint up to Month 12 (Placebo Controlled Period) (Part 2; ITT Population)



7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The oral administration route of risdiplam may be of benefit to SMA patients who are not able to receive, tolerate, or adequately benefit from the two currently approved drugs for SMA, nusinersen and onasemnogene abeparvovec (Zolgensma). Nusinersen must be re-administered intrathecally every 4 months but is difficult to use in patients with poor spinal access or significant anxiety about repeated spinal injection. Recurrent lumbar punctures also carry risks of infection, hemorrhage, and pain. The duration of benefit from Zolgensma has not yet been established and it cannot be administered more than a single time because of AAV antibody development. Further, the proportion of patients with pre-existing AAV antibodies preventing Zolgensma treatment increases from ~2% in infants up to 30% in adults.

7.3. Integrated Assessment of Effectiveness

The placebo-controlled Sunfish Part 2 study is an adequate and well-controlled efficacy

Reference ID: 4646272

study that can support approval of risdiplam for the treatment of children and adults with Types 2 and 3 SMA. It is a well-designed multicenter study that has provided reliable and statistically significant (p=0.016) evidence of an important clinical benefit, motor function improvement, that is inconsistent with the natural course of the disease. The observed improvement of motor function as evidenced by the mean increase in MFM32 score in the risdiplam-treated group (1.4) compared to a mean decrease (-0.2) in the placebo group is not consistent with the natural history of Types 2 and 3 SMA and supports the efficacy of risdiplam. Upper limb function, measured by the mean RULM score change from baseline at Month 12, showed a 1.6 point improvement in the risdiplam-treated group compared to no change in the placebo group (p=0.047). Patient, parent/caregiver, and clinician-reported outcome measures also gave nominal support for the efficacy of risdiplam as measured by the SMAIS and CGI-C scales (SMAIS: +1.7 caregiver-reported for risdiplam; -0.9 caregiver-reported for placebo; +1 patient-reported for risdiplam; -0.4 patient-reported for placebo; CGI-C: 48% for risdiplam; 40% for placebo).

Evidence of efficacy in infants with Type 1 SMA is provided by the Firefish study, an open-label, historically controlled, multi-center study that showed improvements in multiple clinical functional measures compared to the natural history of SMA, including motor function and developmental milestones as well as survival and ventilation-free survival. The finding that 41% of the higher dose Cohort 2 subjects in the open-label Firefish study achieved sitting without support indicates a clinically significant improvement compared to the normal course of Type 1 SMA, in which no patients would be expected to achieve sitting without support.

Additional evidence of motor milestone improvement compared to SMA natural history was found with the CHOP-INTEND and HINE-2 assessments. 88% of the higher dose Cohort 2 achieved an increase of at least 4 points in their CHOP-INTEND score from baseline at Month 12 compared to 0% in the natural history studies of Darras (2016) and Kolb et al. (2017). 53% of the higher dose Cohort 2 achieved head control as measured by the CHOP-INTEND and HINE-2, compared to 39% who achieved only partial head control in in the natural history study of De Sanctis et al. (2016). 77% of the higher dose Cohort 2 was classified as a HINE-2 motor milestone responder at Month 12 compared to 0% in the natural history study of De Sanctis et al. (2016).

The Firefish Part 1 study result provides evidence of reduced mortality and permanent ventilation in the risdiplam group compared to the natural history of Type 1 SMA.
In five natural history studies of Type 1 SMA (CARNI-VAL Type I, PNCR Network, NeuroNEXT SMA Infant Biomarker Study, Oskoui et al. 2007, Rudnik-Schoeneborn et al. 2009), the rates of ventilation-free survival ranged from 9% to 51% at 18 months of age. In the Firefish Part 1 study 94% (16 of 17) of the higher dose Cohort 2 was alive without permanent ventilation at Month 12. At the time of the latest clinical cut-off date seventeen out of twenty-one (81%) patients were alive without permanent ventilation. All alive patients were older than 28 months of age and had at least 24 months of treatment with risdiplam.

Reference ID: 4646272

Because SMA is a progressive disease with worsening motor neuron loss over time, it is important to begin treatment as soon after diagnosis as possible. This conclusion was supported by the Sunfish Part 2 study results, in which the best treatment effect (MFM32, RULM, and CHOP-INTEND score changes) was found in the youngest subjects.

The underlying cause of SMA, a deficiency of survival motor neuron (SMN) protein, is common to patients with all types of SMA (with increasing amounts of SMN corresponding to less severe disease). The two clinical studies, Sunfish in Types 2 and 3 SMA and Firefish in Type 1 SMA, are therefore complementary and support a conclusion of efficacy for SMA in general.

8. Review of Safety

8.1. Safety Review Approach

Safety was assessed by evaluating the results from the placebo-controlled Study BP39055 (SUNFISH) in pediatric and adult patients with later-onset SMA and the open-label Study BP39056 (FIREFISH) in pediatric patients with infantile-onset SMA. Additional supportive safety data was provided from the open-label Study BP39054 (JEWELFISH) in infantile-onset and later-onset SMA patients who have previously participated in clinical trials other than risdiplam trials and/or received currently approved therapies for SMA.

The available narratives for deaths, serious adverse events, laboratory studies, and vital signs were reviewed. Reviewer analyses were conducted on the submitted datasets for the Sunfish and Firefish trials, including adverse events, serious adverse events, deaths, and laboratory value assessments. The adverse event dataset from the placebo-controlled Sunfish Part 2 study was used for calculating the frequency of adverse events. The medical scientific literature was searched where appropriate for additional information. The Jewelfish study had a small population of only twelve subjects, yielded correspondingly limited safety information, and therefore formed only a small part of the safety review.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The size and subject duration of exposure for the risdiplam safety population are described in

Reference ID: 4646272

the following tables. A total of 229 patients with SMA have been exposed to risdiplam.

Table 22: Risdiplam Safety Population, Size, and Denominators. Reviewer's assessment

Safety Database for Risdiplam Individuals in this development program N= 368 (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	Risdiplam (n= 279)	Placebo (n= 89)
Healthy volunteers, Single Dose (Studies BP29840, NP39625, BP39122)	50	13
Controlled trials conducted in SMA patients (Sunfish Study)	155	76
All other trials conducted for risdiplam in SMA patients (Firefish and Jewelfish Studies)	74	0

Table 23: Exposure to Risdiplam. Note that 56 patients received the proposed labelling dose for up to 16 months (0.2 mg/kg for infants <2 years old, 0.25 mg/kg for infants and children >=2 years and <20 kg bodyweight, 5 mg for ≥20 kg bodyweight)

Number of Patients Exposed to Risdiplam:				
<=6 months	>6 to <=12 months	>12 months	>=18 months	>= 24 months
18	107	77	45	10

Given the prevalence of the disease, the exposure is deemed adequate to support a reasonable assessment of safety.

8.2.2. Relevant Characteristics of the Safety Population:

The demographic and baseline characteristics for the placebo-controlled population of Type 2 and 3 SMA patients of the Sunfish study are summarized in Section 6.1.2.

Parts 1 and 2 of the open-label Firefish study enrolled 62 patients with Type 1 (infantile-onset) SMA. Thirty-seven patients (60%) were female. At screening, the median age of all patients was

Reference ID: 4646272

146 days (range: 44-203 days). 63% of patients were white/Caucasian and 29% were Asian. 34% of patients were from Italy, 18% from China, 13% from France, and 6% from the United States.

8.2.3. Adequacy of the safety database:

For chronically administered drugs, the International Conference on Harmonisation (ICH) E-1 guidelines recommend having studied drug exposure in 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures must occur at the dose or dose range believed to be efficacious.

When compared to the ICH guidelines, the overall number of exposed subjects is less than the usual recommendation. However, because SMA is a rare disease, there is no specific minimum number of patients that should be studied to establish clinical safety. The number of subjects exposed ≥ 1 year exceeds the ICH recommendation.

Because SMA is a rare and often terminal illness, the overall subject exposure in the clinical development program is adequate.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The NDA submission was well-organized. The submission quality with respect to the applicant's clinical safety assessments was acceptable.

8.3.2. Categorization of Adverse Events

The applicant's process for recording AEs was appropriate. The applicant categorized adverse events as mild, moderate, or severe. A subject that experienced the same event more than once was counted only once and at the highest severity for that event. Adverse events were coded to MedDRA 21.1. The FDA analysis reviewed AE coding to assess the accuracy of the translation from the verbatim to the preferred terms. This coding was accurate and no clinically significant changes were needed.

8.3.3. Routine Clinical Tests

The safety assessment schedule for the Sunfish study is summarized in Section 6.1.1: Sunfish Study Part 2 Schedule of Key Assessments. The safety assessment schedule for the Firefish

Reference ID: 4646272

study is summarized in Section 6.2.1: Firefish Study Part 1 Schedule of Key Assessments. The clinical testing schedule was adequate. Safety testing included physical examination, neurological examination, vital signs, ECG, hematology, blood chemistry, ophthalmological exam, visual testing, intraocular pressure, slit lamp and fundus examination, SD-OCT, and color fundus photography. The schedules of ophthalmology assessments for the Sunfish and Firefish studies are summarized in Sections 6.1.1 and 6.2.1, respectively.

8.4. Safety Results

The following table summarizes the high-level safety results of the placebo-controlled Sunfish Part 2 study, which were confirmed from the submitted data. Additional details are presented in the following sections. Note that the percentages of AEs and SAEs were similar in both the risdiplam and placebo groups. There were no withdrawals caused by AEs or deaths in either group.

Table 24: Placebo-controlled Experience: Overview of Adverse Events

Category	Risdiplam n (%) out of N= 148	Placebo n (%) out of N=77
At Least 1 Adverse Event (AE)	111 (93%)	55 (92%)
At Least 1 Serious Adverse Event (SAE)	24 (20%)	11 (18%)
At Least 1 AE Leading to dose modification or interruption	8 (7%)	2 (3%)
At Least 1 AE Leading to Study Withdrawal	0	0
Death	0	0

Deaths

There have been no deaths in the Sunfish or Jewelfish studies.

Six deaths (~10% of the study population) were reported overall in the Firefish study (3 deaths in Part 1 and 3 deaths in Part 2), all in patients with Type 1 SMA who died of respiratory complications as summarized in the following table.

Note that death from complications of respiratory failure is commonly observed in infantile onset (Type 1) SMA. It is unlikely that these deaths were caused by the investigational drug.

Reference ID: 4646272

Table 25: Deaths in the Open-Label Firefish Study. All subjects received risdiplam.

Patient Number	Adverse Event Term	Study Day	Days since last risdiplam dose
(b) (6)	respiratory infection (viral)	21	3
	cardiac arrest and respiratory failure	236	1
	respiratory tract infection	387	1
	acute respiratory failure	68	1
	pneumonia	51	1
	pneumonia	79	1

8.4.2. Serious Adverse Events

Controlled Trials:

Serious adverse events that occurred more frequently in the risdiplam group than in placebo are shown in the following table, generated from the submitted data. Pneumonia, bacteremia, and influenza occurred at least 1% more frequently in the risdiplam group than the placebo group. *This difference is difficult to interpret because of the small numbers of subjects affected and the common occurrence of respiratory infections in SMA patients with disease-related weakening of respiratory muscles. The risdiplam-treated subjects already had compromised respiratory function at baseline (requiring BIPAP or cough assistance) which increased their risk of respiratory infections, as shown in the table below. One subject* (b) (6) *was also treated with corticosteroids, which can increase infection risk. Analysis of the system organ class "Infections and infestations" for SAEs found 14% in the risdiplam arm and 12% in the placebo arm. For AEs, the rates for Infections and infestations were 75% for the risdiplam arm and 80% for the placebo arm. Additionally, analysis of the High Level Term (HLT) of AEs for "lower respiratory tract and lung infections" was 17% for risdiplam and 22% for placebo. Overall, these results do not suggest a clinically significant difference in infection rates between the risdiplam and placebo arms of the Sunfish study.*

Reference ID: 4646272

Table 26: Serious Adverse Events in the Controlled Sunfish Part 2 Study that Occurred More Frequently in the Risdiplam (RO7034067) group.

	PART 2 - RO7034067 (N = 120)			PART 2 - PLACEBO (N = 60)		
PT	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Pneumonia	11	9	7.5	1	1	1.67
Bacteraemia	2	2	1.67	0	0	0
Influenza	2	2	1.67	0	0	0
Pyrexia	2	2	1.67	0	0	0
Aspiration	1	1	0.83	0	0	0
Asthma	1	1	0.83	0	0	0
Atelectasis	1	1	0.83	0	0	0
Bronchitis	1	1	0.83	0	0	0
Constipation	1	1	0.83	0	0	0
Fall	1	1	0.83	0	0	0
Febrile convulsion	1	1	0.83	0	0	0
Hydronephrosis	1	1	0.83	0	0	0
Laryngitis	1	1	0.83	0	0	0
Lower respiratory tract infection viral	1	1	0.83	0	0	0
Lung operation	1	1	0.83	0	0	0
Medical device pain	1	1	0.83	0	0	0
Pneumonia aspiration	1	1	0.83	0	0	0
Pneumonia bacterial	1	1	0.83	0	0	0
Upper respiratory tract infection	1	1	0.83	0	0	0
Viral upper respiratory tract infection	1	1	0.83	0	0	0

In the risdiplam arm, the nine patients reported with serious pneumonia were aged 2-15 years. Six patients were female and three were male. The intensity of pneumonia was reported as severe (Grade 3) in 5 out of 9 patients. In 2 patients the intensity was Grade 2 (moderate) and in 2 patients Grade 4 (life-threatening). The events of serious pneumonia resolved despite ongoing treatment with risdiplam after 4-21 days. One 5-year old female patient was reported with Grade 2 serious pneumonia in the placebo arm during the double-blind period.

The following table was generated from the pneumonia SAE narratives.

Table 27: Serious Respiratory Adverse Events in the Sunfish Part 2 Study

Subject number	Serious Adverse Event	Onset study day	Comments
(b) (6)	Pneumonia	Onset on day 307. Last risdiplam dose on day 306. Grade 3 and hospitalized. Resolved by day 325.	4 y.o. male, risdiplam 5mg daily. Needed cough assist daily prior to screening. No change in risdiplam dose. Also had AEs of respiratory tract infection on days 119 & 143
(b) (6)	Pneumonia aspiration	333. No change in	5 y.o. female,

Reference ID: 4646272

Subject number	Serious Adverse Event	Onset study day	Comments
	(after vomiting and excess sputum production)	risdiplam dose.	risdiplam 0.25 mg/kg daily. Needed BIPAP support prior to screening. Prior history of influenza & pneumonia adenoviral
(b) (6)	Pneumonia, asthma, pneumonia mycoplasmal	Pneumonia day 105. Last risdiplam dose on day 104. No change in risdiplam dose. Asthma day 232. Pneumonia mycoplasamal day 412	3 y.o. male, risdiplam 0.25 mg/kg daily. The subject also had AEs of upper respiratory tract infections on days 128 and 339.
(b) (6)	Pneumonia	156. Last risdiplam dose on day 155. No change in risdiplam dose. Resolved on day 168.	3 y.o. female. Needed BIPAP support prior to screening.
(b) (6)	Pneumonia bacterial	171. Last risdiplam dose on day 170. No change in risdiplam dose.	11 y.o. female, risdiplam 5mg daily. Needed BIPAP support prior to screening. The subject also had AE of upper respiratory tract infection on day 163.
(b) (6)	Pneumonia	179. Last risdiplam dose on day 179. No change in risdiplam dose.	6 y.o. female, risdiplam 5mg daily. Needed cough assist daily prior to screening. Also treated with corticosteroids. The subject also had AE of upper respiratory tract infection on day 109.
(b) (6)	Pneumonia (2 events)	Days 212 and 414, with most recent risdiplam doses on same days. No	4 y.o. female, risdiplam 0.25 mg/kg daily. Needed cough assist prior to

Reference ID: 4646272

Subject number	Serious Adverse Event	Onset study day	Comments
		change in risdiplam dose.	screening.
(b) (6)	Pneumonia, Gastrointestinal infection	Pneumonia Day 195, same day as placebo. GI infection day 381, same day as risdiplam dose.	9 y.o. female, placebo, then open-label risdiplam 5mg daily. Needed BIPAP support prior to screening.
(b) (6)	Pneumonia, Laryngitis	Pneumonia day 295, same day as risdiplam. Resolved day 300. Laryngitis day 371.	2 y.o. male, risdiplam 0.25 mg/kg, No change in risdiplam dose. The subject also had AEs of respiratory tract infection on days 139 and 166.
(b) (6)	Pneumonia, Pyrexia	Pneumonia day 160 after risdiplam on day 159. Pyrexia on day 168. Risdiplam interrupted and restarted on day 171.	15 y.o. female, risdiplam 5mg daily. Needed BIPAP and cough support prior to screening. The subject also had AE of respiratory tract infection on day 63.
(b) (6)	Pneumonia, nephrolithiasis, hydronephrosis	Pneumonia day 260, nephrolithiasis & hydronephrosis day 180	14 y.o. female, risdiplam 5 mg daily. Needed BIPAP and cough support prior to screening. No change in risdiplam dose.
(b) (6)	Pneumonia (2 events), viral upper respiratory tract infection, influenza	Pneumonia study day 53 and 91, same day as last risdiplam dose. viral upper respiratory tract infection day 169; influenza day 193	5 y.o. female, risdiplam 0.25 mg/kg daily. Needed BIPAP and cough support prior to screening. No change in risdiplam dose. The subject also had AEs of upper respiratory tract infection on days 278 and 335.
(b) (6)	Pneumonia (2 events), atelectasis, lung	Pneumonia days 47 & 114, atelectasis, lung	6 y.o. male, risdiplam 5mg daily. Needed

Reference ID: 4646272

Subject number	Serious Adverse Event	Onset study day	Comments
	operation (for lobar collapse), bacteremia	operation day 329, bacteremia	BIPAP and cough support prior to screening. The subject also had AEs of upper respiratory tract infection on days 7 and 301.

Four serious adverse events in 4 patients (3.3%) in the risdiplam arm (gastroenteritis, constipation, pyrexia, aspiration) and 2 events in 2 patients (3.3%) in the placebo arm (sleep apnoea syndrome, appendicitis) led to dose interruption.

Uncontrolled Trials:
In the Firefish study (Parts 1 and 2 combined), 16% of subjects experienced an SAE of pneumonia and 5% had acute respiratory failure, as shown in the following table generated from the submitted data. Note that all subjects received risdiplam. *This finding is consistent with the natural history of infantile onset SMA, in which respiratory infections and respiratory failure frequently occur because of disease-related weakening of respiratory muscles.*

Table 28: Serious Treatment-emergent Adverse Events from the Open-label Firefish Study that Occurred in More Than One Subject.

PT	Events	Number of subjects	Proportion (%)
Pneumonia	12	10	16.1
Acute respiratory failure	3	3	4.8
Respiratory distress	3	3	4.8
Respiratory failure	3	3	4.8
Respiratory tract infection viral	3	3	4.8
Cardiac arrest	2	2	3.2
Respiratory tract infection	2	2	3.2

There have been no serious adverse events in the Jewelfish study.

Reference ID: 4646272

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In the Sunfish study there were no withdrawals due to adverse events. A total of 117 patients (97.5%) in the risdiplam arm and 59 patients (98.3%) in the placebo arm completed the placebo-controlled period. Three patients (2.5%) in the risdiplam arm and 1 patient (1.7%) in the placebo arm discontinued study treatment in order to switch to other treatment, specified as nusinersen in 3 patients, and not further specified in 1 patient. SAEs leading to dose interruption occurred in 3.3% of patients in both the risdiplam and placebo arms.

No subjects withdrew from the Firefish study because of adverse events, not including the deaths described in Section 8.4.1. No subjects have withdrawn from the Jewelfish study.

8.4.4. Significant Adverse Events

Adverse events that occurred during the studies were assessed by the Investigators for severity (mild, moderate, or severe).

In the risdiplam arm of the Sunfish study, nine patients reported with serious pneumonia. The intensity of pneumonia was reported as severe (Grade 3) in 5 out of 9 patients, in 2 patients intensity was Grade 2 (moderate) and in 2 patients Grade 4 (life-threatening). Events of serious pneumonia resolved despite ongoing treatment with risdiplam after 4-21 days. One patient was reported with Grade 2 serious pneumonia in the placebo arm during the double-blind period. (See discussion of pneumonias and respiratory tract infection under Section 8.4.2).

Pyrexia occurred in 21% of the risdiplam arm and 17% of the placebo arm. All events of pyrexia resolved and were mild or moderate in intensity.

More patients in the risdiplam arm were reported with an AE coding to the SOC Skin and subcutaneous tissue disorders (53 AEs in 37 patients [30.8%] receiving risdiplam and 7 AEs in 7 patients [11.7%] receiving placebo). AEs reported in more than 1 patient from this SOC in the risdiplam arm were rash (9 patients), eczema (5 patients), erythema (3 patients), rash maculo-papular (3 patients) and (in 2 patients each) acne, dermatitis allergic, dry skin, and rash erythematous. In the placebo arm, all AEs were single occurrences. All events were mild to moderate in intensity and none of the events were reported as an SAE or led to a change in study medication.

In the Firefish open-label study 44% of subjects had Grade 3-5 adverse events. One patient was reported with moderate iron deficiency on Day 55 and had low hemoglobin on Days 14 and 55 at 99 and 98 g/L, respectively (normal range: 105-135 g/L). Reticulocytes were within normal ranges throughout. The event resolved with iron supplementation after 42 days.

Reference ID: 4646272

8.4.5. Adverse Events and Adverse Reactions

Results of the FDA MedDRA-Based Adverse Event Diagnostics (MAED) analysis of AEs in the Sunfish Part 2 placebo-controlled study are shown in the following table, which shows the most common AEs that occurred in at least 5% of patients and were more frequent in the risdiplam group than in the placebo group. The largest differences between risdiplam and placebo were diarrhea (~7% higher in risdiplam), rash (~6% higher in risdiplam), and arthralgia (5% higher in risdiplam).

Table 29: Adverse Events in the Controlled Safety Database: MAED Analysis of Sunfish Part 2 Study

	PART 2 - Risdiplam (N = 120)			*PART 2 - PLACEBO (N = 60)*		
PT	*Events*	*Number of subjects*	*Proportion (%)*	*Events*	*Number of subjects*	*Proportion (%)*
Upper respiratory tract infection	55	38	31.7	26	18	30.0
Pyrexia	43	25	20.8	20	10	16.7
Headache	88	24	20.0	23	10	16.7
Diarrhoea	27	20	16.7	6	6	10.0
Nausea	13	11	9.2	4	3	5.0
Constipation	11	10	8.3	3	3	5.0
Pneumonia	16	10	8.3	4	4	6.7
Rash	11	9	7.5	1	1	1.7
Arthralgia	9	6	5.0	0	0	0.0
Pharyngitis	8	6	5.0	3	3	5.0

Analysis using the custom Office of Drug Evaluation 1 (ODE-1) MedDRA Query yielded the following grouping of adverse events.

Table 30: Adverse Events in the Controlled Safety Database that Occurred More Frequently in the Risdiplam Group: ODE-1 MedDRA Query for Sunfish Part 2 study. Terms highlighted in red occurred at least 5% more frequently in the Risdiplam group.

Grouped Adverse Events	Placebo (N=60)	Risdiplam (N=120)	Placebo (%)	Risdiplam (%)	Risdiplam-Placebo (%)
rash, eruption, dermatitis	1	15	2	13	11
fever	10	26	17	22	5
Urinary Tract Infection (UTI)	0	6	0	5	5
dermatitis	0	6	0	5	5
arthralgia, arthrosis	0	6	0	5	5
headache	10	25	17	21	4
pneumonia	4	12	7	10	3
infection, bacterial	1	6	2	5	3
eczema	1	6	2	5	3
diarrhea, gastroenteritis	12	28	20	23	3
constipation	3	10	5	8	3
URI, cold, rhinitis, upper resp tract infection, flu-like illness	37	76	62	63	2
abdominal pain, distension, bloating	10	21	17	18	1

Reference ID: 4646272

Uncontrolled Adverse Event Data:

Results of the FDA analysis of AEs in the Firefish (Parts 1 and 2) uncontrolled, open-label study are shown in the following table, which shows the most common AEs that occurred in at least 5% of patients. *These AEs are generally similar to those seen in the Sunfish study in the above table, including respiratory failure and respiratory infection, which are consistent with the natural history of SMA.*

Table 31: Treatment-emergent Adverse Events from the Open-label Firefish Study

	Group ID 0: Firefish 1 and 2 (N = 62)		
PT	*Events*	*Number of subjects*	*Proportion (%)*
Pyrexia	46	20	32
Upper respiratory tract infection	23	17	27
Pneumonia	15	13	21
Constipation	10	10	16
Diarrhoea	9	8	13
Vomiting	17	8	13
Nasopharyngitis	11	6	10
Cough	7	5	8
Rash	6	5	8
Teething	6	5	8
Rhinitis	4	4	6
Acute respiratory failure	3	3	5
Ear infection	4	3	5
Eczema	3	3	5
Erythema	4	3	5
Gastrooesophageal reflux disease	4	3	5
Pharyngitis	3	3	5
Respiratory distress	3	3	5
Respiratory failure	3	3	5
Respiratory tract infection	6	3	5
Respiratory tract infection viral	3	3	5
Upper respiratory tract inflammation	4	3	5

Results of the FDA analysis of AEs in the Jewelfish uncontrolled, open-label study are shown in the following table. *These AEs are generally similar to those seen in the Sunfish study in the above table, including respiratory infection, which are consistent with the natural history of SMA.*

Reference ID: 4646272

Table 32: Treatment-emergent Adverse Events from the Open-label Jewelfish Study

	Group ID 0 (N = 12)		
PT	Events	Number of subjects	Proportion (%)
Abdominal discomfort	2	2	17
Headache	3	2	17
Influenza	2	2	17
Nasopharyngitis	5	2	17
Nausea	2	2	17
Pyrexia	4	2	17
Viral infection	3	2	17
Abdominal pain upper	1	1	8
Anxiety	1	1	8
Arthralgia	1	1	8
Contusion	1	1	8
Cyanosis	1	1	8
Diarrhoea	2	1	8
Dry skin	1	1	8
Fall	1	1	8
Hepatic enzyme increased	1	1	8
Influenza like illness	1	1	8
Limb injury	1	1	8
Livedo reticularis	1	1	8
Melanocytic naevus	1	1	8
Muscular weakness	1	1	8
Nephrolithiasis	2	1	8
Pain in extremity	2	1	8
Photopsia	1	1	8
Pneumonia	1	1	8
Pruritus generalised	1	1	8
Rash	1	1	8
Upper respiratory tract infection	2	1	8
Urticaria aquagenic	1	1	8
Vitamin D deficiency	1	1	8
Vomiting	1	1	8
Vulvovaginal mycotic infection	1	1	8

Reference ID: 4646272

8.4.6. Laboratory Findings

Hematology:

The mean changes from baseline in hematologic parameters over all study time points are presented in the following table, generated from the submitted data. There were no clinically significant differences between the risdiplam and placebo groups. Although the mean changes of platelets and hemoglobin appear to differ between the placebo and risdiplam groups, the large standard deviation makes this difference difficult to interpret.

Table 33: Mean Change (Standard Deviation) from Baseline Hematology Parameters in the Controlled Sunfish Study. Source: Reviewer Analysis

Parameter (Units)	Placebo	Risdiplam
Platelets (10^9/L)	9.3 (173.5)	24.3 (161.7)
Hemoglobin (g/L)	0 (37.8)	-3 (34.9)
Hematocrit (%)	0 (0.1)	0 (0.1)
Lymphocytes (10^9/L)	-0.1 (2.6)	-0.1 (2.1)
Monocytes (10^9/L)	0 (0.6)	0.0 (0.5)
Neutrophils (10^9/L)	0 (5.1)	-0.4 (5.0)
Leukocytes (10^9/L)	0 (6.0)	-0.5 (6.0)

Outliers among hematology values were assessed. Risdiplam group subject (b) (6) had a mean increase from baseline platelets of 529 at week 52. This was an isolated abnormal laboratory value (platelets = 870 x 10 ^9/L (normal range 140-450 x 10 ^9/L) in a 10-year-old male with no clinical correlation and other hematology values normal. Risdiplam group subject (b) (6) had a mean decrease from baseline platelets of -193 on day 7. The platelet value on day 7 was 199 x 10^9, which was still in the normal range and down from 392 on study day -25. The platelets increased to 366 on study day 28. This was a 2-year-old female with no clinical correlation or adverse events associated with the platelet change. As described in Section 8.4.4, in the Firefish open-label study one patient was reported with moderate iron deficiency and low hemoglobin with normal reticulocytes that resolved with iron supplementation. See also Section 8.5.3 for further discussion of hematological effects.

Subject (b) (6) in the risdiplam group had a decline in leukocytes in week 4 with a mean change from baseline of -10.1. This decline was preceded by high levels of neutrophils and lymphocytes associated with the adverse events of upper respiratory tract infection, pyrexia, nausea, lymphadenopathy, headache, epistaxis, and upper abdominal pain. The neutrophil count was elevated at screening and day 7 (8.1 and 9.2 x 10^9/L, normal range 1.63-7.55 x 10^9/L) and declined to 3.0 x 10^9/L on day 29. The count increased to 5.5 x 10^9/L on study day 56. This subject was a 6-year-old male with serious adverse events of pneumonia (days 47, 91,

Reference ID: 4646272

114), bacteremia, and lung operation. *The above fluctuation in leukocytes appears to have been related to this subject's recurrent respiratory infections, which are common in SMA patients.*

Chemistry:

In the controlled trial database, *there were no clinically significant differences in key blood chemistry parameters between the placebo and risdiplam groups*, as shown in the table below that was generated from the submitted data. Note that SMN protein levels increased in the blood of patients treated with risdiplam (3.2) and declined slightly in the placebo group (-0.1), a finding which is consistent with the risdiplam mechanism of action. Creatine kinase declined more in the placebo group (-15) than in the risdiplam group (-7.2), a finding which might suggest less muscle atrophy in the risdiplam group. Although alkaline phosphatase had a greater mean increase in the risdiplam group (6.6) than in the placebo group (1.7), other liver function biomarkers did not show such a difference (AST, ALT, GGT, bilirubin).

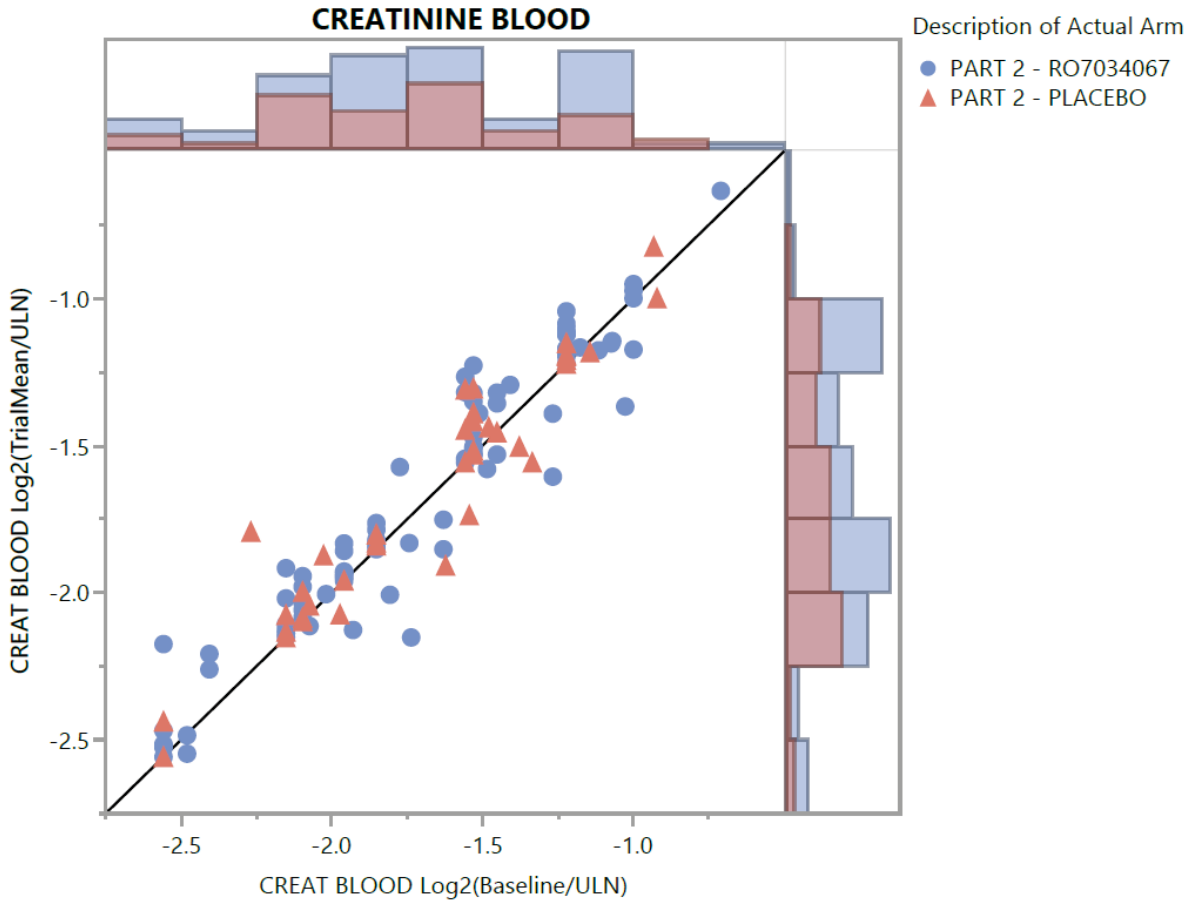
No Hy's law case was identified at any timepoint during the study (no patient had an increase in AST or ALT levels >3x the upper limit of normal [ULN] and total bilirubin >2x ULN. See Section 8.5.4. The mean changes from baseline in the following chemistry parameters were assessed and no clinically significant differences between the placebo and risdiplam groups were seen: alanine aminotransferase, aspartate aminotransferase, bilirubin, alkaline phosphatase, creatinine, blood urea, sodium, potassium, random glucose, total protein, albumin, cholesterol, creatine kinase, bicarbonate, calcium, gamma glutamyl transferase, thyroid stimulating hormone, free thyroxine, triglycerides, activated partial thromboplastin time, and prothrombin international normalized ratio.

Renal Parameters:

The following tables show shifts in blood urea and creatinine from baseline for the risdiplam and placebo groups. Outliers were assessed. Subjects (b) (6) and (b) (6) in the risdiplam arm had low blood urea values at baseline which subsequently entered the normal range for the rest of the study. *There were no clinically significant increases in blood urea or creatinine from baseline.*

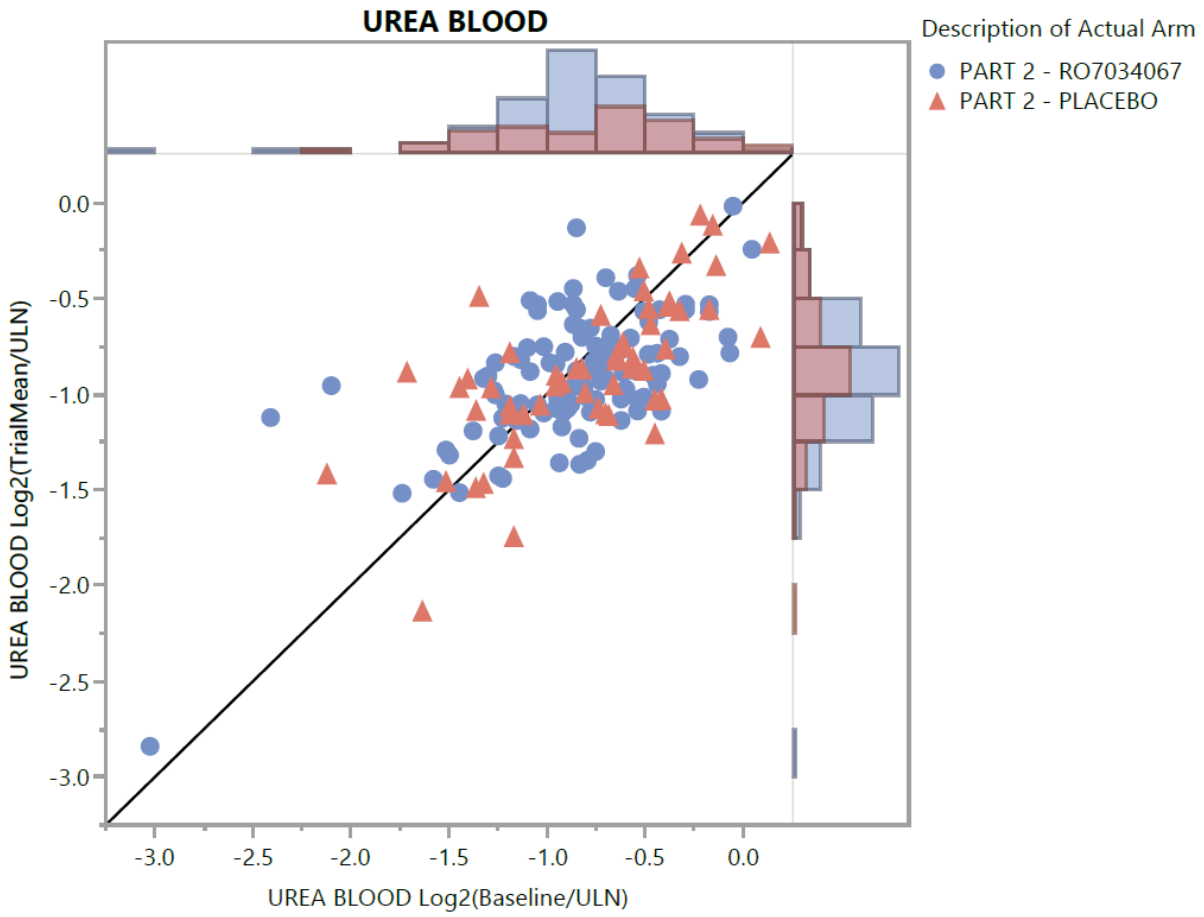
Reference ID: 4646272

Figure 18: Shift Plot of Blood Creatinine in the Sunfish study.



Reference ID: 4646272

Figure 19: Shift Plot of Blood Urea in the Sunfish study.

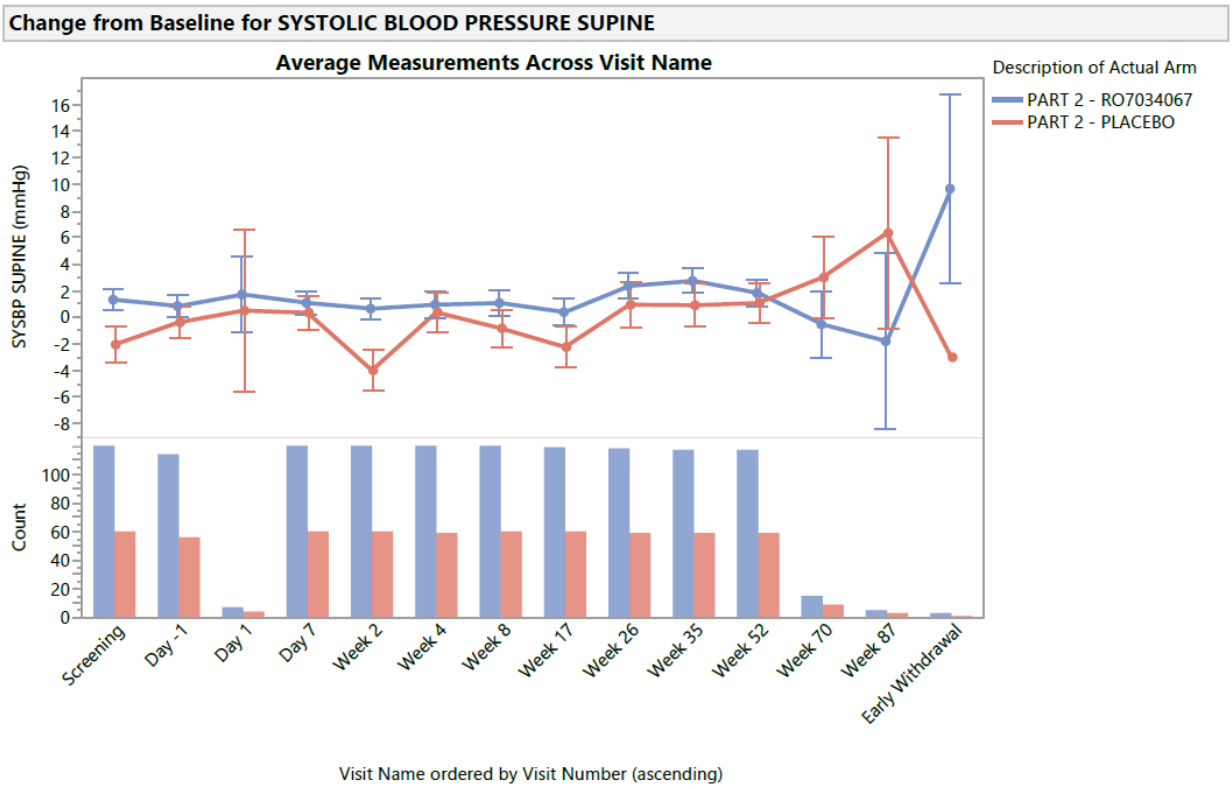


8.4.7. Vital Signs

This reviewer analyzed the applicant's vital signs data including head circumference, height, weight, blood pressure (systolic and diastolic), heart rate, respiratory rate, and temperature. The following figures show change from baseline in vital signs parameters over time. *There were no clinically significant differences in these parameters between the risdiplam and placebo groups as seen in the following figures generated from the submitted data.* Note that the variability of the parameters increased at the final assessments because of fewer subjects completing assessments near the end of the study.

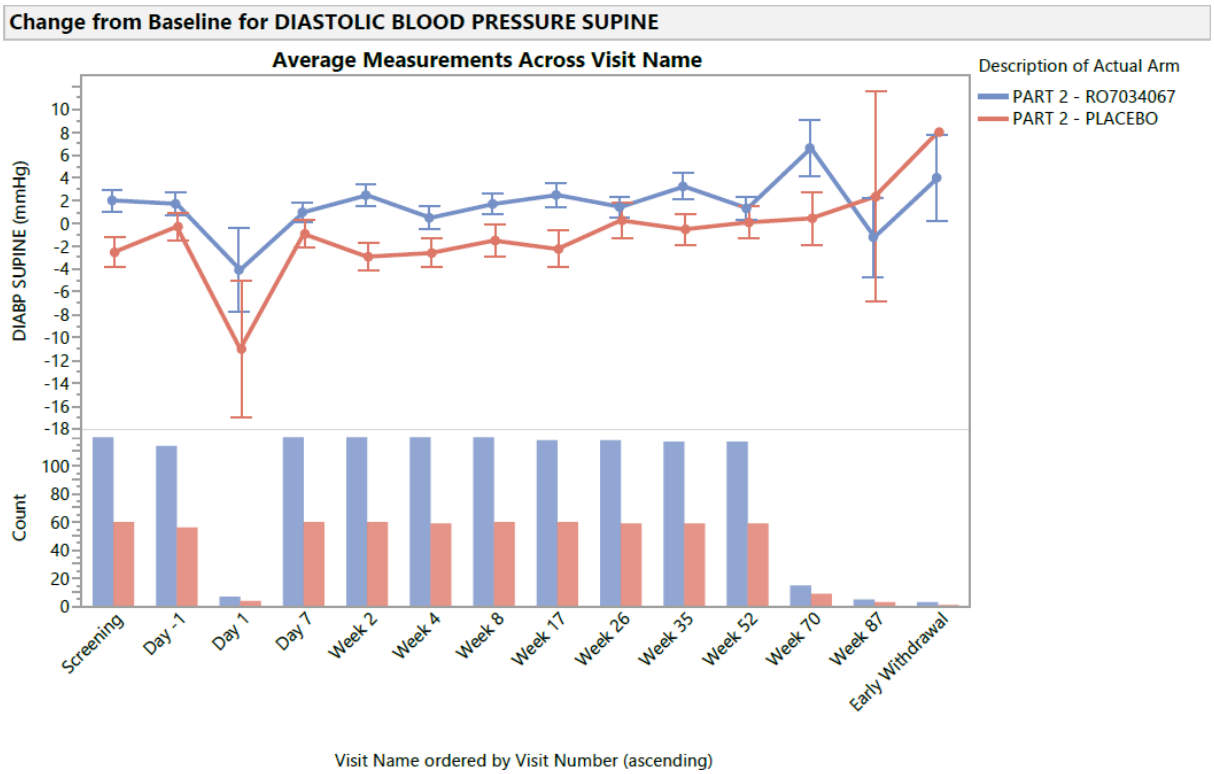
Reference ID: 4646272

Figure 20: Change from Baseline for Systolic Blood Pressure in the Sunfish Study



Reference ID: 4646272

Figure 21: Change from Baseline for Diastolic Blood Pressure in the Sunfish Study



Reference ID: 4646272

Figure 22: Change from Baseline for Heart Rate in the Sunfish Study

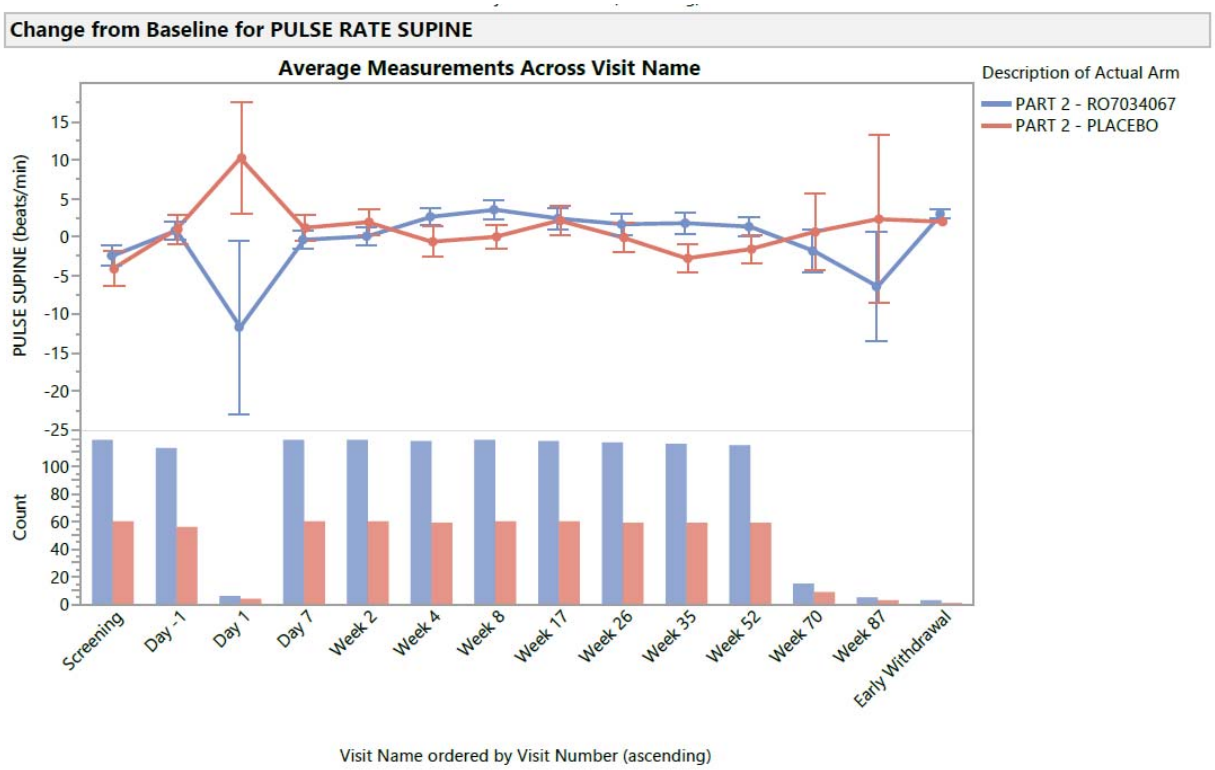
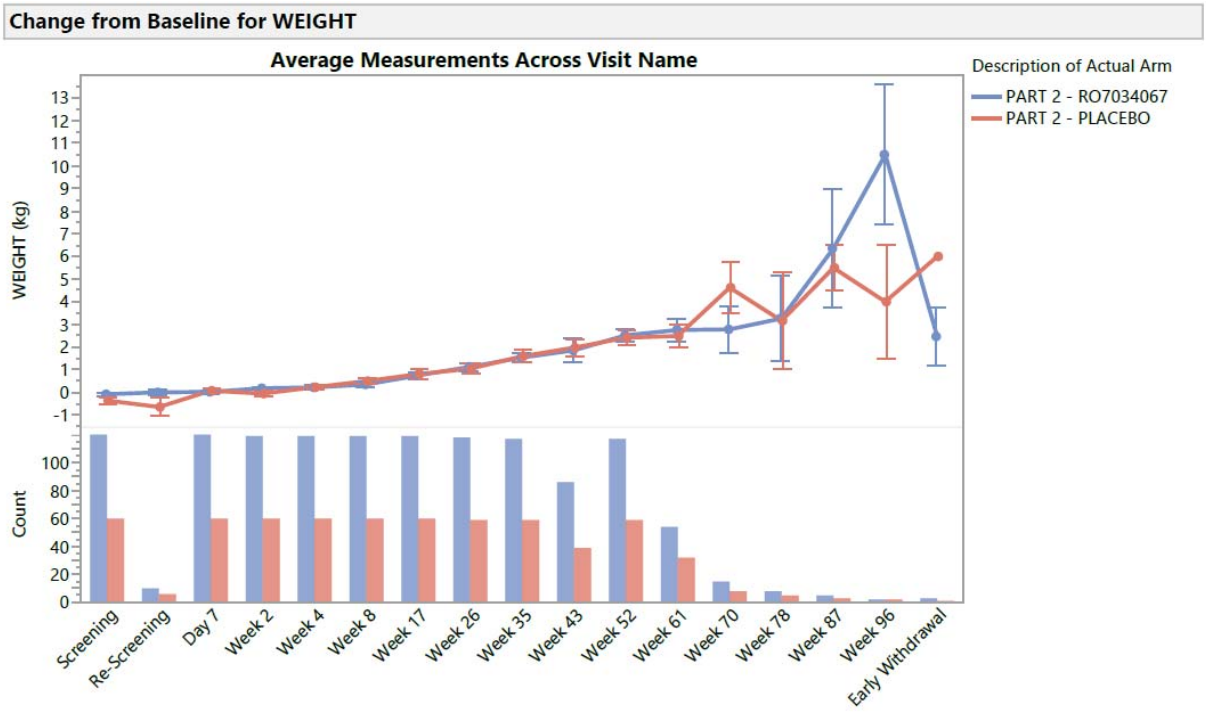


Figure 23: Change from Baseline for Weight in the Sunfish Study



Reference ID: 4646272

Figure 24: Change from Baseline for Head Circumference in the Sunfish Study

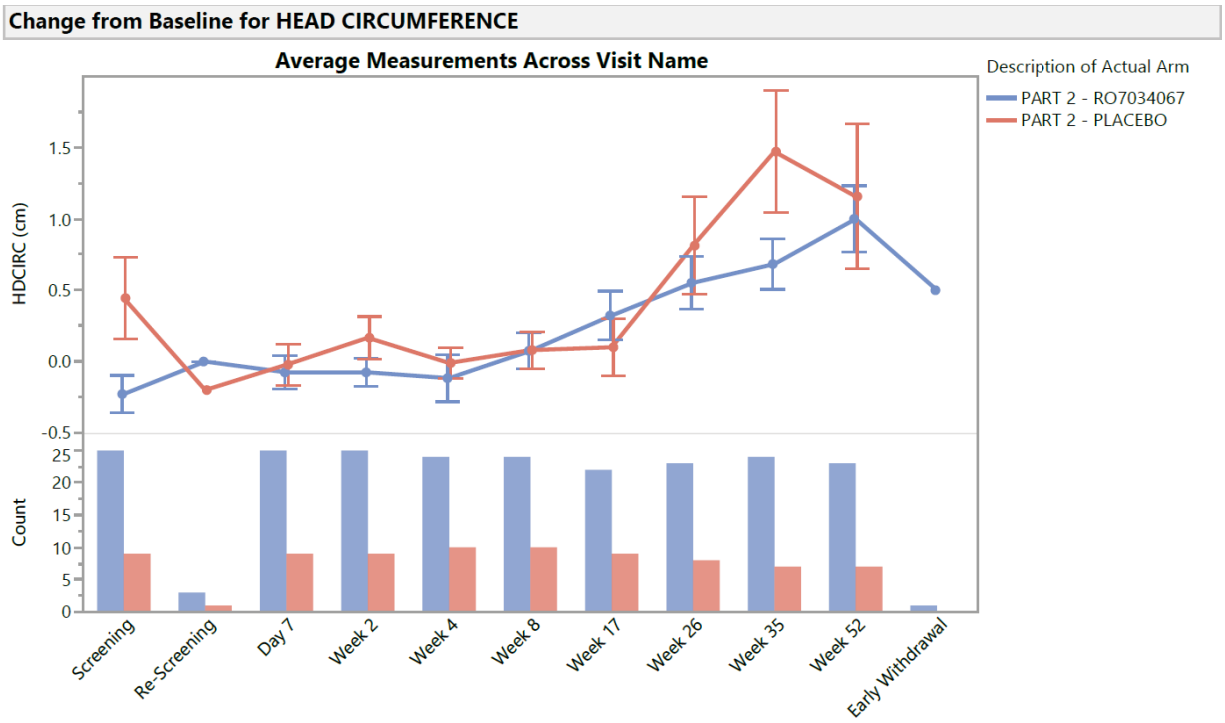
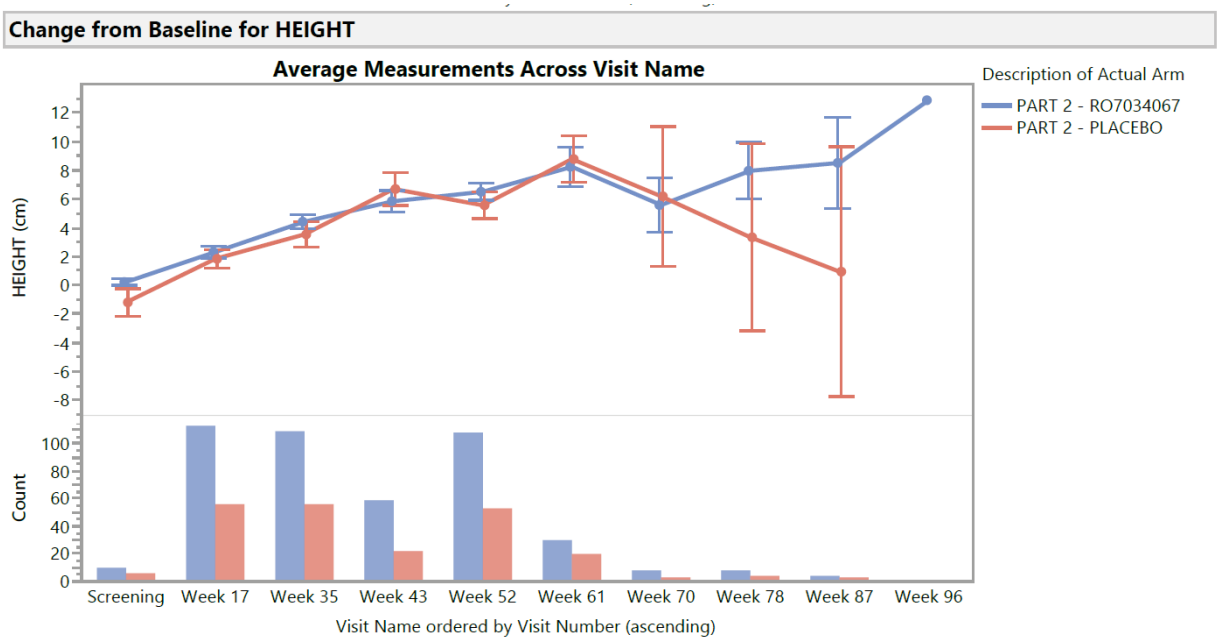


Figure 25: Change from Baseline for Height in the Sunfish Study



8.4.8. Electrocardiograms (ECGs)

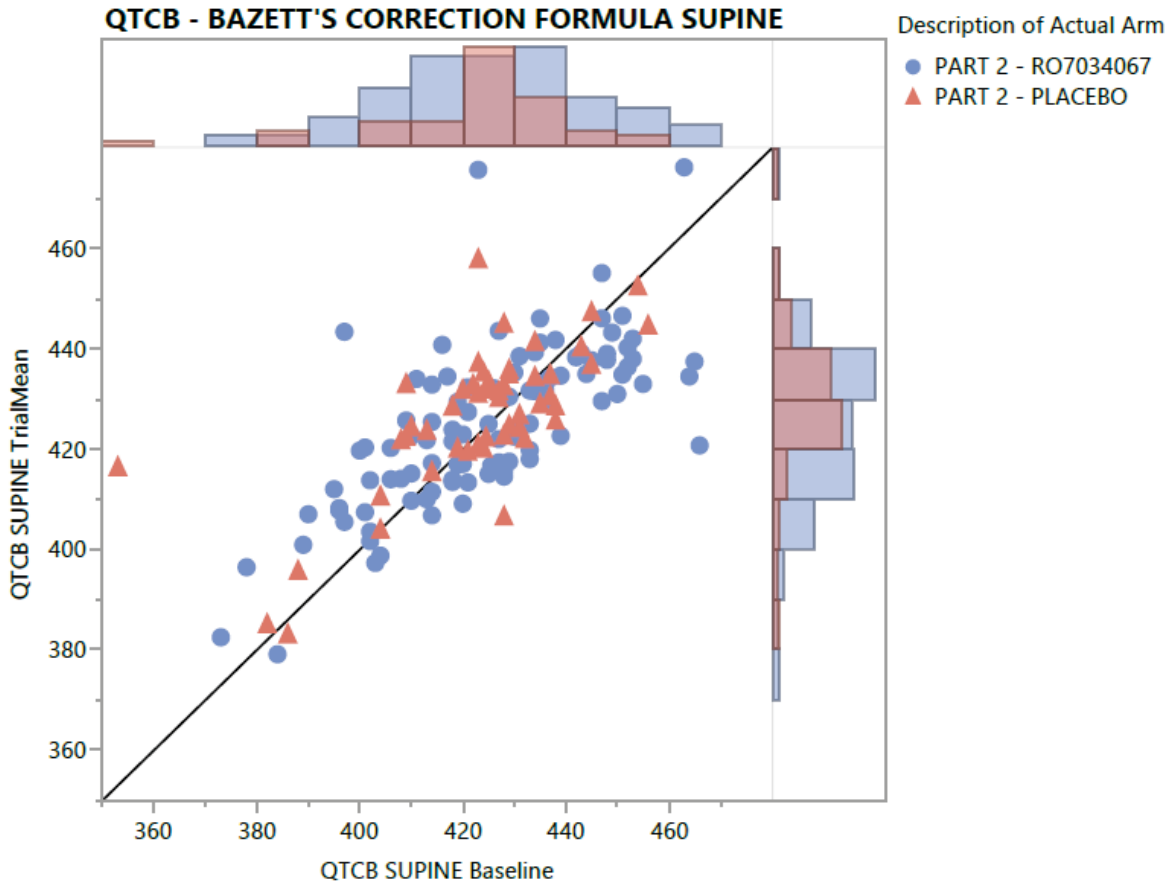
There were no significant mean effects on the mean QTcB (corrected QT; Bazett's formula), PR, or

Reference ID: 4646272

QRS intervals. None of the patients taking risdiplam had QTcF > 480 msec. Six subjects had ΔQTcF > 60 msec from pooled studies BP39055 and BP39056.

I assessed outliers by examining scatterplots of baseline vs. mean post-baseline values. Among subjects receiving risdiplam, subject [redacted] (b) (6) was a 3-year-old female who had elevated QTCB of 570 msec at baseline and up to 591 msec at week 4 with no cardiac adverse events. Subject [redacted] (b) (6) was a 3-year-old female who had elevated QTCB of 463 msec at baseline and up to 584 msec at week 26 with no cardiac adverse events. *Because their baseline values were elevated, no clear association with risdiplam treatment can be made.*

Figure 26: QTCB in the Sunfish study



8.4.9. QT

The applicant reported that nonclinical data did not suggest any potential for risdiplam to bind to hERG or to induce QT prolongation in monkeys in vivo. The applicant submitted exposure-response analysis using 5 clinical studies conducted in healthy subjects (Studies # BP29840; n=26, # NP39625; n=18) and SMA patients (Studies # BP39054; n=12, Part 1 of # BP39055; n=51, and Part 1 of #

Reference ID: 4646272

BP39056; n=21).

The Agency's interdisciplinary review team for QT studies was consulted to review the submitted data and made the following recommendation in their review. The consult confirmed the absence of significant heart rate changes or delayed QTc changes in the submitted data but concluded that "the submitted data are not adequate to characterize the risk of QTc prolongation associated with the oral administration of risdiplam. The PK/ECG data available from these clinical studies are at considerably lower exposures (Cmax) of risdiplam than those expected with therapeutic doses at the steady-state. The QT-IRT recommends that the sponsor characterizes the effect of risdiplam on the QTc interval in a dedicated study at a clinically relevant exposure."

It is acceptable to conduct the recommended QT study in the postmarketing setting because there has not been any clinically significant QT/cardiac safety signal in the risdiplam clinical studies.

8.4.10. Immunogenicity

Not applicable. The drug is a small molecule.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Retinal Toxicity

Retinal toxicity was observed in nonclinical studies and extensive ophthalmologic monitoring was required in clinical studies with risdiplam to assess for this potential safety signal. The following is excerpted from the ophthalmology consult by Dr. Wiley Chambers:

> "In a 39-week study in cynomolgus monkeys, retinal toxicity was observed in all animals at exposures above the no-observed-adverse-effect level (NOAEL) i.e., at approximately 2-fold of the average exposure observed at the pivotal dose selected for patients with SMA. These consisted of peripheral photoreceptor loss and hyper-reflective retinal pigment epithelium which was not fully reversible as well as, at higher exposures, reversible microcystic macular degeneration in the macula. The expected initial clinical symptoms of such structural changes in the peripheral retina would be impaired night vision or loss of peripheral vision. Blindness was not observed in any of the monkeys even at high doses (approximately 4 times the exposures achieved at the pivotal dose in patients with SMA) after 9 months of daily administration of risdiplam. These findings were not observed in albino or pigmented rats when dosed chronically with risdiplam at exposures exceeding those administered to monkeys. Due to this nonclinical finding, a panel of ophthalmological assessments was performed in all clinical studies in SMA patients, including imaging to detect structural changes of the retina, and visual function testing to detect potential functional impairment in central or peripheral vision."

Multifocal peripheral retina degeneration was also reported in nonclinical studies of risdiplam, as described in Section 4.4.3. Retinal safety monitoring is described in Sections 6.1.1 and 6.2.1

Reference ID: 4646272

for the Sunfish and Firefish studies, respectively.

The applicant states that "ophthalmological assessments did not show any evidence of risdiplam-induced retinal toxicity." FDA ophthalmology was consulted previously for the risdiplam IND and again for this NDA to review ophthalmology assessments. The ophthalmology review did not find any significant findings on Optical Coherence Tomography (OCT) and concluded that "in those patients with ocular functional examinations, no significant pattern of abnormal findings were observed… Ocular monitoring of anatomic ocular structures did not reveal any significant pattern of abnormal findings."

For the Firefish study, there were 3 AEs in the system organ class "eye disorder" in 2 subjects: 2 cases of conjunctival hyperemia and 1 case of macular cysts. All cases were mild and resolved without change to risdiplam dosing.

In the double-blind period of the Sunfish study, 10% of patients (7 AEs in 6 subjects) in the placebo arm had AEs coding to the SOC "Eye disorders" compared to 7% of the risdiplam arm (10 AEs in 8 subjects).

All events in subjects on risdiplam resolved except for 3 events in 2 subjects:

> Subject (b) (6): One 5-year-old male had a mild AE of visual impairment with onset on study Day 324. The patient had lost 0.5 diopters at visual acuity testing and was advised to wear glasses. No findings were observed in any of the other assessments performed. Optical coherence tomography (OCT) and best-corrected visual acuity (BCVA) improved compared to baseline at the next visit.
>
> Subject (b) (6): One 13-year-old female patient had mild events of cataract subcapsular (onset study Day 301) and posterior capsule opacification (onset study Day 357) observed by the site ophthalmologist at the scheduled ophthalmological visit. After additional red reflex investigation, the findings could not be confirmed.

During open-label treatment one 2-year-old male patient randomized to Risdiplam during the double-blind stage had a mild event of conjunctivitis allergic with onset on Study day 371 which was reported as recovering at the end of the study.

Subject (b) (6): One 46-year-old subject in the Jewelfish study had a Grade 1 AE of intermittent photopsia that consisted of flashes of light in both closed eyes in the awakening phase of sleep, occurring for a few seconds with onset on Study Day 338, which was also the day of the most recent risdiplam dose. This event was not considered resolved at the end of the study (Study Day 345), the dose was not changed, and the patient did not receive treatment for this AE. Ophthalmological assessments were reported to be without clinically significant changes from baseline. *This subject's photopsia may be caused by age-related vitreous changes.*

Reference ID: 4646272

In the Sunfish Part 1 study, "Retinal disorders" AEs were reported in 1 risdiplam subject (3%, Vision blurred) and 3 placebo subjects (2%; Vision blurred, Visual impairment, Eye naevus). In the Sunfish Part 2 study, "Retinal disorders" AEs were reported in 3 risdiplam subjects (2.5%) and 0 placebo (0%). However, the 3 risdiplam subjects were previously in the placebo group in Part 1 when they had the "retinal disorder" AEs of vision blurred, visual impairment, and eye naevus. Therefore, the percentage of "retinal disorder" AEs that began *after study drug administration* in the risdiplam and placebo groups of Part 2 is zero.

Overall, the vision-related AEs and patient narratives from the Firefish, Sunfish, and Jewelfish studies do not suggest a pattern of retinal toxicity.

8.5.2. Effects on Epithelial Tissues

In chronic toxicology studies in rodents and monkeys, adverse effects on epithelial tissues (skin, larynx, eyelid, and gastrointestinal tract) were observed. The first clinical sign in monkeys was mild parakeratosis at exposures more than 2.5-fold the exposure observed at the pivotal dose selected for patients with SMA. These findings were reversible upon discontinuation of dosing with risdiplam but persisted with continuous dosing and worsened at high doses with breakage of the skin barrier.

In the Sunfish placebo-controlled study, there were no SAEs related to skin conditions. AEs in the system organ class "skin and subcutaneous tissue disorders" occurred in 31% of the risdiplam group compared to 12% of the placebo group. Rash (including eruption and dermatitis) occurred in ~13% of the risdiplam group and ~2% of the placebo group. Cheilitis occurred in ~2% of the risdiplam group and 0% of the placebo group. Skin erosion occurred in 1 subject (~1%) of the risdiplam group and in 0% of the placebo group.

There were AEs in the system organ class "gastrointestinal disorders" in 43% of the risdiplam group and 42% of the placebo group. Mouth ulceration occurred in 4% of the risdiplam group and 0% of the placebo group, and aphthous ulcers occurred in 2.5% of the risdiplam group and 0% of the placebo group. Diarrhea occurred in ~17% of the risdiplam group and 10% of the placebo group. Gastrointestinal disorders SAEs (constipation) occurred in ~1% of the risdiplam group and 0% of the placebo group.

There were AEs and SAEs of gastroenteritis that were higher in the placebo group (AE: 8% risdiplam, 12% placebo; SAE: 2% risdiplam, 3% placebo).

Although there are conflicting signals in the data presented above, the higher rates of rash, mouth/aphthous ulcers, diarrhea, cheilitis, and skin erosion in the risdiplam group suggest that there may be a drug effect on epithelial tissues of the skin and gastrointestinal tract which was generally not serious. This finding should be reported in the risdiplam prescribing information.

Reference ID: 4646272

8.5.3. Hematological Effects

During nonclinical studies with risdiplam, bone marrow depression with decreased cell counts across all 4 blood cell lines (erythroid, granulocytic, monocytic, and megakaryocytic) were observed at exposures at least 4 times higher than the mean exposures observed in the clinical studies. This hematological effect was associated with an effect of risdiplam on the MADD and FOXM1 genes involved in cell division and apoptosis.

Among all subjects with SMA in the risdiplam development program, the mean percentage change from baseline ranged from -13% to 7% for lymphocytes, -32% to 73% for neutrophils, -11% to 6% for erythrocytes and -43 % to 67% for platelets. The greatest individual percentage decrease from baseline was -71% for lymphocytes, -89% for neutrophils, -47% for erythrocytes and -71% for platelets.

Six subjects (three Type 1 and three Type 2 or 3 SMA) had an AE suggestive of a clinically significant decrease in cell lines:

1. One patient had an AE of neutropenia with onset on Day 14 and resolved without change to study medication after 43 days. The patient's neutrophil count was already low at screening (1.03×10^9/L on Day -24; normal range: $2.4\text{-}4.8 \times 10^9$/L). Post-baseline values remained below the lower limit of normal (LLN) but were higher than the value at screening.
2. One patient who was reported with an SAE of neutropenia on Day 280 in the context of pneumonia had a Grade 4 neutropenia on Day 280 at 0.23×10^9/L (normal range: 1.5-8.5×10^9/L) which resolved on Day 294 despite ongoing treatment with risdiplam.
3. One patient who was reported with moderate iron deficiency on Day 55 had low hemoglobin on Days 14 and 55 at 99 and 98 g/L, respectively (normal range: 105-135 g/L). Reticulocytes were within normal ranges throughout. The event resolved with iron supplementation after 42 days. Risdiplam treatment was not changed in response to this event.
4. One patient had an AE of Grade 1 anemia with onset on Day 611, which was not resolved at the CCOD. The patient had low hemoglobin values at 103 g/L and 104 g/L (normal range 105-145 g/L) respectively on Days 483 and 610.
5. One patient had an AE of Grade 1 iron deficiency anemia with onset on Day 418 and resolved after 273 days. The patient had high reticulocyte count on Day 440 (205×10^9/L, normal range $13.5\text{-}123 \times 10^9$/L) and low hemoglobin on the same day at 98 g/L (normal range 123-170 g/L). Hemoglobin values were normal from Study Day 554.
6. One patient had an AE of Grade 1 neutropenia with onset on Day 175, which resolved after 5 days despite ongoing treatment with risdiplam. The patient also had AEs of Grade 3 pneumonia (onset Day 154) and Grade 1 pyrexia (onset Day 190). This patient did not have evidence of neutropenia at any of the assessment timepoints; however possible reactive neutrophilia (10.66×10^9/L, normal range

Reference ID: 4646272

1.54-7.04x10^9/L) was observed on Study Day 239 which returned to within the normal range on Day 363.

Overall, the observed hematologic abnormalities were consistent with underlying disease processes such as respiratory infection and resolved despite continued risdiplam treatment.

8.5.4. Risk of Liver Injury

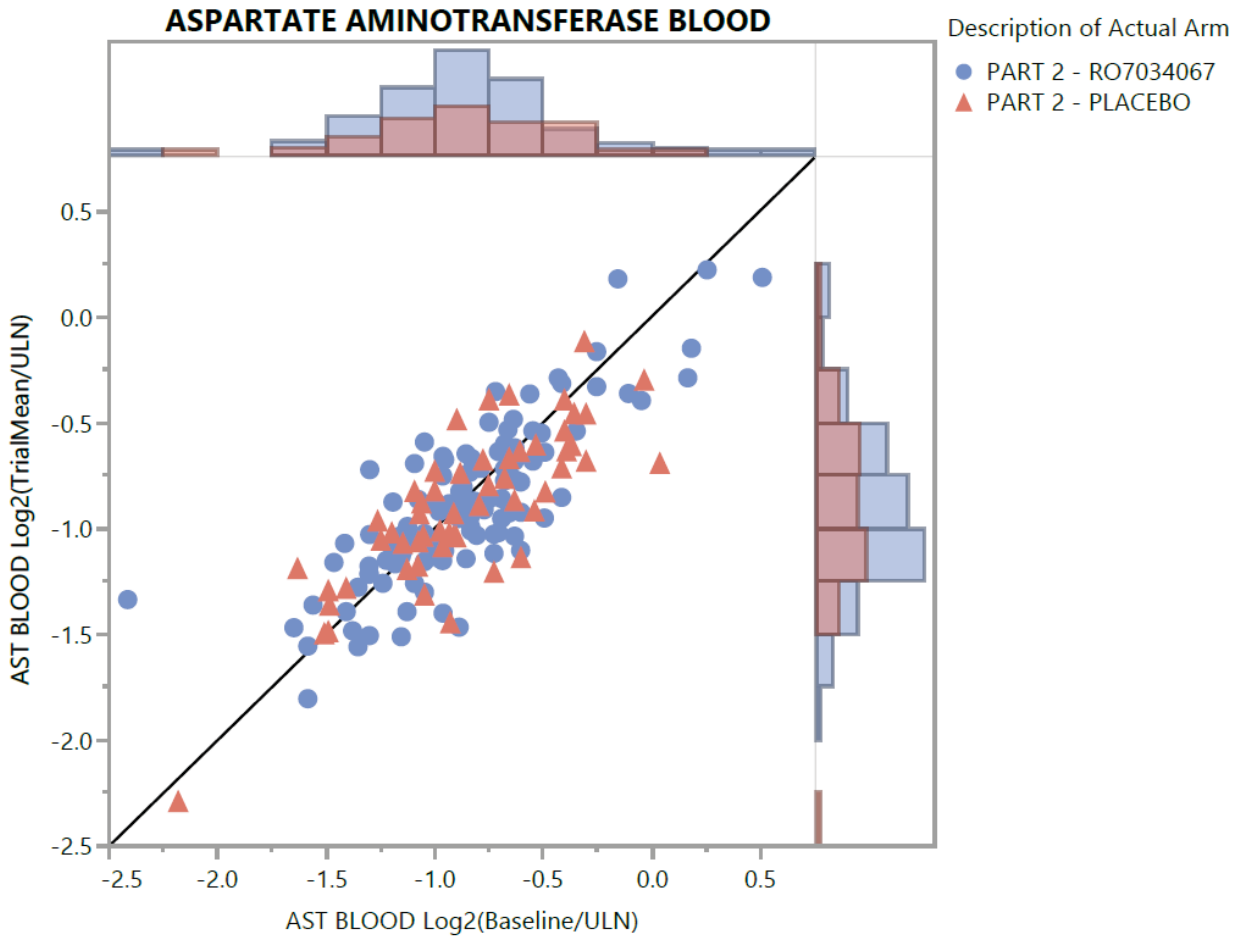
Based on data from metabolism studies with human liver microsomes there is a risk for risdiplam to produce reactive metabolites and possible liver injury. No Hy's Law cases were reported in risdiplam clinical studies. The highest abnormal value in terms of CTCAE grading was Grade 3 for ALT and Grade 2 for AST. No patient had a shift of total bilirubin above 1.5 times the upper limit of normal (ULN) (CTCAE Grade 1).

Among risdiplam-treated subjects, 2.5% had elevations of either AST or ALT > 3 times the upper limit of normal compared to 3.3% of placebo subjects. No risdiplam-treated subjects had bilirubin elevatons greater than 2 times the upper limit of normal, compared to 1.7% of placebo subjects who had bilirubin elevations greater than 2 times the upper limit of normal.

The following figures show shifts in liver function biomarkers from baseline that were generated from the submitted data.

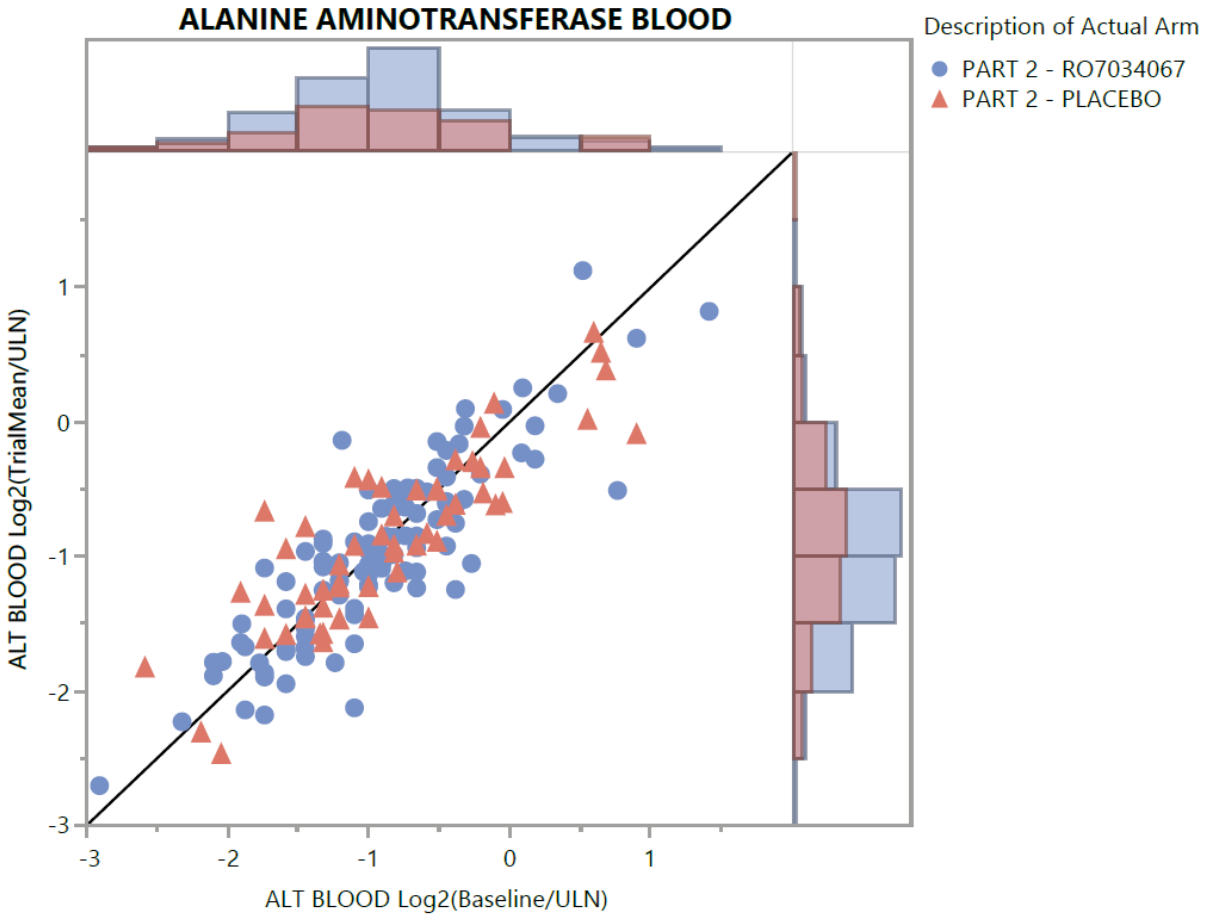
Reference ID: 4646272

Figure 27: Shift Plot of Blood AST in the Sunfish study.



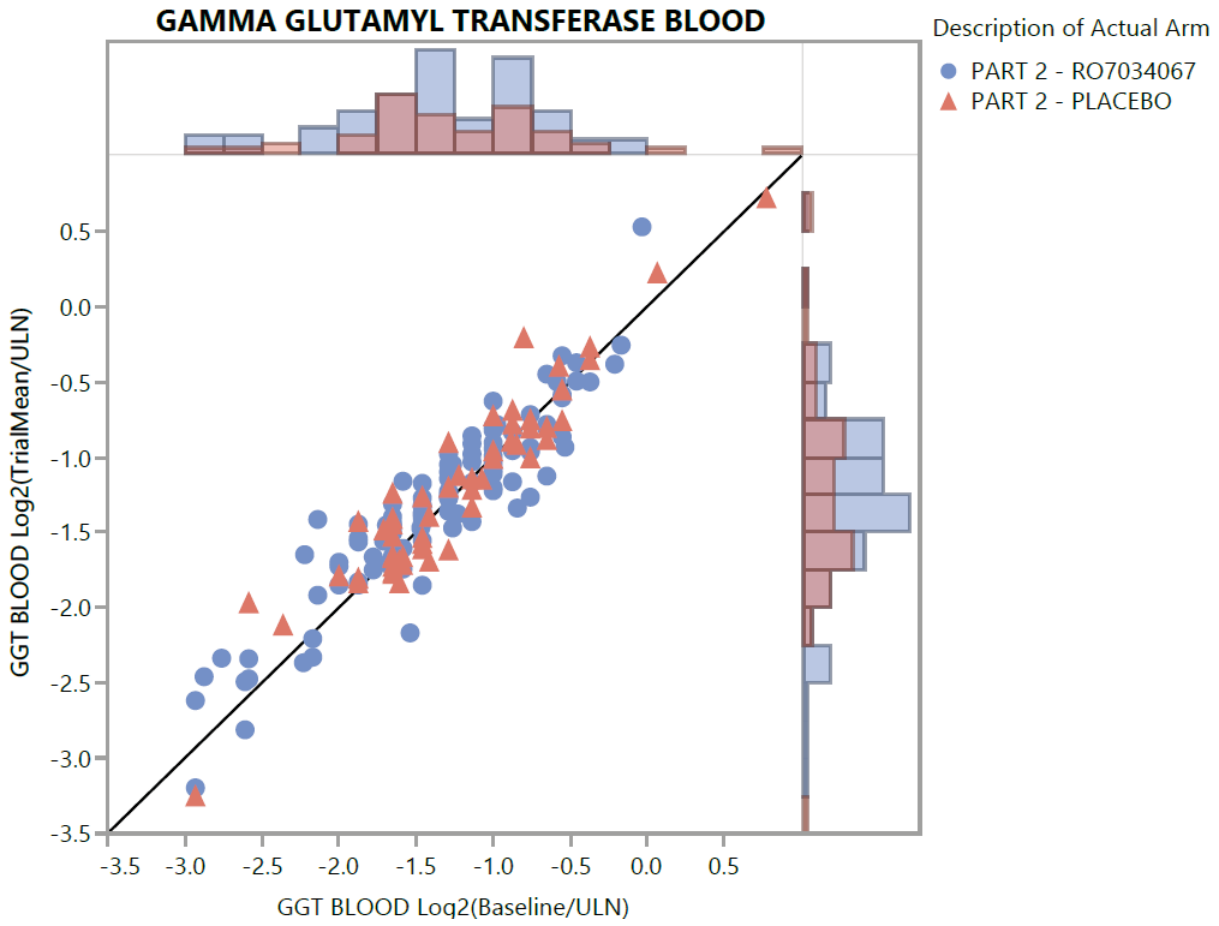
Reference ID: 4646272

Figure 28: Shift Plot of Blood ALT in the Sunfish study.



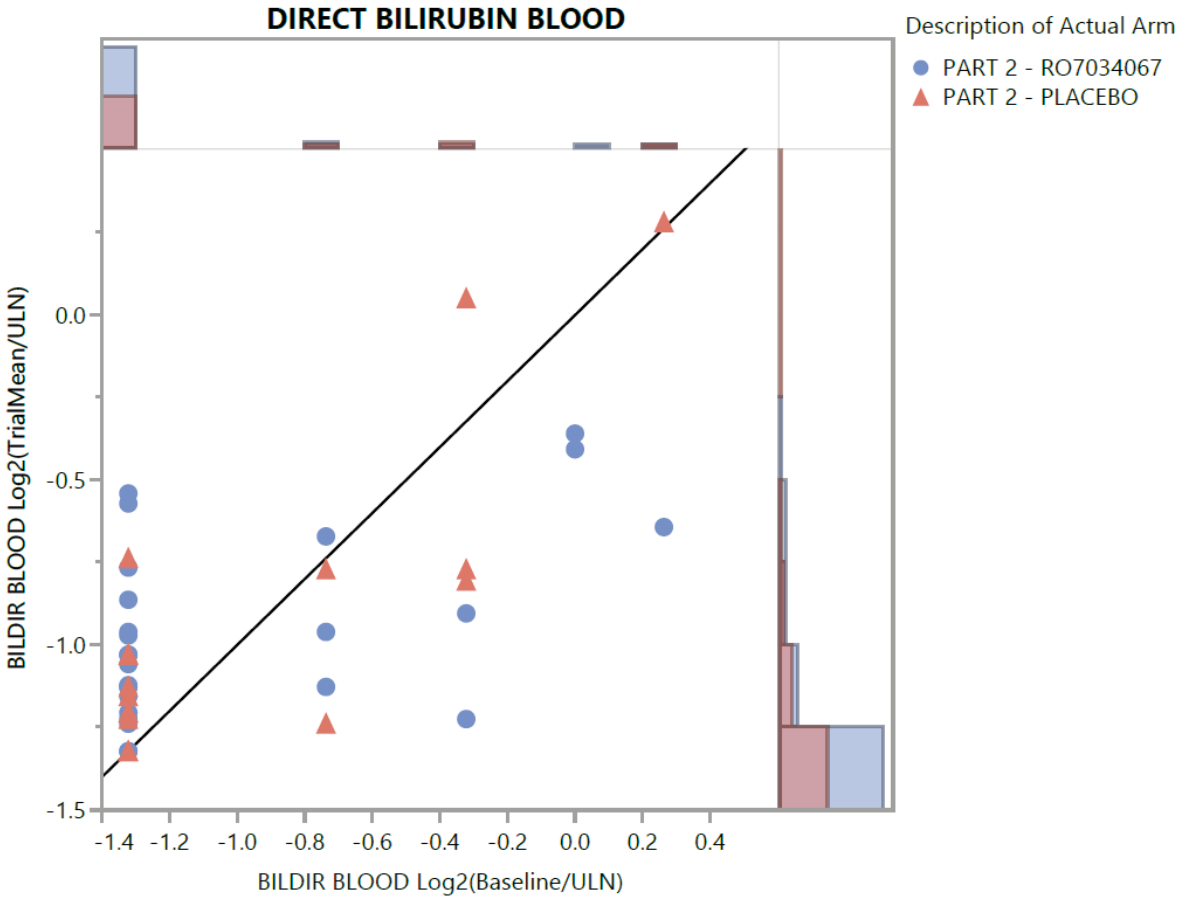
Reference ID: 4646272

Figure 29: Shift Plot of Blood GGT in the Sunfish study.



Reference ID: 4646272

Figure 30: Shift Plot of Blood Direct Bilirubin in the Sunfish study.



Outliers were assessed. Subjects [redacted] (b) (6) and [redacted] (b) (6) had a high direct bilirubin at screening which returned to the normal range during the study.

Among Type 1 SMA patients, five had AST values >3 times ULN at a single post-baseline visit. Their AST values were elevated at baseline and remained elevated at all post-baseline visits. One patient was reported with mild hepatocellular injury on Day 58 with AST and ALT below 1.5 times ULN on Day 58. The event lasted for 11 days (outcome unknown). Risdiplam treatment was not changed in response to this event.

Among Type 2 and 3 SMA patients, one developed ALT above 2 times ULN at the last post-baseline assessment. The patient had ongoing hand-foot-and-mouth disease. One patient with baseline values of ALT 49 U/L (ULN 41 U/L) and AST within the normal range, had a significant increase in ALT >5 times ULN (CTCAE Grade 3) and AST >2 times ULN (CTCAE Grade 1) on Day 56. Both values had returned to baseline levels at the next assessment (Day 118). The patient's bilirubin values remained within the normal range. At the time of the abnormal ALT and AST

Reference ID: 4646272

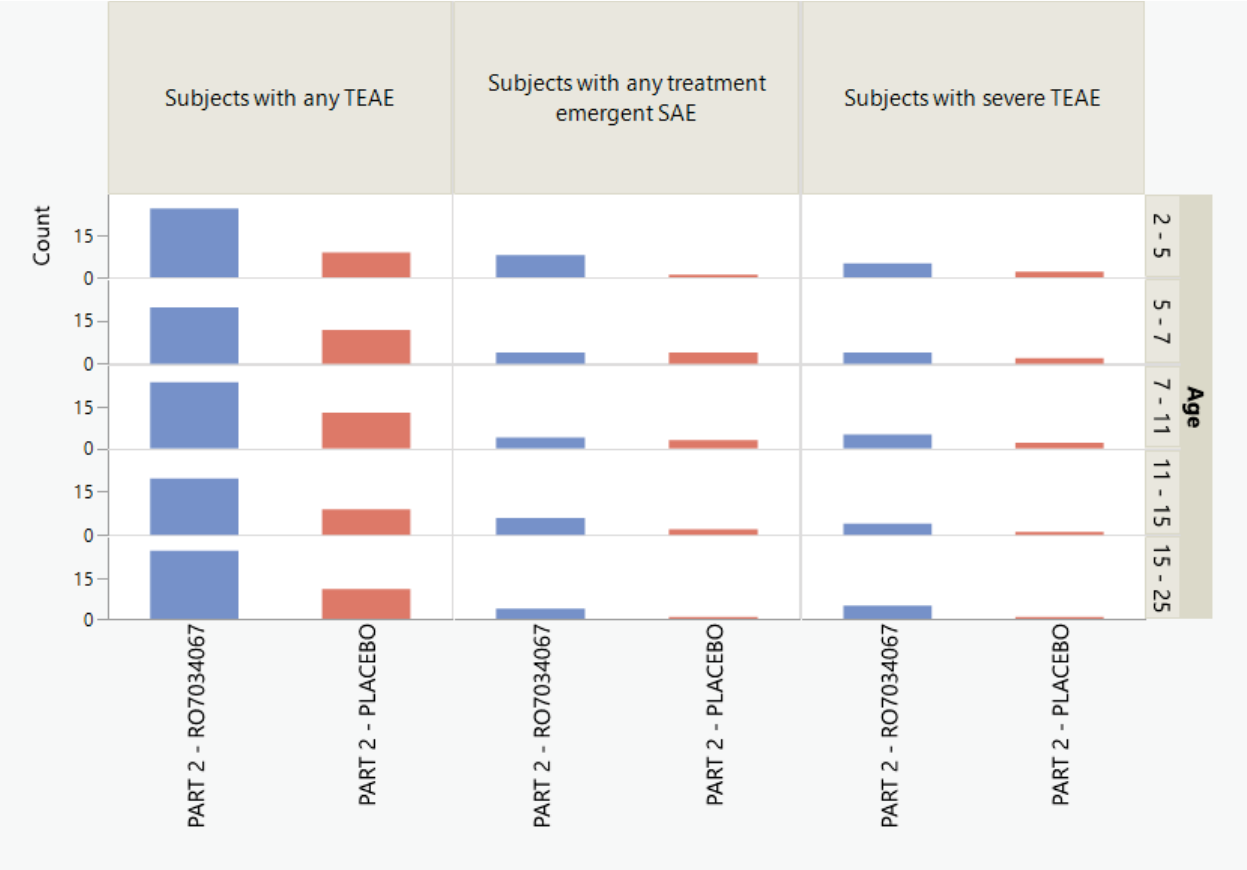
values, the patient had been treated with paracetamol for several days due to an AE of influenza-like illness. Treatment with risdiplam was not changed in response to this event.

There is no clinically significant difference in the risk of liver injury between the placebo and risdiplam-treated subjects.

8.6. Safety Analyses by Demographic Subgroups

The following figure shows that there is no notable difference in the proportions of adverse events, serious adverse events, or severe adverse events as a function of age in the Sunfish study.

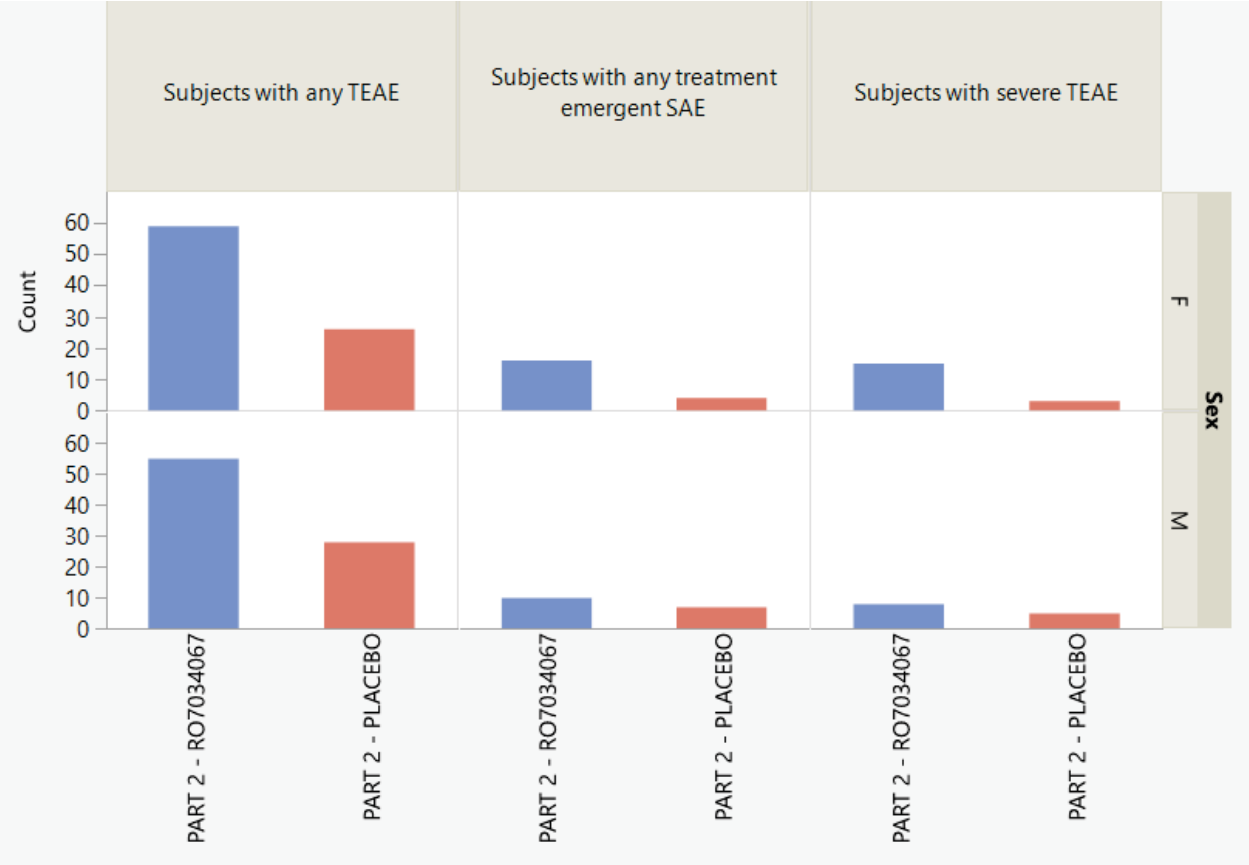
Figure 31: Treatment Emergent Adverse Events Description by Age (in years)



The following figure shows that there is no notable difference in the proportions of adverse events, serious adverse events, or severe adverse events as a function of sex in the Sunfish study.

Reference ID: 4646272

Figure 32: Treatment Emergent Adverse Events Description by Sex



8.7. Specific Safety Studies/Clinical Trials

Not applicable.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

A carcinogenicity study using rasH2 transgenic mice with 6 months duration of treatment did not generate any evidence for a tumorigenic potential of risdiplam. The applicant plans to conduct a two-year carcinogenicity study in rats as a post-marketing commitment.

8.8.2. Human Reproduction and Pregnancy

Reference ID: 4646272

There are no clinical data from the use of risdiplam in pregnant women. Risdiplam has been shown to be embryo-fetotoxic and teratogenic in animals. Based on the findings from animal studies, risdiplam crosses the placental barrier and may cause fetal harm.

Nonclinical studies have shown that the lack of SMN protein has detrimental effects on male germ cells in animals (Ottesen et al. 2016). Therefore, risdiplam-associated increase in SMN protein could have positive effects on male fertility. The effect of risdiplam on male germ cells has not been evaluated in clinical studies.

These potential risks should be described in the risdiplam prescribing information

8.8.3. Pediatrics and Assessment of Effects on Growth

This reviewer analyzed the applicant's vital signs data in Section 8.4.7, including head circumference, height, and weight. There was no clinically significant difference in these parameters between the risdiplam and placebo groups in the Sunfish study.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Risdiplam likely has a narrow therapeutic window. Exposures approximately 10-fold above the cap of 2000 ng.h/mL (AUC0-24h) are associated with severe conditions, including death in animals. There is no antidote.

There is limited clinical trial experience in SMA with doses higher than the proposed dose of risdiplam. In the All Patients with SMA pooled population, 19 out of 125 patients received doses more than 10% above the prescribed dose, which were also more than 10% above the pivotal dose. Doses above the pivotal dose were administered for up to 35 consecutive days and were up to 33% higher than the pivotal dose. Two patients received double the planned dose for a single day. One AE was associated with a high risdiplam dose: Grade 1 rhinorrhea in 1 patient that resolved 7 days later while the patient was still receiving a dose above the pivotal dose.

No information is available regarding withdrawal or rebound effects of risdiplam.

The Controlled Substance Staff conducted a review of risdiplam and concluded that "the mechanism of action, general nonclinical responses, and associated CNS-related adverse events (AEs)) shown with risdiplam did not present a signal of abuse potential."

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable. Risdiplam is not yet marketed.

8.9.2. Expectations on Safety in the Postmarket Setting

Reference ID: 4646272

The patterns in adverse reactions in the postmarketing data will likely be similar to the patterns observed in the pre-marketing data.

8.9.3. Additional Safety Issues From Other Disciplines

None.

8.10. Integrated Assessment of Safety

The overall conclusion of this safety review is that the safety profile of risdiplam is acceptable given the evidence of efficacy in the treatment of spinal muscular atrophy (SMA) and the poor prognosis for SMA patients. The most commonly observed (≥ 10%) adverse events associated with the use of risdiplam in the placebo-controlled 12-month Sunfish study were upper respiratory tract infections, pyrexia, headache, diarrhea, and rash.

No adverse event caused patients to stop taking risdiplam across the three clinical studies (one placebo-controlled and two open-label studies) submitted. There were no deaths in the placebo-controlled Sunfish or the open-label Jewelfish studies of older patients with milder forms of SMA. Six deaths occurred in the open-label Firefish study of the most lethal form of SMA, Type 1 infantile onset SMA. The narratives of these deaths were reviewed, and all were found to be consistent with the natural history of infantile onset SMA.

An imbalance of respiratory serious adverse events was found favoring the placebo group. Specifically, pneumonia, bacteremia, and influenza occurred at least 1% more frequently in the risdiplam group than the placebo group. A serious adverse event of pneumonia occurred in 8% of the risdiplam group compared to 2% of the placebo group. The narratives for these cases were reviewed and found to be consistent with the natural history of SMA. These subjects already had compromised respiratory function before entering the study, demonstrated by a requirement for BIPAP or cough assistance, which increased their risk of respiratory infections. Analysis of the system organ class “Infections and infestations” for SAEs found 14% in the risdiplam arm and 12% in the placebo arm. For AEs, the rates for Infections and infestations were 75% for the risdiplam arm and 80% for the placebo arm. Overall, these results do not suggest a clinically significant difference in infection rates between the risdiplam and placebo arms of the Sunfish study.

Submission-specific safety issues included retinal toxicity, effects on epithelial tissues, hematological effects, and risk of liver injury.

Reference ID: 4646272

Based on the ophthalmology consultant's review of submitted ophthalmology assessments and this reviewer's analysis of vision-related AEs and patient narratives from the Firefish, Sunfish, and Jewelfish studies, there is no pattern of retinal toxicity in the submitted data.

Adverse events in the system organ class (SOC) of "skin and subcutaneous tissue disorders" occurred more frequently in the risdiplam group (31%) than in the placebo group (12%). There were higher rates of rash, including eruption and dermatitis, (13% risdiplam; 2% placebo), mouth ulcers (4% risdiplam; 0% placebo), aphthous ulcers (2.5% risdiplam, 0% placebo), diarrhea (17% risdiplam; 10% placebo), cheilitis (2% risdiplam; 0% placebo), and skin erosion (1% risdiplam; 0% placebo) in the risdiplam group than in the placebo group. These findings suggest that there may be a drug effect on epithelial tissues of the skin and gastrointestinal tract which was not serious and which was also seen in nonclinical studies. This finding should be reported in the risdiplam prescribing information.

The mean changes from baseline in hematologic parameters over all study time points and narratives of outliers were reviewed. There were no clinically significant differences between the risdiplam and placebo groups.

No Hy's Law cases were reported in risdiplam clinical studies. Liver function test results were compared between the placebo and risdiplam groups. There is no clinically significant difference in the risk of liver injury between the placebo and risdiplam-treated subjects.

The Agency's interdisciplinary review team for QT studies confirmed the absence of significant heart rate changes or delayed QTc changes in the submitted data but concluded that "the submitted data are not adequate to characterize the risk of QTc prolongation associated with the oral administration of risdiplam." The QT-IRT recommends that the sponsor characterizes the effect of risdiplam on the QTc interval in a dedicated study. It is acceptable to conduct the QT study in the postmarket setting because there has not been any clinically significant QT/cardiac safety signal in the risdiplam clinical studies.

This reviewer concludes that the safety profile of risdiplam is acceptable.

9. Advisory Committee Meeting and Other External Consultations

Not applicable.

Reference ID: 4646272

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The applicant is proposing the following (b) (4) labeling:

(b) (4)

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

None recommended.

12. Postmarketing Requirements and Commitments

The applicant plans to conduct a two-year carcinogenicity study in rats as a post-marketing commitment.

Reference ID: 4646272

13. Appendices

13.1. References

- Arkblad, E., Tulinius, M., Kroksmark, A., Henricsson, M., & Darin, N. (2009, May). A population-based study of genotypic and phenotypic variability in children with spinal muscular atrophy. *Acta Paediatr, 98*(5), 865-872.
- Arnold, W., Kassar, D., & Kissel, J. (2015, Feb). Spinal muscular atrophy: diagnosis and management in a new therapeutic era. *Muscle Nerve, 51*(2), 157-167.
- Bayley N. Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). 2006.
- Bérard, C., Payan, C., Hodgkinson, I., et al. (2005). A motor function measure scale for neuromuscular diseases. Construction and validation study. *Neuromuscular Disorders* 15: 463-470
- Bonadio, W. (1992, Jun). The cerebrospinal fluid: physiologic aspects and alterations associated with bacterial meningitis. *Pediatr Infect Dis J., 11*(6), 423-431.
- ClinicalTrials.gov identifier: NCT00661453: Phase I/II Trial of Valproic Acid and Carnitine in Infants With Spinal Muscular Atrophy Type I (CARNI-VAL Type I) (https://www.clinicaltrials.gov/ct2/show/NCT00661453)
- Darras, BT (2016). SMA Type I Outcome Measures. Spinal muscular atrophy workshop European Medicines Agency 2016 (oral presentation, 11 November 2016). (http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2016/12/WC500217540.pdf)
- De Sanctis, R., Coratti, G., Pasternak, A., & et al. (2016, Nov). Developmental milestones in type I spinal muscular atrophy. *Neuromuscul Disord, 26*(11), 754-759.
- De Sanctis R, Pane M, Coratti G, et al. Clinical phenotypes and trajectories of disease progression in type 1 spinal muscular atrophy. *Neuromuscular Disorders*. 2018 Jan 1;28(1):24-8.
- Finkel, R. (2013). Electrophysiological and motor function scale association in a pre-symptomatic infant with spinal muscular atrophy type I. *Neuromuscular Disorders* 23: 112–115
- Finkel, R., Bertini, E., Muntoni, F., & Mercuri, E. (2015, Jul). 209th ENMC International Workshop: Outcome Measures and Clinical Trial Readiness in Spinal Muscular Atrophy 7-9 November 2014, Heemskerk, The Netherlands. *Neuromuscul Disord, 25*(7), 593-602.
- Finkel, R., McDermott, M., Kaufmann, P., & et al. (2014, Aug 26). Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology, 83*(9), 810-817.
- Finkel RS, Weiner DJ, Mayer OH, et al. Respiratory muscle function in infants with spinal muscular atrophy type I. *Pediatric pulmonology*. 2014a Dec 1;49(12):1234-42.

Reference ID: 4646272

- Glanzman, A., Mazzone , E., Main, M., Pelliccioni, M., Wood, J., Swoboda , K., et al. (2010, Mar). The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND): test development and reliability. *Neuromuscul Disord, 20*(3), 155-161.
- Glanzman, A., O'Hagen, J., McDermott, M., Martens, W., Flickinger, J., Riley, S., et al. (2011, Dec). Validation of the Expanded Hammersmith Functional Motor Scale in spinal muscular atrophy type II and III. *J Child Neurol, 26*(12), 1499-1507.
- Gregoretti, C., Ottonello, G., Chiarini Testa, M., & et al. (2013, May). Survival of patients with spinal muscular atrophy type 1. *Pediatrics, 131*(5), e1509-1514.
- Jedrzejowska, M., Milewski, M., Zimowski, J., & et al. (2010). Incidence of spinal muscular atrophy in Poland--more frequent than predicted? *Neuroepidemiology, 34*(3), 152-157.
- Kang, P., Gooch, C., McDermott, M., & et al. (2014, May). The motor neuron response to SMN1 deficiency in spinal muscular atrophy. *Muscle Nerve, 49*(5), 636-644.
- Kaufmann, P., McDermott, M., Darras, B., Finkel, R., & et al. (2012, Oct 30). Prospective cohort study of spinal muscular atrophy types 2 and 3. *Neurology, 79*(18), 1889-1897.
- Kolb SJ, Coffey CS, Yankey, JW, et al. (2016). Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. *Annals of Clinical and Translational Neurology*. 3(2): 132–145.
- Kolb SJ, Coffey CS, Yankey JW, et al. (2017). Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol.* 82:883-91.
- Lewelt, A., Krosschell, K., Scott, C., & et al. (2010, Nov). Compound muscle action potential and motor function in children with spinal muscular atrophy. *Muscle Nerve, 42*(5), 703-708.
- Mannaa MM, Kalra M, Wong B, Cohen AP, et al. (2009). Survival probabilities of patients with childhood spinal muscle atrophy. *Journal of clinical neuromuscular disease*. Mar 1;10(3):85-9.
- Matsuzawa, J., Matsui, M., Konishi, T., Noguchi, K., Gur, R., Bilker, W., et al. (2001, Apr). Age-related volumetric changes of brain gray and white matter in healthy infants and children. *Cereb Cortex, 11*(4), 335-342.
- Mazzone, E., Mayhew, A., Montes, J., & et al. (2017, Jun). Revised upper limb module for spinal muscular atrophy: Development of a new module. *Muscle Nerve,* 55(6), 869-874.
- Mercuri, E., Bertini, E., & Iannaccone, S. (2012, May). Childhood spinal muscular atrophy: controversies and challenges. *Lancet Neurol, 11*(5), 443-452.
- Mercuri, E., Finkel, R., Montes, J., & et al. (2016, Feb). Patterns of disease progression in type 2 and 3 SMA: Implications for clinical trials. *Neuromuscul Disord, 26*(2), 126-131.
- O'Hagen, J., Glanzman, A., McDermott, M., & et al. (2007, Oct). An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients. *Neuromuscul Disord, 17*(9-10), 693-697.

Reference ID: 4646272

- Ottesen, E., Howell, M., Singh, N., et al. (2016). Severe impairment of male reproductive organ development in a low SMN expressing mouse model of spinal muscular atrophy. *Scientific Reports,* 6:20193
- Oskoui M, Levy G, Garland CJ, et al. (2007). The changing natural history of spinal muscular atrophy type 1. *Neurology.* Nov 13;69(20):1931-6.
- Park HB, Lee SM, Lee JS, et al. (2010). Survival analysis of spinal muscular atrophy type I. *Korean journal of pediatrics*. Nov 1;53(11):965-70.
- Pera , M., Coratti, G., Mazzone, E., et al. (2019). Revised upper limb module for spinal muscular atrophy: 12 month changes. *Muscle Nerve.* Apr;59(4):426-430.
- Prior, T. (2010, Mar). Perspectives and diagnostic considerations in spinal muscular atrophy. *Genet Med, 12*(3), 145-152.
- Rudnik-Schöneborn S, Berg C, Zerres K, et al. (2009). Genotype–phenotype studies in infantile spinal muscular atrophy (SMA) type I in Germany: implications for clinical trials and genetic counselling. *Clinical genetics*. Aug 1;76(2):168-78.
- Shefner, J., Watson, M., Simionescu, L., & et al. (2011, Jul). Multipoint incremental motor unit number estimation as an outcome measure in ALS. *Neurology, 77*(3), 235-241.
- Sproule DM, Hasnain R, Koenigsberger D, et al. (2012). Age at disease onset predicts likelihood and rapidity of growth failure among infants and young children with spinal muscular atrophy types 1 and 2. *Journal of child neurology.* Jul;27(7):845-51.
- Sugarman, E., Nagan, N., Zhu, H., & et al. (2012, Jan). Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72,400 specimens. *Eur J Hum Genet, 20*(1), 27-32.
- Swoboda, K., Prior, T., Scott, C., & et al. (2005, May). Natural history of denervation in SMA: relation to age, SMN2 copy number, and function. *Ann Neurol, 57*(5), 704-712.
- Swoboda, K., Scott, C., Crawford, T., & et al. (2010, Aug 19). SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. *PLoS One, 5*(8), e12140.
- Wang, C., Finkel, R., Bertini, E., Schroth, M., Simonds, A., Wong, B., et al. (2007, Aug). Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol, 22*(8), 1027-1049.

Reference ID: 4646272

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Sunfish, Firefish, Jewelfish

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: ~600_____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0 _____		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4_____		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 4 _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0_____		
Is an attachment provided with the reason:	N/A☐	No ☐ (Request explanation from Applicant)

Reference ID: 4646272

13.3. CHOP INTEND Scoring Sheet. Source: Glanzman et al., 2010

The **C**hildren's **H**ospital *of* **P**hiladelphia **In**fant **Te**st of **N**euromuscular **D**isorders

CHOP INTEND

Name: _____ Diagnosis:_____ Gestational age: _____weeks

Medical Record Number: _____ Date of Birth: _____ Age_____

Date of Evaluation: ___/___/____ Time of evaluation: _____ Time since last feeding:

Current health: Good health ☐ URI☐ Other illness ☐:_____ Recent surgery ☐:_____

Feeding support: None ☐ Nasogastric Tube ☐ Gastrostomy Tube ☐

Respiratory support: None ☐ BiPAP☐ for ____ hours/day____Time off BiPAP at testing___

	Position	Test Procedure	Graded Response		Score	
1 Spontaneous movement (Upper extremity)	Supine	Observe throughout testing May unweight limb or stimulate infant to facilitate response	Antigravity shoulder movement (achieves elbow off surface)	4	L R	Best side: Brazelton State:
			Antigravity elbow movement (achieves hand and forearm off surface)	3		
			Wrist movement	2		
			Finger movement	1		
			No movement of limbs	0		
2 Spontaneous movement (Lower extremity)	Supine	Observe throughout testing May unweight limb or stimulate infant to facilitate response	Antigravity hip movement (achieves feet and knees off surface)	4	L R	Best side: Brazelton State:
			Antigravity hip adduction/internal rotation (knees off surface)	3		
			Active gravity eliminated knee movement	2		
			Ankle movement	1		
			No movement of limbs	0		
3 Hand grip	Supine	Grip strength: place finger in palm and lift until shoulder comes off surface observe when infant looses grasp May use toy of similar diameter for older children	Maintains hand grip with shoulder off bed	4	L R	Best side: Brazelton State:
			Maintains grip with elbow off surface (shoulders on surface)	3		
			Maintains grip with forearm off surface (elbow supported on surface)	2		
			Maintains grip only with no traction	1		
			No attempt to maintain grasp	0		
4 Head in midline with visual stimulation*	Supine head midline	Visual stimulation is given with toy. ***If head is maintained in midline for 5 seconds:*** Place head in maximum available rotation and provide visual stimulation to encourage midline	Rotates from maximum rotation to midline	4	L>R R>L	Best side: Brazelton State:
			Turns head part way back to midline	3		
			Maintains midline for 5 or more seconds	2		
			Maintains midline, less than 5 seconds	1		
			Head falls to side, no attempts to regain midline	0		
5 Hipadductors	Supine, no diaper	Hips flexed and adducted Feet hip width apart and thighs parallel, knees slightly apart	Keeps knee off surface of bed > 5 sec or lifts foot off surface	4	L R	Best side: Brazelton State:
			Keeps knees off surface of bed 1-5 sec	2		
			No attempt to maintain knees off surface	0		

Reference ID: 4646272

Reference ID: 4646272

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

RAINER PAINE
07/24/2020 11:55:25 AM

TERESA J BURACCHIO
07/24/2020 11:58:11 AM