Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Risdiplam

Proprietary Product Name: Evrysdi

Sponsor: Roche Products Pty Ltd

August 2021

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
ADR	Adverse drug reaction
AE	Adverse event
ARTG	Australian Register of Therapeutic Goods
ASA	Australia specific annex
AUC	Area under the concentration versus time curve
$AUC_{0\text{-}24h}$	Area under the concentration versus time curve from time zero (dosing) to 24 hours
AusPARs	Australian Public Assessment Report
BMI	Body mass index
BSID-III	Bayley Scales of Infant and Toddler Development (Third edition)
CCOD	Clinical cutoff date
CHOP-INTEND	Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CI	Confidence interval
CL/F	Oral clearance
C_{max}	Maximum plasma concentration
CSR	Clinical study report
CYP	Cytochrome P450
DDI	Drug-drug interaction
DLP	Data lock point
EU	European Union
FDA	Food and Drug Administration (United States of America)
FMO1	Flavin monooxygenase 1
FMO3	Flavin monooxygenase 3
GVP	Good Pharmacovigilance Practices

Abbreviation	Meaning
HFMSE	Hammersmith Functional Motor Scale Expanded
HINE-2	Hammersmith Infant Neurological Examination Module 2
MFM32	Motor function measure 32
MMRM	Mixed model repeated measures
MRHD	Maximum recommended human dose
NNT	Number of patient needed to treat
NOAEL	No observable effect level
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PopPK	Population pharmakinetic(s)
PSUR	Periodic safety update report
PT	Preferred Term
PY	Patient-years
RMP	Risk management plan
RPE	Retinal pigment epithelium
RULM	Revised upper limb module
SAE	Serious adverse event
SMA	Spinal muscular atrophy
SMN1	Survival of motor neuron 1
SMN2	Survival of motor neuron 2
SMNΔ7	SMN2 transcripts that lacks exon 7
SOC	System Organ Class
TGA	Therapeutic Goods Administration
T_{max}	Time of maximum concentration
URTI	Upper respiratory tract infection
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Product name:	Evrysdi
Active ingredient:	Risdiplam
Decision:	Approved
Date of decision:	2 June 2021
Date of entry onto ARTG:	2 June 2021
ARTG number:	340350
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Roche Products Pty Limited Level 8, 30-34 Hickson Road Sydney, NSW, 2000
Dose form:	Powder for oral liquid
Strength:	0.75 mg/mL
Container:	Bottle
Pack size:	One
Approved therapeutic use:	*Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients aged 2 months and older.*
Routes of administration:	Oral and nasogastric
Dosage:	The recommended once daily dose of Evrysdi for spinal muscular atrophy (SMA) patients is determined by age and body weight. For further information regarding dosage, refer to the Product Information.

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Roche Products Pty Ltd (the sponsor) to register Evrysdi (risdiplam) 0.75 mg/mL, powder for oral liquid (via bottle, powder for oral solution) for the following proposed indication:

For the treatment of 5q spinal muscular atrophy (SMA).

Risdiplam is a first-in-class, orally administered small molecule splicing modifier for the survival of motor neuron 2 gene (*SMN2*) pre-messenger ribonucleic acid (mRNA). Risdiplam is designed to treat 5q spinal muscular atrophy (SMA).

5q spinal muscular atrophy is the most common form of SMA;[2] there are a number of rare non-5q SMAs that are genetically and clinically diverse. In this AusPAR, only 5q SMA will be considered and therefore referred to as 'SMA.' SMA is a rare autosomal recessive neuromuscular disorder caused by homozygous deletion (95% of cases) or mutation in both alleles of the *survival of motor neuron 1* (*SMN1*) gene on chromosome 5q (locus 5q13). *SMN1* encodes SMN protein, an essential protein expressed in both neuronal and non-neuronal cells. In humans, there are two *SMN* genes, the *SMN1* gene and its paralog *SMN2*. The *SMN2* pre-mRNA undergoes alternative splicing that excludes exon 7 from 85% to 90% of mature *SMN2* transcripts, which produces an unstable *SMN2* transcripts that lacks exon 7 (SMNΔ7) protein that is rapidly degraded. Full-length *SMN2* mRNA is generated in only 10% to 15% of splicing events. SMA is the consequence of decreased, insufficient levels of functional SMN protein due to the lack of functional protein from the *SMN1* gene and the limited amount of functional protein produced by the *SMN2* gene. Those with multiple copies of the *SMN2* gene have milder phenotypes.

[2] Autosomal recessive proximal spinal muscular atrophy, responsible for 90 to 95% of cases is usually referred to simply as spinal muscular atrophy (SMA), associated with a genetic mutation on the *SMN1* gene on chromosome 5q (locus 5q13). The human chromosome 5 contains two near identical genes at location 5q13: a telomeric copy *SMN1* and a centromeric copy *SMN2*. In healthy individuals, the *SMN1* gene codes the survival of motor neuron protein (SMN) which, plays a crucial role in survival of motor neurons. The *SMN2* gene, due to a variation in a single nucleotide (840.C→T) undergoes alternative splicing at the junction of intron 6 to exon 8, with only 10 to 20% of *SMN2* transcripts coding a fully functional survival of motor neuron protein (SMN-fl) and 80 to 90% of transcripts resulting in a truncated protein compound (SMNΔ7) which is rapidly degraded in the cell.
The localised spinal muscular atrophies (5 to 10% of cases) are much more rare conditions, in some instances described in but a few patients in the world, which are associated with mutations of genes other than *SMN1* and for this reason sometimes termed simply *non-5q spinal muscular atrophies*.

Spinal muscular atrophy is characterised by the dysfunction of alpha motor neurons within the anterior horn of the spinal cord, leading to skeletal muscle weakness and atrophy. Clinically, muscle weakness and atrophy are symmetrical and most severe in the proximal limbs. The most severe infantile onset disease results in failure to gain motor milestones, no meaningful motor function and loss of respiratory and bulbar muscle function leading to early death. In later onset disease, the distribution of weakness is the same, leading to profound disability due to poor mobility and poor proximal upper limb function, with many patients requiring respiratory and feeding support.

Spinal muscular atrophy subtypes are defined by age at onset and the most advanced motor milestone achieved during development and are classified as Types 0 through to 4;[3] where Types 1, 2 and 3 represent approximately 99% of the SMA population. Type 0 (congenital SMA) is rare and most patients do not survive beyond 6 months of age. SMA Type 4 (adult onset) accounts for approximately 1% of all SMA cases. Although SMA is clinically classified into these different 'types', which reflect the severity of its impact, SMA can be better considered as encapsulating a disease spectrum or continuum. It is the leading genetic cause of mortality in infants and young children, with an estimated incidence of 1 in 6,000 to 1 in 10,000 live births and with a carrier frequency of 1 in 40 to 60 individuals. The estimated prevalence is less than 5 in 10,000 individuals.

In Australia, Spinraza (nusinersen) is approved for the treatment of SMA.[4] Nusinersen is drug, administered intrathecally (or via the spinal canal) and is a*SMN2* targeting antisense oligonucleotide, first registered in 2017. Spinraza (nusinersen) is indicated '*for the treatment of 5q spinal muscular atrophy (SMA)*'. Maintenance dosing of nusinersen is administered every four months.

[3] Classically, the types of SMA are characterised as follows:
SMA Type 0 is the most severe form, characterised by decreased fetal movement, joint abnormalities, difficulty swallowing and respiratory failure.
SMA Type 1 is the most common type and is also a severe form. Infants with SMA Type 1 experience severe weakness before 6 months of age and never sit independently. Muscle weakness, lack of motor development and poor muscle tone are major clinical manifestations of SMA type 1. Infants with the gravest prognosis have problems sucking or swallowing. Abdominal breathing may be present in the first few months of life. Muscle weakness occurs on both sides of the body and the ocular muscles are not affected. Twitching of the tongue is often seen. Intelligence is normal. Most affected children die before two years of age but survival may be dependent on the degree of respiratory function.
SMA Type 2 has an onset of muscle weakness typically between 6 and 12 months. Affected children are able to sit independently early in development but are unable to walk less than 3 metres independently. Tremor of the fingers is notable. Approximately 70% of those affected do not have deep tendon reflexes. Those affected with SMA Type 2 are usually not able to sit independently by the mid-teens or later.
SMA Type 3 may be characterised by the ability to learn to walk but fall frequently, with great trouble walking up and down stairs at 2 to 3 years of age. The legs are more severely affected than the arms. The long-term prognosis depends on the degree of motor function attained as a child.
SMA Type 4 presents with the onset of muscle weakness typically after the age of 10 years; patients with SMA Type 4 are usually ambulatory until age 60 years.
Complications of SMA include respiratory difficulty and distress, scoliosis, joint contractures, pneumonia and metabolic abnormalities such as severe metabolic acidosis and dicarboxylic aciduria.
[4] **Spinraza** is registered on the ARTG on 3 November 2017, ARTG number: 282522. See the AusPAR: Spinraza Nusinersen (as heptadecasodium) Biogen Australia Pty Ltd PM-2016-04042-1-3 at https://www.tga.gov.au/auspar/auspar-nusinersen-heptadecasodium

Zolgensma (onasemnogene abeparvovec) is an intravenously administered gene replacement therapy that only needs to be administered once per patient, that delivers a functional copy of the *SMN* gene. Zolgensma has been approved in Australia,[5] the United States of America (USA) and Japan for paediatric patients with SMA. In the European Union (EU), Zolgensma is approved conditionally for the treatment of patients up to 21 kg in weight with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1, or with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to three copies of the *SMN2* gene.

Regulatory status

This product is considered a new chemical entity for Australian regulatory purposes.

At the time the TGA considered this application, similar applications had been approved in the European Union (EU) on 26 March 2021 and the United States of America (USA) on the 7 August 2020. At the time this submission was considered, Evrysdi was under consideration in Canada, Japan, Switzerland and the United Kingdom.

Table 1: International regulatory status

Region	Submission date	Status	Approved indications
European Union	21 July 2020	Marketing authorisation approved on 26 March 2021	*Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients 2 months of age and older, with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four SMN2 copies*
United States of America	17 September 2019	Approved on 7 August 2020	*Evrysdi is indicated for the treatment of spinal muscular atrophy (SMA) in patients 2 months of age and older*
Canada	July 2020	Under consideration	Under consideration
Japan	October 2020	Under consideration	Under consideration
Switzerland	19 August 2020	Under consideration	Under consideration
United Kingdom	21 July 2020 (as part of the European Union filing)	Under consideration	Under consideration

[5] **Zolgensma** is registered on the ARTG on 4 March 2021, ARTG number: 327905, 327906 and 327907. See the AusPAR Zolgensma Onasemnogene abeparvovec Novartis Pharmaceuticals Australia Pty Ltd PM-2019-05979-1-3 at https://www.tga.gov.au/auspar/auspar-onasemnogene-abeparvovec

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2020-03580-1-3

Description	Date
Positive Designation as: Orphan;[6] Priority;[7]	 30 June 2020 30 June 2020
Submission dossier accepted and first round evaluation commenced	31 August 2020
Evaluation completed	23 February 2021
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	3 March 2021
Sponsor's pre-Advisory Committee response	17 March 2021
Advisory Committee meeting	8 and 9 April 2021
Registration decision (Outcome)	2 June 2021
Completion of administrative activities and registration on the ARTG	2 June 2021
Number of working days from submission dossier acceptance to registration decision*	145

*Target timeframe for priority applications is 150 working days from acceptance for evaluation to the decision.

[6] 'Orphan drugs' are often developed to treat small and very specific patient populations who suffer from rare diseases and conditions. In order to facilitate orphan drug access to the Australian marketplace and help offset orphan drug development costs the TGA waives application and evaluation fees for prescription medicine registration applications if a related **orphan designation** is in force. A medicine may be eligible for orphan drug designation if all orphan criteria set by the TGA are met. The orphan designation application precedes the registration application and the designation is specific to the sponsor, orphan indication for which designation was granted and dosage form of the medicine.

[7] The TGA has implemented a **priority pathway** for the registration of novel prescription medicines for Australian patients. The priority pathway provides a formal mechanism for faster assessment of vital and life-saving prescription medicines. The target timeframe of 150 working days is up to three months shorter than the standard prescription medicines registration process.

III. Submission overview and risk/benefit assessment

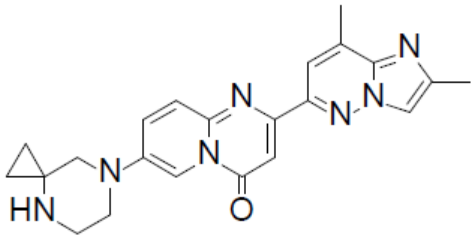
The submission was summarised in the following Delegate's overview and recommendations.

Quality

The quality evaluator recommended approval of the proposed product from a pharmaceutical chemistry perspective. There were no outstanding issues.

The proposed formulation is a powder for oral solution. Evrysdi is supplied in a glass bottle filled with 2 g of powder containing 60 mg of risdiplam, in a carton. The powder is reconstituted with 79 mL of purified water or sterile water for injections (not supplied) to form an oral solution containing risdiplam 0.75 mg/mL. Reconstitution of the powder is to be performed by a healthcare professional. The chemical structure of risdiplam is shown in Figure 1.

Figure 1: Chemical structure of risdiplam



Nonclinical

The nonclinical evaluator did not support the approval of risdiplam on nonclinical grounds. The nonclinical data identified a number of serious toxicities with little or no safety margins at the maximum recommended human dose (MRHD) based on relative exposure. The most serious of these was retinal toxicity, which has a delayed onset and displays irreversibility. There was a narrow margin between exposures that were well tolerated and those associated with severe toxicities, including mortality, in nonclinical studies. Many of the toxicities were related to secondary pharmacological effects, which were associated with low relative exposures.

The primary pharmacology data supported the proposed use, with *in vitro* and *in vivo* studies demonstrating that risdiplam can increase levels of full length *SMN2* transcripts translating to an increase in SMN protein (≤ 3 times). Risdiplam improved survival, weight gain and neuromuscular connectivity in a mouse model of severe SMA.

Secondary pharmacology data indicated a lack of specificity of risdiplam for the *SMN2* gene at clinically relevant concentrations. Toxicities associated with these off target effects were seen in repeat dose toxicity studies conducted in adult and juvenile rats and monkeys. Given that risdiplam is not pharmacologically-active in any animal species (due to absence of the *SMN2* gene), the chosen species were appropriate for screening splice modification of off target pre-mRNA of other genes, albeit with the possibility for potential species differences in pre-mRNA consensus positions and SR proteins.[8] Secondary pharmacological effects were observed in rats and monkeys at low relative exposures, and

[8] SR proteins are a highly conserved family of proteins involved in ribonucleic acid (RNA) splicing. SR proteins are named because they contain a protein domain with long repeats of serine and arginine amino acid residues, whose standard abbreviations are 'S' (for serine) and 'R' for arginine.

are a plausible explanation for some of the observed toxicities in skin, gastrointestinal tissues, male reproductive tissues, bone marrow and possibly retina. It is reasonable to expect that all these effects may occur in patients given their occurrence at relatively low exposure multiples in animals. Six additional genes were identified as having their splicing altered by risdiplam, including those involved in cell cycle regulation:

- forkhead box protein M1 (encoded by the *FOXM1* gene), a transcription factor involved in cell cycle regulation and other cellular functions, with the enrichment of the inactive transcript observed (leading to mitotic arrest).
- mitogen activating protein kinase (*MAPK*) activating death domain, an apoptosis regulator which is involved in spermatogenesis. The nonclinical data indicates enrichment of potential two transcript variants, one of which is pro-apoptotic, and the other with unknown function.
- striatin 3 (*STRN3*), which is a multi-function gene with roles in non-genomic oestrogen signalling, cell cycle progression and signal transduction. The functional consequence of the enriched transcript variant is not known.
- amyloid β precursor-like protein 2, a transmembrane glycoprotein encoded for by the amyloid precursor protein (*APP*) gene. The alternative splicing affected an exon expressing a domain which inhibits the coagulation factor XV1a, and plays a role in regulating cerebral thrombosis.
- Solute carrier family 25 member 17, encoded for by the *SLC25A17* gene, a peroxisomal transporter. The functional effects of splice variants are unknown.
- Gamma-glutamylcyclotransferase, encoded by the *GGCT* gene, involved in glutathione homeostasis and intrinsic apoptosis. The functional effects of splice variants are unknown.

The nonclinical evaluator considered the identified secondary pharmacology effects were probably monitorable to varying extents. However, the splicing changes reported *in vitro* and *in vivo* also include increased expression of splice variants with unknown functional effects. The following key target organs for toxicity were identified and are considered to be of likely relevance to patients: retina (reactive gliosis leading to retinopathy which was not clearly reversible), gastrointestinal tract (single cell necrosis and/or apoptosis, crypt micro-abscess), skin/eyelid (hyperplasia, parakeratosis, apoptosis, erosion/ulcer), testis/ epididymis (atrophy, degeneration and/or vacuolation), and haematopoietic system/ bone marrow (micronuclei induction, atrophy of marrow and/or lymphoid tissues, reduced erythrocyte and/or lymphocyte parameters). In skin, hyperplasia was also observed suggesting a regenerative response. The consequences of prolonged cell cycle perturbations, including in tissues such as bone marrow, have not been fully investigated in animal studies (that is in lifetime studies).

Risdiplam binds strongly to melanin and leads to marked accumulation and retention in pigmented tissues, including the retinal pigment epithelium (RPE), choroid and retinal tissue in the eye. Retinal toxicity occurred at only 3.3 times the anticipated clinical exposure with a delayed onset. Similar toxicity was observed for the related molecule RO6885247 at a similar relative exposure, which led to termination of the clinical trials for this molecule. In pigmented rats, accumulation of risdiplam was more pronounced than that observed for RO6885247, even when administered at a lower dose. The concentrations of risdiplam observed in ocular tissue in rats and monkeys markedly exceeded the levels shown to be cytotoxic, impair lysosome function and lead to autophagosome accumulation *in vitro*.

Reductions in sperm count, motility and an increase in morphological abnormalities were observed in male rats that had received oral risdiplam at low exposure margins (approximately 4 times) but there was no effect on mating performance or fertility index.

There were no clear effects on reproductive tissues in female monkeys. Risdiplam caused maternal and embryofetal toxicity without signs of malformations in rats (No observed effect levels (NOAEL) in exposure ratio based on area under concentration time curve (AUC) of 3.4 times). In rabbits, risdiplam was severely maternotoxic and teratogenic. Exposure at the NOAEL was marginally above clinical exposures. Findings in the rat pre-postnatal study included dystocia and delayed sexual and impaired reproductive function in female offspring. Exposures at the NOAEL were clinically relevant. The sponsor has proposed Pregnancy Category D;[9] which is appropriate given concerns over the malformations seen in rabbits and the embryofetal toxicity seen in rats and rabbits at low exposure margins. Even though teratogenicity was only noted in the rabbit at a maternotoxic level, the possibility of a dysmorphogenic effect of risdiplam in the human cannot be discounted.

Clinical

The clinical dossier consisted of:

- five pharmacology studies (Studies BP29840, BP39122, NP39625, BP41361 and BP40995);
- one population pharmacokinetics (PopPK) study;
- two ongoing pivotal efficacy/safety Phase III studies (Part 2 of BP39056 and Part 2 of BP39055);
- two ongoing Phase II dose-finding studies (Part 1 of BP39056 and Part 1 of BP39055);
- safety data from one ongoing Phase II open label (OL) study (Study BP39054).

Note that Study BP39055 is also known as the SUNFISH trial, Study 39056 as the FIREFISH trial and Study BP39054 as the JEWELFISH trial.

Pharmacology

Pharmacokinetics

Pharmacokinetics (PK) parameters for Evrysdi have been characterised in healthy adult subjects and in patients with SMA. No dedicated PK studies were undertaken in patients with SMA.

In healthy adult subjects risdiplam was rapidly absorbed, with first quantifiable concentrations observed for all subjects between 0.5 and 1 hours post-dose in the 0.6 to 18 mg dose range. Risdiplam is classified as highly permeable, with passive diffusion the most likely mechanism for its cell permeability. Median time to maximum plasma concentration (T_{max}) of risdiplam was approximately 2 to 3 hours in healthy adults in the fasted state, after single risdiplam doses and between 2 to 4 hours in healthy subjects at steady state. Most of the absorption is estimated to take place in the duodenum (32.7%) and jejunum (55.1%), with the remaining risdiplam absorbed further down the gastrointestinal tract.

No absolute bioavailability study was conducted. Results from the mass balance study were generally supportive of moderate to high oral bioavailability.

The presence of food delayed risdiplam median T_{max} by approximately 2.5 hours. This was not clinically meaningful and is generally consistent with delayed gastric emptying

[9] **Pregnancy Category D**: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

observed with food administration. Presence of food did not appear to have a clinically meaningful effect on risdiplam exposure (maximum plasma concentration (C_{max}) and AUC). However, these results should be interpreted with caution, as there was no formal crossover study, the study lacked statistical power and a non-marketed formulation was used. In the clinical efficacy studies, risdiplam was administered with a morning meal or after breastfeeding.

The estimated exposure based on the mean area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24h}) for infantile onset SMA patients (age 2 to 7 months at enrolment) at the therapeutic dose of 0.2 mg/kg once daily was 1930 ng x h/mL. The estimated exposure for later onset SMA patients (2 to 25 years old at enrolment) in Part 2 of the SUNFISH trial (Study BP39055)

) at the therapeutic dose (0.25 mg/kg once daily for patients with a body weight < 20 kg; 5 mg once daily for patients with a body weight ≥ 20 kg) was 2070 ng x h/mL. The mean observed C_{max} was 194 ng/mL at 0.2 mg/kg in Study 39056 (the FIREFISH trial) and Study BP39054 as the JEWELFISH trial and 120 ng/mL in SUNFISH trial Part 2 (Study BP39055).

The population PK parameter estimates were 98 L for the apparent central volume of distribution, 93 L for the peripheral volume, and 0.68 L/hour for the inter-compartment clearance.

Risdiplam is predominantly bound to serum albumin, with a free fraction of 11%.

Risdiplam turnover was found to be greatest in liver followed by kidney and intestine. Main contributors to the metabolism of risdiplam were flavin monooxygenase 1 and 3 (FMO1 and 3) and cytochrome P450 (CYP) CYP3A enzymes,[10] particularly CYP3A4. Other CYP enzymes included CYP1A and CYP2J2.

No dose adjustments are needed in paediatric (aged 2 months and older) and adult populations when risdiplam is co-administered with strong CYP3A inhibitors (for example, itraconazole) or CYP3A substrates (for example, midazolam).

Population PK analyses estimated an apparent clearance (CL/F) of 2.6 L/h for risdiplam. The effective half-life of risdiplam was approximately 50 hours in SMA patients.

Risdiplam is not a substrate of human multidrug resistance protein 1.

Approximately 53% of the dose (14% unchanged risdiplam) was excreted in the faeces and 28% in urine (8% unchanged risdiplam). This indicates that the hepatic/biliary route is important for excretion of risdiplam and its metabolites. Parent drug was the major component found in plasma, accounting for 83% of drug related material in circulation. The pharmacologically inactive metabolite M1 was identified as the major circulating metabolite.

Mild and moderate hepatic impairment had no impact on the PK of Evrysdi. After administration of Evrysdi 5 mg, the mean ratios for C_{max} and AUC were 0.95 and 0.80 in mild (n = 8) and 1.20 and 1.08 in moderate hepatic impaired subjects (n = 8) versus

[10] **Cytochrome P450 (CYP) enzymes:** CYPs are the major enzymes involved in drug metabolism, accounting for large part of the total metabolism. Most drugs undergo deactivation by CYPs, either directly or by facilitated excretion from the body. Also, many substances are bioactivated by CYPs to form their active compounds.
Many drugs may increase or decrease the activity of various CYP isozymes either by inducing the biosynthesis of an isozyme (enzyme induction) or by directly inhibiting the activity of the CYP (enzyme inhibition). This is a major source of adverse drug interactions, since changes in CYP enzyme activity may affect the metabolism and clearance of various drugs. Such drug interactions are especially important to take into account when using drugs of vital importance to the patient, drugs with important side-effects and drugs with small therapeutic windows, but any drug may be subject to an altered plasma concentration due to altered drug metabolism.

matched healthy controls (n = 10). The safety and PK in patients with severe hepatic impairment have not been studied.

No studies have been conducted to investigate the PK of Evrysdi in patients with renal impairment. Elimination of risdiplam as an unchanged entity via renal excretion is minor (8%).

No dedicated studies have been conducted to investigate the PK of Evrysdi in patients with SMA above 60 years of age. Patients with SMA up to 60 years of age were included in Study BP39054 (the JEWELFISH trial). Subjects without SMA up to 69 years of age were included in clinical PK studies, which indicates that no dose adjustment is required for patients up to 69 years of age.

Body weight and age were identified as covariates in the population PK analysis. The dose is therefore adjusted based on age (below and above 2 years) and body weight (up to 20 kg) to obtain similar exposure across the age and body weight range. No data are available in patients less than 2 months of age.

Population pharmacokinetic data

The submission included the population pharmacokinetic (PopPK) analysis 1102699 which included rich and sparse plasma concentration data obtained from three ongoing Phase II/III studies in SMA patients (Studies BP39054, BP39055 and BP39056) and two completed Phase I studies in healthy adult subjects (Studies BP29840 and BP41361). The final PopPK model of risdiplam was developed on 10,222 plasma concentration data points of risdiplam collected from 525 subjects (healthy subjects: n = 61; SMA patients: n = 464).

The median age of patients was 12.3 years (Range: 2 months to 61 years), with median body weight of 33.0 kg (Range: 4.1 to 109 kg). There were 279 males, 248 females, 61 healthy subjects, 77 patients with SMA Type 1, 272 patients with SMA Type 2, 93 patients with SMA Type 3 (non-ambulatory) and 23 patients with ambulatory Type 3 SMA. Most participants were White (n = 379; 71.9%).

The PK of risdiplam were described by a three transit compartment absorption model connected to a two compartment model for disposition with first order elimination. PK were comparable in healthy subjects and SMA populations. BW and age had significant effects on PK. Hence, the proposed dose regimens were based on patient age and BW to achieve the targeted mean $AUC_{0\text{-}24h}$ of approximately 2000 ng xh/mL across all studies, irrespective of SMA Type (1, 2 or 3) or gender. Although patient numbers were small, Asian race (Japanese; n = 16 or Chinese; n = 27 origin) was not a statistically or clinically relevant covariate. Risdiplam had an apparent clearance (CL/F) of 2.6 L/h.

There were 41 (7.8%) SMA patients (Type 1; n = 5) with records of risdiplam taken with concomitant antacids (of any class). This percentage did not attain the pre-specified 10% minimum number of patients to be included as a covariate in the PopPK model. The influence of antacid use on relative bioavailability of the final PopPK model was estimated as a reduction of 7.2%, which is not regarded as clinically significant (≥ 20%). However, the relative standard error was 57.6%, which is indicative of high uncertainty for the estimate. The transit rate constant remained generally unchanged irrespective of antacid exposure.

Pharmacodynamics

Median time to maximum effect was reached between 4 and 8 hours post-dose, across all dose groups. The population analysis found treatment with risdiplam led to an approximate two-fold median increase in SMN protein versus Baseline in the Phase III clinical studies in SMA patients. SMN protein increased rapidly within 4 weeks after treatment initiation and the increased SMN protein level was maintained over the entire treatment duration.

There was a positive correlation between risdiplam plasma exposure and the effect on the splicing modification expressed as the $AUC_{0\text{-}24h}$ of the full length *SMN2* over SMNΔ7 mRNA ratio. At the highest risdiplam concentrations, depletion of SMNΔ7 mRNA was almost complete.

There were no meaningful differences in treatment effect on mRNA or SMN protein between Caucasian and Japanese subjects. The population analysis found no meaningful differences in treatment effect on mRNA or SMN protein, by age or gender distribution.

No dedicated thorough QT/QTc (tQT) study was submitted but the sponsor provided an analysis of QTc;[11] based on available electrocardiogram and PK data and a *post-hoc* analysis of paediatric patients from Study BP39056 Part 2 (the Firefish trial). There was no clear cardiac/QT safety signal following risdiplam exposure. This conclusion is supported by the findings of a Clinical Review issued by the US Food and Drug Administration (FDA), which recommended a thorough QT study be undertaken on a post-approval basis, to meet the FDA's regulatory requirements.

Efficacy

The submission included primary analysis results from two ongoing Phase III pivotal studies (Part 2 of Study BP39056 (the Firefish trial) in infantile onset SMA Type 1 and Part 2 of Study BP39055 (the Sunfish trial) in later onset SMA Types 2 and 3 (non-ambulatory)) and their ongoing Part 1 phases.

Pivotal Study BP39056 (FIREFISH trial), Part 2

Study BP39056 was a two part, multicentre, single arm, open label study that consisted of an ongoing Phase II dose finding Part 1, an ongoing confirmatory Phase III Part 2, of 24 months duration, followed by an open label extension phase (open label extension). The study objectives were to investigate the safety, tolerability, PK, pharmacodynamics and efficacy of risdiplam in infants (aged 1 to 7 months at enrolment) with symptomatic SMA Type 1.

The study included infants born at gestational age of 37 to 42 weeks, aged 1 to 7 months, with a confirmed diagnosis of 5q-autosomal recessive SMA with two *SMN2* gene copies. Patients were excluded if they required invasive ventilation, tracheostomy or had hypoxemia with or without ventilation support. Patients were also excluded if they had been hospitalised for a pulmonary event within the last two months or had received concomitant or previous treatment with a *SMN2* targeting antisense oligonucleotide, a *SMN2* splicing modifier or gene therapy.

The following starting dose levels were selected for Study BP39056 Part 2:

- infants > 1 month old and below 3 months of age at enrolment: 0.04 mg/kg;
- infants at least 3 months of age but below 5 months of age at enrolment: 0.08 mg/kg;
- infants 5 months of age or older at enrolment: 0.2 mg/kg.

The dose for infants aged < 5 months of age was subsequently increased to 0.2 mg/kg.

No randomisation or blinding was undertaken due to the open label study design. 41 patients with SMA Type 1 across 14 sites from ten countries were enrolled into Study BP39056 Part 2. 53.7% of subjects were female and 46.3% were male. Median age

[11] The QT interval is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.
The **corrected QT interval (QTc)** estimates the QT interval at a standard heart rate. This allows comparison of QT values over time at different heart rates and improves detection of patients at increased risk of arrhythmias.

at enrolment was 5.3 months (range: 2.2 to 6.9 months). 53.7% of patients were older than 5 months. Most patients were White (53.7%) or Asian (34.1%); and from Europe (58.5%). Patients' weight for age values were at or below the 50th percentile at Baseline, based on World Health Organization (WHO) child growth standards, for the majority of patients (29 out of 41, 70.7%). The median weight for age percentile of 24 (Range: 0.2 to 99th percentile); and length/height for age values were > the 50th percentile for most patients (63.4%), with median length/height for age percentile of 66.2 (Range: 0.3 to 100th percentile).

The primary efficacy endpoint was the proportion of patients sitting without support for at least five seconds, as assessed by Item 22 of the Bayley Scales of Infant and Toddler Development Third Edition (BSID-III);[12] gross motor scale at Month 12. Risdiplam treatment was associated with an approximate six fold greater improvement compared to the pre-specified natural history performance criterion of 5% (See Table 3). This difference was both statistically significant and clinically meaningful. Compared to the natural history of (untreated) SMA Type 1, with a threshold criterion of 5%, the number of patients needed to treat (NNT) to achieve a positive treatment effect from risdiplam, at the pivotal dose, over 12 months of treatment, was approximately 4.

The results of the sensitivity analyses and the subgroup analyses for the primary efficacy endpoint were generally consistent with the primary analysis except for male patients, who had a lower proportion achieving the primary endpoint compared to female subjects, that is 5.3% (n = 1) versus 50.0% (n = 11), respectively. This comparison included 3 male infants who died before the Month 12 efficacy analysis and were categorised as non-responders, as per protocol.

Table 3: Study BP39056 Results for the primary efficacy endpoint

Endpoint	Risdiplam (N=41)	Performance Criterion	p-value [a]
Primary Efficacy Endpoint			
Proportion of patients sitting without support for at least 5 seconds (BSID-III) (90% CI)	29.3% (17.8%, 43.1%)	5%	<0.0001

N = number of participants; BSID-III = Bayley Scales of Infant and Toddler Development (third edition); CI = confidence interval.

The key secondary efficacy endpoints at Month 12 (in hierarchical order) were the:

- proportion of patients who achieve a Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND) score of 40 or higher;[13]
- proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from Baseline;
- proportion of motor milestone responders, as assessed by the Hammersmith Infant Neurological Examination Module 2 (HINE-2);[14]

[12] The **Bayley Scales of Infant and Toddler Development (third edition)** (BSID-III)is one of the most comprehensive tools to assess children from as young as one-month-old.
Children are assessed in the five key developmental domains of: cognition; language; social-emotional; motor and adaptive behaviour. Bayley-III identifies infant and toddler strengths and competencies, as well as their weakness. It also provides a valid and reliable measure of a child's abilities.
[13] The **Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders** (CHOP-INTEND) is a reliable measure of motor skills in patients with SMA-I and neuromuscular disorders presenting in infancy.
[14] The **Hammersmith Infant Neurological Examination** (HINE-2) consists of 26 items that assess different aspects of neurological function: cranial nerve function, movements, reflexes and protective reactions and behaviour, as well as some age dependent items that reflect the development of gross and fine motor function. The HINE is aimed to be used for infants between 3 and 24 months of age.

- proportion of patients alive without permanent ventilation.

After 12 months, risdiplam treatment was associated with statistically significant and clinically meaningful improvements in key motor function and development milestones, as well as ventilation free survival (See Table 4).

Table 4: Study BP39056 Results for the key secondary efficacy endpoints

Key secondary efficacy endpoint	Risdiplam (N =41)	Performance criterion	P-value	NNT
Proportion of patients who achieve a CHOP-INTEND score of 40 or higher (90% CI): Key 01	56.1% (42.1%, 69.4%)	17%	<0.0001	3
Proportion of patients who achieve an increase of at least 4 points in their CHOP-INTEND score from baseline (90% CI): Key 02	90.2% (79.1%, 96.6%)	17%	<0.0001	1
Proportion of motor milestone responders as assessed by the HINE-2 (90% CI): Key 03	78.0% (64.8%, 88.0%)	12%	<0.0001	2
Proportion of patients alive without permanent ventilation (90% CI): Key 04	85.4% (73.4%, 92.2%)	42%	<0.0001	2

CHOP-INTEND = Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2 = Hammersmith Infant Neurological Examination Module 2; NNT = numbers needed to treat; CI = confidence interval.

Pivotal Study BP39055 (SUNFISH trial), Part 2

Study BP39055 is a two part, multicentre study that consisted of a Phase II, randomised, placebo controlled, double blind dose finding Part 1, and an ongoing pivotal Phase III Part 2, randomised, placebo controlled, double blind period of 12 months duration, followed by a 12 month blinded period at the pivotal dose selected from Part 1, and an open label extension period (See Figure 2). The study objectives were to evaluate the efficacy (including motor and respiratory function) of risdiplam in patients with SMA Type 2 and non-ambulant SMA Type 3 in patients aged 2 to 25 years.

Figure 2: Study BP3905 Study plan

The study included subjects aged 2 to 25 years of age at screening, with a confirmed diagnosis of 5q-autosomal recessive SMA, including clinical symptoms attributable to SMA Type 2 or Type 3. Non-ambulant participants had to have revised upper limb module (RULM) entry;[15] item A at screening ≥ 2 and an ability to sit independently. Exclusion

[15] The revised upper limb module for SMA has been devised to assess motor performance in the upper limbs for individuals with spinal muscular atrophy. This scale consisted of 20 items that test proximal and distal motor functions of the arm, administered by a trained physiotherapist or other trained administrator. It is simple to administer, measures functions related to everyday life and is applicable to children from 2 years of age. The scores range from 0 = no tasks completed to 37 = all tasks independently completed. Based on natural

criteria were similar to Study BP39056 but with additional exclusions for patients with a history of cell therapy, surgery for scoliosis or hip fixation in the past year or planned within 18 months or a history of ophthalmological diseases.

Subjects were randomised to once daily oral risdiplam at the pivotal dose for age and weight, or placebo, in a 2:1 ratio. Randomisation was stratified by age group (2 to 5 years, 6 to 11 years, 12 to 17 years and 18 to 25 years). Patients and site personnel (except the pharmacist) were blinded to initial treatment assignment until the last patient completed the Month 24 assessment, while the sponsor remained blinded until the last patient randomised completed their Month 12 assessment.

Demographic, baseline characteristics and disease baseline characteristics were evenly distributed across treatment arms. 49.4% of subjects were male and 50.6% were female. Median patient age at screening was 9.0 years (Range: 2 to 25 years). Median weight at Baseline was 27.1 kg (Range: 10.4 to 112.0 kg) and median BMI was 15.7 kg/m2 (Range: 7.8 to 34.6 kg/m2). Most patients were White (67.2%) or Asian (19.4%) and from Europe (68.9%). Most patients had three *SMN2* copies and SMA Type 2 disease. Overall median age at onset of symptoms was 12.4 months (Range: 0 to 135 months). Most patients could not stand or walk. More patients in the risdiplam group (20.9%) had one or more fractures than in the placebo group (11.7%). Most patients had scoliosis: risdiplam, 63.3% and placebo, 73.3%. Fewer patients in the risdiplam arm had severe scoliosis (28.3% versus 38.3%, respectively). Most patients (61.1%) did not require pulmonary care.

The primary endpoint was the change from Baseline in the total motor function measure 32 (MFM32);[16] score at Month 12 (mixed model repeated measures (MMRM) analysis). Improvement in the MMRM analysis of change from baseline in MFM32 total score at Month 12 with risdiplam compared to placebo was both clinically and statistically significant. The results of the sensitivity and subgroup analyses were consistent with those of the primary analysis. However, for patients aged 18 to 25 years no improvement from Baseline was observed; mean treatment difference (95% confidence interval (CI)) was -0.65 (-4.03, 2.74). There appeared to be an inverse relationship with age, whereby the youngest patients derived the greatest mean treatment benefit. No improvements from Baseline were also observed in patients from China and Japan, however there were small patient numbers in the subgroup (≤ 16 per group).

A *post hoc* analysis by concomitant use of risdiplam and antacids suggested there may be a potential drug drug interaction (DDI) that may result in loss of efficacy in patients who received more than 30 or 90 days of continuous antacid treatment (of any class), based on MFM32;[16] and RULM;[15] total scores.

Table 5: Study BP39055 Result for the primary efficacy endpoint

Endpoint	Evrysdi N=120	Placebo N=60
Primary Endpoint		
Change from baseline in MFM32 total score[1] at Month 12 LS Mean (95%, CI)	1.36 (0.61, 2.11)	-0.19 (-1.22, 0.84)
Difference from Placebo Estimate (95% CI) p-value[2]	1.55 (0.30, 2.81) 0.0156	

MFM32 = 32-item Motor Function Measurement scale; LS Mean = least squares of the mean; CI = confidence interval; N = number of participants.

history for SMA Type 2 and non-ambulant Type 3, an increase ≥ 2 points reflects a clinically meaningful benefit. Note: Over a 12 month period, the natural history is for a mean of a -0.4 point decline.

[16] The **Motor Function Measurement 32** (MFM32) is a 32 item quantitative scale that measures motor functional abilities in a person with neuromuscular disease.

The key secondary efficacy endpoints (in hierarchical order) were:

- proportion of patients with a change from Baseline MFM32 total score of ≥ 3 at Month 12;
- change from Baseline in total score of the revised upper limb module (RULM);[15] at Month 12;
- change from Baseline in best percentage predicted value of the forced vital capacity at Month 12; and change from Baseline in total score of the Hammersmith Functional Motor Scale Expanded (HFMSE) at Month 12;
- change from Baseline in total score of caregiver-reported SMA independence scale at Month 12 (in patients aged 2 to 25-years only); and
- the proportion of patients rated by clinicians as no change or improved (rated as no change, minimally improved, much improved or very much improved) in clinical global impression of change scale at Month 12.

Risdiplam treatment demonstrated statistical separation over placebo treatment for the first two key secondary endpoints (See Table 6). Both results were also clinically significant.

Table 6: Study BP39055 Results for the first two key secondary efficacy endpoints

Endpoint	Evrysdi N=120	Placebo N=60
Secondary Endpoints		
Proportion of patients with a change from baseline in MFM32 total score[1] of 3 or more at Month 12 (95% CI)	38.3% (28.9, 47.6)	23.7% (12.0, 35.4)
Odds ratio for overall response (95% CI) Adjusted (unadjusted) p-value[3,4]	2.35 (1.01, 5.44) 0.0469 (0.0469)	
Change from baseline in RULM total score[5] at Month 12 LS Mean (95% CI)	1.61 (1.00, 2.22)	0.02 (-0.83, 0.87)
Difference from Placebo Estimate (95% CI) adjusted (unadjusted) p-value[2,4]	1.59 (0.55, 2.62) 0.0469 (0.0028)	

RULM = revised upper limb module; MFM32 = 32 item motor function measurement scale; CI = confidence interval; LS = least squares; N = number of participants

Supportive Study BP39056, Part 1

Part 1 of Study BP39056 was a Phase II, multicentre, open label study. Patients in this dose finding/dose escalation phase continued into an ongoing open label extension phase (at the pivotal dose). Inclusion and exclusion criteria were similar to that described for Part 2 but there were additional age and weight requirements for the first three patients enrolled.

Patients were enrolled in a staggered dose escalation manner, initially at dose level 1 (cohort 1; n = 4: target exposure of mean $AUC_{0\text{-}24h}$, steady state 700 ng xh/mL), and subsequently all further enrolled patients were treated at dose level 2 (cohort 2; n = 17: target exposure of mean $AUC_{0\text{-}24h}$, steady state ≤ 2000 ng*h/mL that is to maximise SMN protein increase below the exposure cap).

21 symptomatic patients with SMA Type 1 were enrolled. Most were female (71.4%) and White (61.9%); with median age at enrolment of 6.7 months (Range: 3.3 to 6.9 months); 15 (71.4%) patients were older than 5 months; median age at diagnosis was 3.0 months (Range: 0.9 to 5.4 months); and age at onset of symptoms ranged from 0.9 to 3.0 months. Baseline disease characteristics were generally consistent with Part 2 participants. At the clinical cutoff date (CCOD), 18 of 21 (85.7%) patients were still ongoing. Three (14.3%) deaths due to SMA related respiratory complications were recorded.

Key efficacy results at Month 12 were:

- 33.3% of patients sat without support (Item 22 of the BSID-III);[12]
- 66.7% of patients were motor milestone responders (HINE-2);[14]
- 52.4% of patients achieved a CHOP-INTEND score ≥ 40 and 85.7% had a change from Baseline in the CHOP-INTEND ≥ 4 points;[13] and
- Most patients were alive without permanent ventilation at Month 12 that is 19 (90.5%) patients; and at Month 18 that is 18 (85.7%) patients.

Supportive Study BP39055, Part 1

Part 1 of Study BP39055 was a Phase II, multicentre, randomised, double blinded, placebo controlled, dose finding study. Inclusion and exclusion criteria were similar to that described for Part 2 except for the inclusion of ambulatory SMA Type 3 patients. Patients were randomised (2:1 risdiplam to placebo). Initial doses (for escalation) were 0.02, 0.05, 0.25 mg/kg for 2 to 11 year old patients; and 3 and 5 mg for 12 to 25 year old patients. Patients were switched to the pivotal dose after the 12 week placebo controlled period that is 5 mg (body weight ≥ 20 kg) and 0.25 mg/kg (body weight < 20 kg), orally once daily.

The study enrolled 51 patients (35 risdiplam and 16 placebo). One patient discontinued during the open label extension phase. Of 51 enrolled patients, 37 (73%) had Type 2 and 14 (27%) had Type 3. There were 7 ambulatory patients (6 in the younger age-group). Most patients were female (52.9%), White (94.1%), with median age at screening of 7 year old (Range: 2 to 24 years) and 20 (39.2%) patients were 12 years or older. Mean weight, height and body mass index (BMI) were at the 22nd, 30th and 26th percentile, respectively. Type 2 and Type 3 patients were similarly distributed between the age groups and most patients (86.3%) were non-ambulatory, 29 (60%) patients had scoliosis at screening (including 6 with severe scoliosis) and most patients (90.2%) had three copies of the *SMN2* gene.

Table 7 summarises the results for the primary endpoint. The improvements in motor function with risdiplam treatment observed at Month 12 were maintained or improved at Month 24, independent of baseline motor function scores, disease duration and age. These results were further supported from results of an exploratory comparison with an historical cohort (weighted on key prognostic factors), in which the positive values of MFM;[16] total change from Baseline in patients who received risdiplam for 12 months and 24 months, were markedly greater than the corresponding decline in motor function in the natural history cohort. The latter decline in motor function is expected due to disease progression. However, since the efficacy endpoints were exploratory, their generalisability to a broader population should be interpreted with caution.

Of note, patients in the younger age group consistently achieved greater clinical benefit compared to older aged patients (adolescents and young adults). However, the treatment effect in older patients was still markedly clinically meaningful compared to the natural history of untreated disease. Although the efficacy results obtained from Part 1 of Study BP39055 are exploratory, there is reasonably high concordance at Month 12 with the pivotal Part 2 results at Month 12 for the primary and key secondary efficacy endpoints. The results from Part 1 are both supportive of efficacy in SMA Types 2 and 3, and provided valuable long-term data (up to 2 years) to suggest that efficacy is improved or sustained with risdiplam treatment, at the pivotal dose, for up to 24 months.

Table 7: Study BP39055 (Part 1) Motor function measurement 32 (MFM32) results at 12 and 24 months of risdiplam treatment (motor function measurement population)

Endpoint	Patients Ages 2–11 Years (n=31)	Patients Ages 12–25 Years (n=20)	All Patients All Ages (2–25 years) (n=51)
MFM32 Total Score (excluding patients who completed the MFM20)[a]			
Baseline, Mean (SD)	44.4 (11.9)	40.9 (18.2)	42.9 (15.0)
Month 12	**n=24**	**n=19**	**n=43**
Change from baseline, Mean (SD)	3.47 (3.77)	1.64 (3.43)	2.66 (3.70)
Proportion of patients (95% CI) who achieved change from baseline of ≥3	70.8% (48.91%, 87.38%)	42.1% (20.25%, 66.50%)	58.1% (42.13%, 72.99%)
Proportion of patients (95% CI) who achieved change from baseline of ≥0	91.7% (73.00%, 98.97%)	68.4% (43.35%, 87.42%)	81.4% (66.60%, 91.61%)
Month 24	**n=24**	**n=19**	**n=43**
Change from baseline, Mean (SD)	3.69 (4.67)	1.54 (4.99)	2.74 (4.88)
Proportion of patients who achieved a change from baseline of ≥3	66.7% (44.68%, 84.37%)	47.4% (24.45%, 71.14%)	58.1% (42.13%, 72.99%)
Proportion of patients (95% CI) who achieved change from baseline of ≥0	91.7% (73.00%, 98.97%)	68.4% (43.45%, 87.42%)	81.4% (66.60%, 91.61%)

MFM = motor function measure; MFM32 = item 32 of the MFM; n = number of participants; SD = standard deviation; CI = confidence interval.

Notes: Baseline is the last measurement prior to patient first dose of risdiplam

Clinical cutoff date: 15 January 2020.

Safety

As the listed Phase II and Phase III clinical studies submitted for safety are still ongoing, the integrated safety analysis provided in this application was not fully comprehensive. The safety profile of risdiplam was characterised in 465 paediatric and adult patients (aged 2 months to 60 years of age) with SMA Types 1, 2 and 3 (non-ambulatory), treated with risdiplam for up to three years, from five ongoing clinical studies. Most patients had SMA Type 2 or 3 (83.4%; n = 388) compared to 16.6% (n = 77) who had SMA Type 1. The overall extent of population exposure was 521.4 patient-years (PY) with 480.9 PY of exposure to the pivotal dose (77.9 PY for SMA Type 1; and 403.0 PY for SMA Types 2 and 3). Median duration of exposure to risdiplam for the SMA Type 1 group was 15.2 months (Range: 0.1 to 34.6) and 9.3 months (range: 0.0 to 38.9) for SMA Types 2 and 3 group.

Across the risdiplam clinical SMA program, adverse events (AEs) with the highest incidence of treatment emergent adverse events and adverse drug reactions (ADR) were in the Infections and infestations; General disorders and administration site conditions and Gastrointestinal disorders System Organ Class (SOC) categories. Across the clinical studies, the types of AE by Preferred Term (PT) experienced by patients were generally similar, apart from some age related AEs. Overall AEs with highest incidence were: upper respiratory tract infection (URTI), pyrexia, nasopharyngitis, headache and vomiting. A greater proportion of patients with SMA Type 1 had Grade ≥ 3 AEs and serious adverse events (SAE) compared to patients with SMA Types 2 and 3 (non-ambulatory). This is generally consistent with the more severe phenotype of patients with SMA Type 1, in which more serious respiratory complications (especially pneumonia) occur more frequently.

Dose dependency was not investigated in the clinical SMA studies, since a single pivotal dose was administered. However, rates of overall AEs, severe AEs and SAEs tended to follow time dependent reductions over the duration of the clinical studies. Since most reported AEs and SAEs were generally associated with underlying disease or disease

progression, reduction in AE rates is likely to be indicative of the therapeutic benefit of risdiplam treatment.

Across the studies, few patients experienced AEs or SAEs leading to study drug discontinuation or dose interruption. The types and distribution of these AEs appeared to be associated with the underlying condition, disease progression or were age related. Most AEs resolved despite ongoing treatment with risdiplam or did not recur on re-initiation with risdiplam treatment.

During the risdiplam clinical development program seven deaths were recorded, all in the SMA Type 1 group. Six deaths occurred during patient participation in Study BP39056 (three in Part 1 and three in Part 2 of the study). An additional patient death occurred 3.5 months after treatment discontinuation. All of these deaths were attributed to SMA related respiratory complications. In Study BP39056 Part 2, three (7.3%) infants died within the first three months of risdiplam treatment (two from pneumonia and one from acute respiratory failure). All three infants were male and died one day after receiving their last dose of risdiplam. In Study BP39056 Part 1, three (14.3%) infants died (two from Grade 5 respiratory tract infections, one from cardiac arrest and respiratory failure). All three infants were female and died within 1 to 3 days after receiving their last dose of risdiplam.

The clinical evaluator noted nonclinical toxicology findings that included effects on epithelial tissues, retinal toxicity and haematological effects. In particular, the photoreceptor degeneration in the periphery of the retina which was not fully reversible and the microcystic macular degeneration in the central retina, which was reversible with improvement of functional impairment as measured by electroretinography. Off target safety effects on epithelial tissues and haematological effects were not observed in any patient in the clinical SMA program, when risdiplam was administered at the pivotal dose. Similarly, despite extensive ophthalmological monitoring, risdiplam exposure did not show any evidence of retinal toxicity. No ocular risdiplam related SAEs or study discontinuations due to ocular AEs were reported.

No risdiplam associated risks were identified following review of vital signs, electrocardigrams, safety laboratory data and suicidal assessments. Risdiplam did not appear to be nephrotoxic and there was no evidence of drug-induced serious liver injury. No Hy's law;[17] case was identified across the risdiplam clinical program.

Apart from growth parameters, physical examination findings generally remained unchanged throughout the duration of the studies. SMA patients under 12 years of age, irrespective of SMA Type, consistently demonstrated growth and development for up to 12 months duration in the pivotal studies and for up to 24 months in an exploratory study.

Study BP39054 (also referred to as JEWELFISH trial) is an ongoing multicentre, OL, non-comparative, single arm, exploratory Phase II study in SMA patients previously enrolled in Study BP29420 with the splicing modifier RO6885247 (n = 13) or previously treated with nusinersen (n = 76),[4] onasemnogene abeparvovec (n = 14) or olesoxime (n = 71). Treatment with oral risdiplam is planned for a 24 month period using the pivotal dose. Fifteen patients had SMA Type 1, 108 patients had SMA Type 2 and 51 patients had SMA Type 3, and were aged 6 months to 60 years at enrolment (27.6% were aged 2 to 12 years and 33.3% were aged 12 to 17 years). Interim clinical study report (CSR) safety data collected in Study BP39054 indicated that patients previously treated with nusinersen;[4] and AVXS-101 (onasemnogene) can be safely switched to risdiplam after a previous SMA

[17] **Hy's Law**: Evidence of hepatocellular injury with a rise in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 3 x the upper limit of normal (ULN) and total bilirubin > 2 x ULN, and no other reason to explain rise in aminotransferases and total bilirubin. Hy's law is a rule of thumb that a patient is at high risk of a fatal drug-induced liver injury if given a medication that causes hepatocellular injury with jaundice.

disease modifying treatment. The AE profile for treatment naïve and previously treated patients was generally comparable.

In general, there were no clinically meaningful differences in risdiplam related AEs based on gender, race group or age category. Since few subjects older than 65 years of age were dosed with risdiplam in the clinical studies, caution should be exercised in this age group.

There was no clear evidence of risdiplam related cardiotoxicity or QT;[18] prolongation in the clinical SMA program. These findings were generally supported by the results of an exposure QT analysis and a clinical review issued by the US FDA.

There were no clinical data from use of risdiplam in pregnant women. Risdiplam has been shown to be embryo fetotoxic and teratogenic in animals. Risdiplam should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. Although risdiplam is excreted into the milk of rats, it is not known whether risdiplam is excreted in human breast milk. Risdiplam treatment is therefore not recommended for breastfeeding mothers. Risdiplam has be categorised as a Pregnancy Category D medicine.[19]

Clinical evaluator's recommendation

The clinical evaluator recommended approval of risdiplam for the proposed indication. Conditions for approval outlined by the clinical evaluator included requested changes to the Product Information (PI) and Consumer Medicines Information (CMI), the submission of the results of ongoing clinical studies (including a comprehensive safety analysis), the thorough QT study, and the drug drug interaction study with omeprazole; and to closely monitor risdiplam in the post-market and clinical trial setting for new safety signals including clarification of retinal risk.

Risk management plan

The sponsor has submitted EU-Risk management plan (RMP) version 0.1 (date 24 June 2020; data lock point (DLP) 31 January 2020) and Australia Specific annex (ASA) version 1.0 (date 1 July 2020) in support of this application. In the response to TGA questions, the sponsor submitted ASA version 2.0 (date 19 November 2020). In the response to further TGA questions, the sponsor submitted ASA version 3.0 (date 6 January 2021). In the response to rolling questions by TGA, the sponsor submitted ASA version 4.0 (date 8 February 2021). In response to the second round of RMP evaluation the sponsor submitted ASA version 1.5 (date 25 February 2021). At fourth round of RMP evaluation, the sponsor submitted EU-RMP version 1.0 (date 5 March 2021; DLP 31 January 2020) and ASA version 2.1 (date 27 May 2021).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 8.[20]

[18] The **QT interval** is the time from the start of the QRS wave complex to the end of the corresponding T wave. It approximates to the time taken for ventricular depolarisation and repolarisation, that is to say, the period of ventricular systole from ventricular isovolumetric contraction to isovolumetric relaxation.

[19] **Pregnancy Category D:** Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

[20] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;

Table 8: Summary of safety concerns and their associated risk monitoring and mitigation strategies

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	None	–	–	–	–
Important potential risks	Retinal toxicity	ü	ü‡	ü	–
	Medication error†	ü	–	ü	–
	Drug-drug interaction with antacids*†	ü	ü*	ü	–
	Embryofoetal toxicity	ü	ü§	ü	–
	Effect on epithelial tissues	ü	ü‡	ü	–
Missing information	Withdrawal and rebound effects†	ü	–	–	–
	Concomitant use of risdiplam with the available 5q SMA targeting agents†	ü	–	–	–
	Long-term safety	ü	ü‡	–	–

* Bioavailability study

† Australian specific safety concerns

‡ Clinical studies

§ Pregnancy surveillance study

The sponsor was asked to consider adding cardiovascular, hepatic, renal and immunocompromised patients to the summary of safety concerns as missing information, as these populations were not studied in clinical trials. In the response to TGA's questions, the sponsor justified the exclusion of these safety concerns by stating that Evrysdi does not pose an increased risk in these patient groups. In response to the recommendations of the clinical evaluator, the sponsor agreed to add 'Medication error' and 'Drug-drug interaction with antacids' as important potential risks, and 'Withdrawal and rebound effects' as missing information, however the sponsor did not amend the summary of safety concerns in ASA version 3. In ASA version 4.0 and subsequent ASA version 1.5, the

- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

sponsor has included 'Concomitant use of risdiplam with the available 5q SMA targeting agents' as missing information and added the safety concerns recommended by the clinical evaluator. The summary of safety concerns is acceptable.

The sponsor proposes routine pharmacovigilance but no additional pharmacovigilance, however in response to TGA's questions the sponsor has clarified that OLE phases of the pivotal studies will be conducted, and that collaboration with multinational established SMA patient registries will ensure long term follow up of patients treated with risdiplam. In response to the second round of TGA's questions, the sponsor confirmed collaboration with Australian patient registries. The sponsor also committed to including a bioavailability study for the dispersible tablet formulation for the 'Drug-drug interactions with antacids' safety concern. In response to TGA's questions, the bioavailability Study BP42066 was described in ASA version 4.0 but was not added to the table of additional pharmacovigilance activities for the important potential risk 'Drug-drug interaction with antacids'. In ASA version 1.5 the sponsor has populated the additional pharmacovigilance table as requested, with further additional pharmacovigilance activities added to the ASA at fourth round of evaluation for retinal and embryofetal toxicity, effect on epithelial tissues and long term safety. The pharmacovigilance plan is acceptable.

Routine risk minimisation activities only are proposed and this is acceptable at this stage. The sponsor proposes to include Instructions for Reconstitution and Instructions for Use documents in the product packaging. The sponsor has updated the safety documents in response to rolling questions and the instructions for reconstitution and instructions for use documents are acceptable. In response to the second round evaluation the CMI was revised as requested and is acceptable. At the fourth round of evaluation, the sponsor submitted a Dear Health Care Provider letter to minimise the risk of leaking bottles, which was not tied to a specific safety concern. The risk minimisation plan is acceptable.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The Evrysdi EU-RMP (version 1.0, dated 5 March 2021, data lock point 31 January 2020), with Australian Specific annex (version 2.1, dated 27 May 2021), included with submission PM-2020-03580-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII- periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As Evrysdi is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration. The following wording is recommended for the condition of registration:

Evrysdi (risdiplam) is to be included in the Black Triangle Scheme. The PI and CMI for Evrysdi must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Risk-benefit analysis

Delegate's considerations

Spinal muscular atrophy is a rare, progressive neurodegenerative condition. In Australia, there is currently one approved treatment for SMA, the intrathecally administered antisense oligonucleotide nusinersen.[4] Both nusinersen and risdiplam are intended for long-term use, but risdiplam has an advantage in that it can be administered orally and may be used in the home environment.

The submission presents data from 465 patients treated with the orally administered splicing modifier risdiplam, with a median duration of exposure of 15.2 months in SMA Type 1 and 9.3 months in SMA Types 2 and 3. At present, only 12 months of efficacy data is available and the maintenance of beneficial effects in the longer term is yet to be established.

Results from the primary analysis of the two pivotal studies indicate that risdiplam supported the efficacy of 12 months of risdiplam treatment in symptomatic SMA patients. In pivotal Study BP39056 Part 2 (SMA Type 1), 29.3% of patients were able to sit unassisted for at least 5 seconds. This result was both statistically and clinically significant. Treatment was also associated with statistically significant and clinically meaningful improvements in key motor function and development milestones, as well as ventilation free survival. The study used a historical control group which was acceptable given the well described natural history of SMA and the severity of the condition. Study results diverged markedly from the natural history of Type 1 SMA. At 12 months of age, 92.7% of patients were alive and had attained major motor milestones when only 60% of untreated patients would be expected to be alive at this time point.

In pivotal Study BP39055 Part 2 (SMA Types 2 and 3), patients achieved statistically and clinically significant improvement and/or stabilisation in motor function at 12 months, in the placebo controlled period. Younger aged patients, particularly the 2 to < 6 years group, obtained the greatest benefit from risdiplam treatment compared to older children and young adults. Although stabilisation of SMA was generally achieved in most older patients. This suggests there is a benefit to early diagnosis and initiation of risdiplam treatment.

The submitted data from the pivotal studies included 12 month efficacy data but whether these effects are maintained long-term remains unknown. However, Study BP39055 Part 1 provided supportive evidence that efficacy is improved or maintained for up to 24 months. Further clinical efficacy data is expected to become available later this year.

The Delegate has some concerns regarding the potential for use in patient subgroups not included in the submitted clinical studies. In particular, SMA Types 0 and IV, patients who already require invasive or permanent ventilation, presymptomatic individuals, and those less than two months of age. The Delegate seeks the Advisory Committee on Medicines (ACM) advice on whether the proposed wording of the indication is appropriate:

The use of risdiplam in more advanced disease, such as SMA Type 0, and patients who already require invasive or permanent ventilation, have not been established. However, the inclusion of these patients in the broad SMA indication is probably acceptable based on the known mechanism of action, the potential for stabilisation of disease and the small proportion of the total SMA population diagnosed Types 0. There is a potential for benefit from risdiplam treatment in this patient group. Similarly, risdiplam may offer benefit stabilising disease in those with less advanced disease, such as SMA Type IV. Previous

ACM advice has supported the inclusion SMA Types 0 and IV under the broad SMA indication. The Delegate proposes inclusion of a precautionary statement in PI indicating that Types 0 and IV have not been studied. The clinical studies for nusinersen did not include patients with SMA Types 0 and IV and a similar statement is included in Section 4.4 of the Spinraza (nusinersen) PI.[4]

The benefit of risdiplam treatment for presymptomatic individuals has not yet been established but the results of Study BP39055 suggest there is a benefit from the early initiation of risdiplam treatment. The RAINBOWFISH trial (Study BN40703) is an ongoing study in pre-symptomatic SMA patients aged from birth to six weeks. This study was not formally evaluated in this application. The proposed wording of the PI potentially allows for the treatment of presymptomatic individuals. Historically, presymptomatic SMA tended to be diagnosed on screening after the diagnosis of a sibling or relative. Changes to Australian genetic screening programs could potentially increase the proportion of patients that receive a diagnosis prior to symptom onset. Given the progressive nature of the disease and the suggested benefits of early diagnosis and treatment, the Delegate is of the opinion that the indication does not need to be restricted to those with symptomatic disease.

The safety and efficacy of risdiplam in patients less than two months of age has not been established. The proposed PI includes this information in Section 4.2 of the PI but it is noted that the US PI includes the minimum two month age limit in the indication. The Delegate is of the opinion that inclusion of this information in Section 4.2 of the PI is appropriate and aligns with the TGA's general approach to products intended for paediatric use.

The proposed PI allows for the initiation of treatment by non-specialist practitioners. The Delegate suggests including a statement in Section 4.2 of the PI restricting the initiation and supervision of treatment to specialist medical practitioners experienced in the diagnosis and management of SMA. A similar requirement has been included in the Spinraza (nusinersen) PI.[4]

The safety profile of risdiplam has not yet been fully characterised but will become clearer when the results from the open label extension phases of ongoing clinical studies become available. The initial benefit-risk balance for risdiplam for safety is positive. Although overall patient exposure is considered sufficient for registration, the initial conclusions are based on interim results. Incidences of AEs or SAEs that led to study drug discontinuation were generally low. The overall incidence of AEs, SAEs (including deaths) and severe AEs were generally higher in SMA Type 1 patients than in patients with less severe SMA disease, particularly respiratory conditions such as pneumonia. These findings are consistent with a more severe phenotype. The reductions in observed AE rates over time for all SMA patients, irrespective of type, are likely to be indicative of the therapeutic benefit of risdiplam treatment.

Overall, there were seven deaths across the clinical program at the time of clinical cutoff date. All seven deaths occurred in SMA Type 1 patients and for all patients the cause of death was considered unrelated to risdiplam treatment and attributed to the underlying disease. This is consistent with the more severe phenotype seen with SMA Type 1 compared to SMA Types 2 and 3.

There remain concerns that the limited duration of exposure makes it difficult to characterise the risk of less common events. The off target safety effects on epithelial tissues, haematological effects and retinal toxicity identified from nonclinical safety findings, were not observed in any patient in the clinical SMA program. The risk of retinal toxicity has been included in the summary of safety concerns as an important potential risk and is described in Section 5.3 of the PI but there are no recommendations for clinicians regarding monitoring patients for this potential reaction. The Delegate is

concerned about the potential for the delayed onset of irreversible retinal toxicity and the associated challenges of identifying associated changes in a paediatric patient population. Advice is sought from the ACM about whether a precautionary statement in the PI is warranted.

The other off target effects from the nonclinical program that did not appear in the target population were included skin, gastrointestinal tract, male reproductive system and bone marrow effects. Male fertility effects were not evaluated in clinical studies. The nonclinical evaluator has indicated that patients can probably be monitored for these effects. The effects on epithelial tissues in animal studies are described in Section 5.3 of the PI and Section 4.6 of the PI discusses the effects on the male reproductive system including fertility preservation advice. The Delegate considers this adequate but welcomes comment from the ACM committee.

Potential risks from medication errors and a potential DDI between risdiplam and antacids were identified by the clinical evaluator. In regards to medication errors, risdiplam administration to the youngest patients with more severe disease, gave rise to considerably more dosing errors than patients with SMA Types 2 and 3. In Australia, the sponsor proposes to include two different sized oral syringes in the carton, with the reconstituted risdiplam solution. The Delegate agrees with the clinical evaluator's assessment that provision of both syringes to the parent/carer may inadvertently contribute towards dosing errors and that provision of a single syringe size to the parent/carer at the time of dispensing, may help mitigate this risk.

A DDI with antacids cannot be excluded based on the available efficacy evidence. There is a theoretical risk that risdiplam will precipitate out of solution in alkaline or near alkaline conditions. The evaluator has recommended a dedicated DDI study be undertaken post approval and a bioavailability study is planned to address this issue.[21] DDI with antacid is listed as an important potential risk in the summary of safety concerns.

There was no clear evidence of risdiplam related cardiotoxicity or QT prolongation in the clinical SMA program and the FDA clinical review did not find a cardiac safety signal following risdiplam exposure. The sponsor has committed to a post-approval dedicated positively controlled thorough QT study. Based on the available evidence, no routine cardiac monitoring is recommended in younger SMA Type 1 patients, unless clinically indicated.

Proposed action

As outlined above, there are several limitations to the clinical data, such as the lack of completed studies, long-term data and a comprehensive integrated safety analysis. These limitations make the characterisation of less common AEs challenging. As a result, there are outstanding concerns regarding the potential for toxicity related to off target effects identified in the nonclinical studies. Due to the serious, life limiting nature of this progressive neurodegenerative condition, subject to advice from ACM, the preliminary view tends towards a favourable benefit-risk profile for risdiplam for the treatment of SMA patients ≥ 2 months of age, based on the interim results of the submitted pivotal clinical studies.

Questions for the sponsor

The sponsor provided the following response to questions from the Delegate.

[21] Sponsor clarification: The sponsor has set up a bioequivalence study in healthy volunteers, a phase I, open label, multi-period crossover study to investigate the safety, food effect, bioavailability and bioequivalence of oral doses of two different formulations in healthy subjects. Omeprazole will be used to assess the food effect.

1. ***Please provide an update on the current international regulatory status of similar submissions overseas? Have the submission been rejected, withdrawn or deferred in any country or region?***

Risdiplam has been granted Marketing Authorisation in seven countries: USA, Brazil, Chile, Georgia, South Korea, Russia and Ukraine.

Applications for Marketing Authorisation are under review in 58 countries worldwide, including review by the EU's EMA, which granted a positive Committee for Medicinal Products for Human Use opinion on 26 February 2021.

The application was not rejected, withdrawn, or deferred in any region or country.

2. ***It is noted that risdiplam and related molecule RO6885247 displayed similar retinal toxicity at a similar relative exposure and that this led to the termination of clinical trials with RO6885247. What were the reasons for terminating clinical trials with RO6885247? What was the rationale for continuing clinical trials with risdiplam?***

Retinal toxicity for RO6885247 was initially discovered by tissue histopathology at the end of the dosing phase of a chronic toxicity 39 week study in monkeys. At that time, it was unknown whether this type of toxicity could be monitored in-life and therefore as a precautionary measure, the clinical trials with RO6885247 were put on hold. Several months later, the feasibility of monitoring the histopathology findings in life by optical coherence tomography was demonstrated in animals (in the recovery phase animals of the same 39 week chronic toxicity study in monkeys for RO6885247 and also during the chronic toxicity study for risdiplam, which had been selected as a back up clinical candidate for RO6885247).

Subsequent to having determined the feasibility to monitor the retinal toxicity by optical coherence tomography, clinical trials with RO6885247 were not resumed. Further efforts in clinical development were focussed on risdiplam instead as risdiplam offered a better therapeutic window. This was later substantiated in clinical trials that the full ability to force *SMN2* exon 7 inclusion and to generate *SMN2*-driven protein was established with risdiplam rather than RO6885247 at the no observed adverse-effect level of retinal toxicity in monkeys. Further, risdiplam offered a number of distinct safety advantages over RO6885247, which were important for patients, such as absence of phototoxicity, absence of hERG (cardiac potassium ion) channel affinity and QT prolongation, and a lower volume of distribution. The details are published in Ratni et al., 2018.[22]

In conclusion, the reasons for:

- Termination of the clinical trial with RO6885247: at the time, there was no knowledge on how to perform a proper retinal safety follow up in humans; thus, to ensure safety, the program was interrupted.
- Starting clinical development of risdiplam: risdiplam offered a better safety profile in general and a better therapeutic window for retinal toxicity compared to RO6885247, and optical coherence tomography was established as an optimal method for evaluation of retinal abnormalities by the time of the clinical development start.

3. ***Given that the longer-term ongoing studies are open-label, how does the sponsor propose to distinguish the long-term safety of risdiplam from the natural history of SMA?***

[22] Ratni H, et al. Discovery of Risdiplam, a Selective Survival of Motor Neuron-2 (*SMN2*) Gene Splicing Modifier for the Treatment of Spinal Muscular Atrophy (SMA). *J Med Chem*. 2018;61(15):6501-6517.

The sponsor will not perform a systematic analysis of the safety profile of risdiplam compared to the natural history of SMA for all safety endpoints due to the lack of comparable datasets in untreated patients with SMA.

Nevertheless, endpoints such as survival in patients with Type 1 SMA and hospitalisations will be compared with available natural history data also in the long term.

Furthermore, adverse events and serious adverse event rates will be analysed over time to rule out any increased rates over long term exposure. In the event of unexpected rare events, the sponsor may rely on registries or insurance claim databases to contextualise the findings in addition to an evaluation of the causal association using an algorithm adapted from the Bradford Hill criteria.[23]

Laboratory parameters including also haematological parameters will be analysed for trends over time over the five year treatment period.

Advisory Committee considerations[24]

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

Specific advice to the Delegate

1. Can the committee comment on the process for diagnosing 5q SMA in Australia. Do the majority of patients receive formal genetic testing/screening to confirm the diagnosis?

The ACM advised that the standard pathway for diagnosing 5q SMA in Australia consists of clinical suspicion (for example, a child presenting with floppiness), followed by formal genetic testing for *SMN1* deletion and then *SMN2* copy number, followed by confirmation and then appropriate treatment. The ACM highlighted that within Australia, treatment should not occur without a confirmed diagnosis.

The ACM advised that there is a push in Australia for an expansion of newborn screening to include 5q SMA.

2. Can the committee comment on the proposed wording of the indication, specifically:

a. whether an age limit of 2 months and older should be included in the indication

The ACM advised that an age limit of 2 months and older should be included in the indication as no evidence has been provided in the clinical data set to support the use of risdiplam in patients less than 2 months of age.

b. the inclusion of patients with Type 0 and Type IV SMA

[23] Hill, Austin Bradford (1965). 'The Environment and Disease: Association or Causation?'. Proceedings of the Royal Society of Medicine. 58 (5): 295–300.

[24] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

The ACM was of the view that patients with Type 0 SMA are unlikely to benefit from treatment due to the severity of disease, the early age of onset and the low *SMN2* copy number. However, Type 0 SMA is very rare and the age limit of 2 months and older would exclude these patients from treatment with risdiplam.

The ACM were supportive of patients with Type IV SMA having access to this treatment option. While the ACM noted that patients with Type IV SMA were not included within the clinical trials, they were of the view that it is likely this treatment would be efficacious within this population. Additionally the oral dose form is appropriate for this cohort and clinical practice suggests that the Type IIIc and Type IV SMA symptom picture is similar.

c. the inclusion of pre-symptomatic patients

While the benefit of risdiplam treatment for pre-symptomatic individuals has not yet been established, the ACM was of the view that the results of Study BP39055 suggest there is benefit from early initiation of risdiplam treatment and that pre-symptomatic patients should not be excluded from the indication. In providing this advice, the ACM commented that other SMA treatments have shown increased efficacy with earlier treatment, particularly in pre-symptomatic individuals.

The ACM noted that the RAINBOWFISH trial (Study BN40703) is an ongoing study in pre-symptomatic SMA patients aged from birth to six weeks, however this study was not formally evaluated in this application.

The ACM advised that there may be an increase in the number of pre-symptomatic patients in the future due to increasing rates of preconception and prenatal SMA genetic testing, and expressed support for the inclusion of 5q SMA screening within the newborn screening panel.

3. The Delegate proposes to limit to medical specialists with experience in the diagnosis and management of patients with SMA. Is this reasonable in the context of the likely use of risdiplam in clinical practice?

The ACM advised that the current practice is that children with SMA are treated within specialised clinics, with care from a multidisciplinary team due to the complexity of managing this particular condition. While the ACM acknowledged that this is an oral therapy, they expressed strong support for patients receiving risdiplam to have ongoing treatment under the supervision of an expert in SMA within a specialised clinic. This is especially important given the concerns detailed in Question 5, below, regarding the potential for dosing errors.

4. The nonclinical evaluator has raised concerns about the toxicity of risdiplam in retina, skin, gastrointestinal tract, male reproductive system and bone marrow.

a. retinal toxicity has been included as an important potential risk in the RMP. Does the committee consider this sufficient? Is a precautionary statement in the Product Information warranted? If so, what advice should be provided to clinicians regarding monitoring?

The ACM agreed that the potential for retinal toxicity is significant based on the toxicities observed in the nonclinical studies at doses near or marginally above the proposed clinical dose regime. They also noted that similar toxicities were observed in nonclinical studies with a related drug.

The ACM noted that there has been no evidence of retinal toxicity in the clinical studies to date, consisting of 474 patients with 200 of these followed up to 2 years. The ACM also discussed a recently published paper by Sergott et al. (2021);[25] reporting ophthalmologic

[25] Sergott, R.C. et al. Risdiplam treatment has not led to retinal toxicity in patients with spinal muscular atrophy. *Ann Clin Transl Neurol*, 2021; 8: 54-65.

assessments of 245 patients treated with risdiplam, which found no evidence of retinal toxicity in any of the patients.

The ACM agreed that the clinical findings thus far are reassuring, however, they emphasised the importance of the sponsor providing ongoing studies evaluating the eyes of risdiplam-treated patients in order to add to the understanding of the safety profile of risdiplam, particularly to determine if there is a cumulative effect over time.

The ACM was of the view that the risks of retinal toxicity have been adequately addressed in the RMP and draft PI.

b. The other potential off-target effects are described in Sections 4.6 and 5.3 of the Product Information. Does the committee consider this sufficient?

The ACM advised that the warning relating to effects on epithelial tissue in Section 5.3 is appropriate and should provide for adequate risk management. The ACM also considered the warnings relating to potential effects on male fertility in Section 4.6 to be appropriate, as is the Pregnancy Category D classification based on the nonclinical findings. The ACM was of the view that the potential for cardiotoxicity or QT prolongation has been adequately addressed and is consistent with the US FDA approach. The warning of potential interaction with antacids is also considered to be appropriate.

c. Should the sponsor be requested to do ongoing studies into these adverse events?

The ACM advised that the limited data available to date suggest the risks of these AEs should be manageable and will be better informed by longer-term follow-up of clinical trial patients. As such, the ACM agreed that the sponsor should be requested to submit to the TGA, the planned ongoing studies into these AEs in order to better understand the safety profile of risdiplam, and particularly to identify any cumulative effects of the drug.

The ACM also highlighted that inclusion in an SMA registry should be an important aspect of post market surveillance.

5. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

The ACM noted that medication error has been added to the RMP and discussed whether the dosing instructions in the draft PI are sufficient to help mitigate potential dosing errors. The ACM advised that the dosing instructions in the draft PI seem reasonable, provided that prescription of the drug is limited to medical specialists with experience in the diagnosis and management of patients with SMA.

Conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients aged 2 months and older, excluding those with type 0 SMA.*

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Evrysdi (risdiplam) 0.75 mg/mL, powder for oral liquid, bottle, indicated for:

> *Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients aged 2 months and older.*

Specific conditions of registration applying to these goods

- Evrysdi (risdiplam) is to be included in the Black Triangle Scheme. The PI and CMI for Evrysdi must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The Evrysdi EU-RMP (version 1.0, dated 5 March 2021, DLP 31 January 2020), with ASA (version 2.1, dated 27 May 2021), included with submission PM-2020-03580-1-3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

  An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- Provide the final study reports for each of the following studies:
  - BP39056
  - BP39055
  - BP39054
  - BP42066
  - Integrated safety analysis
  - Thorough QT study

Attachment 1. Product Information

The PI for Evrysdi approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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