EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment report

Evrysdi (risdiplam)
Treatment of Spinal Muscular Atrophy
EU/3/19/2145
Sponsor: Roche Registration GmbH

Note
Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Risdiplam
Other name(s)	Evrysdi, Risdiplam
International Non-Proprietary Name	-
Tradename	-
Orphan condition	Treatment of Spinal Muscular Atrophy
Sponsor's details:	Roche Registration GmbH Emil-Barell-Strasse 1 Grenzach 79639 Grenzach-Wyhlen Baden-Wuerttemberg Germany
Orphan medicinal product designation procedural history	
Sponsor/applicant	Roche Registration GmbH
COMP opinion	24 January 2019
EC decision	26 February 2019
EC registration number	EU/3/19/2145
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Bruno Sepodes / Armando Genazzani
Applicant	Roche Registration GmbH
Application submission	21 July 2020
Procedure start	13 August 2020
Procedure number	EMA/H/C/005145/0000
Invented name	Evrysdi
Proposed therapeutic indication	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 Further information on Evrysdi can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Evrysdi
CHMP opinion	25 February 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Eva Malikova / Dinah Duarte
Sponsor's report submission	14 August 2020
COMP discussion and adoption of list of questions	03-05 December 2020
Oral explanation	cancelled
COMP opinion (adoption via written procedure)	02 March 2021

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2019 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing risdiplam was considered justified based on preliminary clinical observations in affected patients that support improved survival and motor function;
- the condition is chronically debilitating and life-threatening due to muscle wasting, weakness, failure to thrive, pulmonary and orthopaedic complications;
- the condition was estimated to be affecting approximately 0.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing risdiplam will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations in treated patients that compare favourably to the described effects of the authorized counterpart in motor function and survival. Moreover, the oral formulation of the product could find applicability in a broader patient population. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

There have been no changes in the classification of the disease since the designation stage. Spinal muscular atrophy is a neurodegenerative disease manifesting with progressive alpha motor neuron degeneration and subsequent muscle atrophy. In approximately 95% of cases it is caused by aberrations in the SMN1 gene on chromosome 5q and is inherited as an autosomal recessive disease. The SMN gene is present in multiple copies in the human genome: one SMN1 (telomeric) and several SMN2 (centromeric). SMN2 transcripts are not able to translate properly, as during mRNA splicing exon7 is not included, resulting in a presumably unstable and not functional protein that is degraded. Consequently, in case SMN1 function is lost, even though several SMN2 copies may exist, they cannot fully compensate for the loss of expression of SMN protein. Correct splicing may vary by the severity of the disease occur in as low as about 10% of SMN2 transcripts (Lunn 2008 Lancet; 371:2120-33).

The disease has been traditionally classified according to the clinical severity and age of onset as: Type I (severe, Werdnig-Hoffmann disease) Type II (intermediate), Type III (mild, Kugelberg-Welander disease) and Type IV (adult).

The therapeutic indication is: "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", which lies entirely within the orphan indication.

Intention to diagnose, prevent or treat

The medical plausibility is justified based on the positive benefit/risk assessment of the CHMP. Please refer to the respective EPAR.

Chronically debilitating and/or life-threatening nature

The COMP has previously acknowledged that the condition is life-threatening and chronically debilitating due to muscle wasting, weakness, failure to thrive, pulmonary and orthopedic complications. This view is retained.

Number of people affected or at risk

A literature review was conducted, and the following sources were discussed:

- A 2016 national prevalence study in Croatia, which identified a total of 392 SMA patients. For a population of ~4.2 million inhabitants, the prevalence of SMA was 9.3 per 100,000 persons (Drausnik et al. Croat Med J. 2019;60:488–93).
- A national survey performed in Greece in 2017. A prevalence of 1.5-1.6 per 100,000 persons was reported, based on 160-170 SMA patients and a population of ~10.8 million inhabitants (Kekou et al. J Neuromuscul Disord. 2020;7:247-56).
- With reference to a source from the Hordaland County of Norway, 22 adults with at least one ICD-10 code of SMA recorded in the County hospital database were identified for approximately 500,000 adults living in the hospital's catchment area. A prevalence of 4.4 per 100,000 persons was estimated (Husebye et al. Neuromuscular Disord. 2020;30:181-5).
- These figures are in line with Sponsor's previous empirical prevalence estimates derived from the literature (1.0-4.1 per 100,000 persons) and with the model-based prevalence estimated by Roche (2.5 per 100,000 persons) for SMA in Europe.

The COMP has previously considered estimates of less than 0.4 per 10,000 and this was retained for this procedure, in line with the justifications above.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are two authorised products in the sought orphan condition of SMA:

- Nusinersen (Spinraza), which is a 2′-O-(2-methoxyethyl) antisense oligonucleotide (ASO) which has received a centralised MA in the EU and is indicated for "the treatment of 5q Spinal Muscular Atrophy".

- Onasemnogene abeparvovec (Zolgensma), which is a gene therapy authorised centrally for " patients with 5q spinal muscular atrophy (SMA) with a biallelic mutation in the SMN1 gene and a clinical diagnosis of SMA Type 1, or patients with 5q SMA with a bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene."

Significant benefit

By way of introduction, the sponsor received protocol assistance in which the COMP agreed to the development plan, noting at the same time that contextualisation and data are needed to support the issue of significant benefit vs the currently available products at the time of the review.

For this procedure, a comparison versus the two authorised products was discussed. As regards the comparison versus *onasemnogene abeparvovec (Zolgensma)*, this was considered favourable on the basis of the therapeutic indication of Evrysdi, that covers additional populations and in particular patients with more than 3 SMN2 copies. The sponsor stressed that patients with four SMN2 copies have been included in SUNFISH and JEWELFISH studies. In SUNFISH trial, 10 such patients have been included in the active arm and 8 in the placebo arm, and the following table recapitulates the respective observations after 12 m of treatment. As for JEWELFISH efficacy observations are not yet available as the population includes patients with later onset, slower progressing disease requiring further times of observations (all patients with at least 12 m treatment).

Table 1. MMRM Analysis on Change from Baseline in MFM32, HFMSE and RULM Total Score and Responder Analysis at Month 12 for Patients with 4 SMN2 Copies in Study BP39055 (SUNFISH) Part 2 (Placebo-Controlled Period, ITT Population)

	MFM32		MFM32 responders ≥3 points		HFMSE		RULM	
	Risdiplam n#, Placebo n#	Estimate* [95% CI]	Risdiplam n#, Placebo n#	OR** [95% CI]	Risdiplam n#, Placebo n#	Estimate* [95% CI]	Risdiplam n#, Placebo n#	Estimate* [95% CI]
Overall	115, 59	1.55 [0.30, 2.81]	115, 59	2.35 [1.01, 5.44]	120, 60	0.58 [-0.53, 1.69]	119, 58	1.59 [0.55, 2.62]
4 *SMN2* copies	9, 8	1.43 [-2.48, 5.33]	9, 8	7.83 [1.25, 49.15]	10, 8	2.71 [-0.66, 6.08]	10, 8	1.70 [-1.45, 4.86]

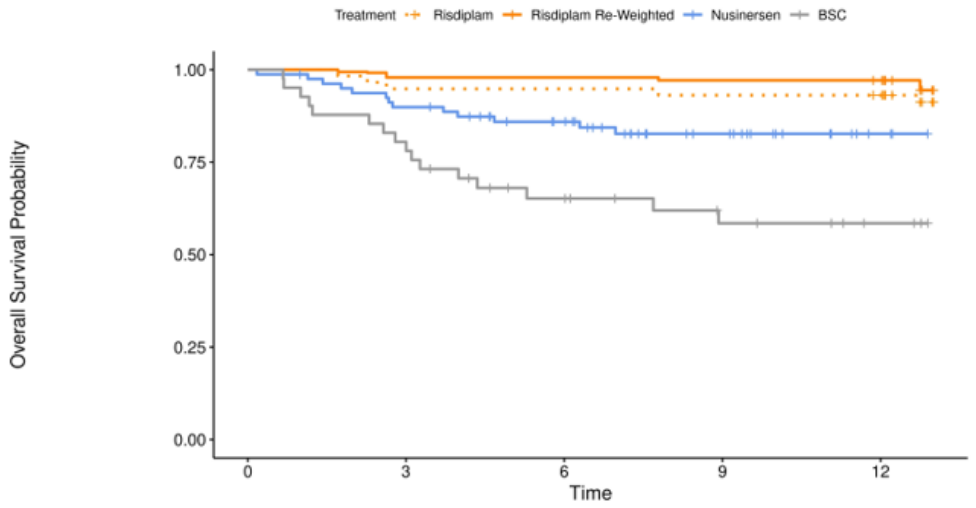
*Estimate; difference in mean change from baseline between risdiplam and placebo
**OR: Odds Ratio
#Number of patients with valid baseline total score
Adapted from Study BP39055 (SUNFISH) Primary CSR 1099250
MFM32= Motor Function Measure 32-item version
HFMSE= Hammersmith Functional Motor Scale Expanded
RULM= Revised Upper Limb Module

The COMP acknowledged the differences in the authorised indications between Evrysdi and Zolgensma, and subsequently the Significant Benefit discussion focused on the comparison versus *nusinersen (Spinraza)*. The sponsor proposed both improved efficacy, improved safety, and major contribution to patient care arguments.

As regards improved efficacy versus nusinersen, the sponsor presented an indirect comparison in type 1 patients by comparing the results of FIREFISH (for the product) and ENDEAR (nusinersen) studies. That comparison included a naive (unweighted) comparison and a ***matching-adjusted indirect comparison (MAIC)***, with pooled Part 1 and Part 2 data from FIREFISH and compensation for the difference in treatment durations.

In that analysis of efficacy comparison in Type 1 SMA patients the endpoints that are in common between ENDEAR and FIREFISH were evaluated, including ventilation free survival, overall survival, HINE-2 milestone responders, and CHOP-INTEND score increase from baseline.

Figure 1. OS curves adopted form the sponsor's documents.



The following results were reported during the maintenance discussion:

- Overall survival, with the hazard ratio of Evrysdi (risdiplam) versus Spinraza (nusinersen) being 0.44 (95%CI 0.09; 1.02) in the naïve analysis and is further reduced to 0.26 (95%CI 0.03; 0.66) in the MAIC analysis.
- Regarding ventilation free survival, the hazard ratio is 0.24 (95%CI 0.09; 0.46) in the naïve analysis and is further reduced to 0.20 (95%CI 0.06; 0.42) in the MAIC analysis.
- As per the proportion of HINE-2 motor milestone responders in ENDEAR, motor milestone achievement was evaluated at the later of the following visits: Day 183, Day 302 and Day 394. For FIREFISH, in the modified dataset, the motor milestone achievement based on HINE-2 was assessed at the later of the following visits: Days 0, Day 119, Day 245 and Day 364. The naïve analysis shows a trend for improved efficacy with Evrysdi (risdiplam) compared to Spinraza (nusinersen) on the primary endpoint of ENDEAR, HINE-2 motor milestone response OR: 1.71, 95%CI 0.85, 3.56. MAIC results also indicate OR: 3.97; 95%CI 2.03, 8.38.
- ITC analyses were conducted for CHOP-INTEND score improvement of at least 4 points. Results using the modified FIREFISH data set at the latest visit 6 months prior to data cutsuggest higher efficacy of Everysdi (risdiplam) in CHOP-INTEND score improvement of ≥4 points outcome OR: 3.50, 95%CI 1.48; 12.08. MAIC analysis results indicate OR: 7.59, 95%CI 3.06; 35.71

Additional efficacy arguments were also examined but were considered less clear. On one point, efficacy in patients previously exposed to other products was discussed. It was noted that the JEWELFISH study had included 76 patients previously treated with Spinraza, out of whom 35 have reported tolerability and safety reasons for switching, while 22 lack or loss of efficacy. It was reported in that context that one previous Spinraza recipient has been classified as a responder with Risdiplam as per HINE-2 score. Moreover, the sponsor also expected that the obtained SMN protein increase with Risdiplam would be maintained at a constant level throughout the entire treatment period, because of the daily oral posology which was considered important especially for Type 1 patients affected by a

rapidly progressive disease. In the absence of data-driven clinical comparisons, these arguments were not considered justified.

An improved safety argument was also put forward but remained rather qualitative. It was discussed that as an oral treatment risdiplam does not expose patients to the known risks of lumbar puncture and the adjunctive treatments and referred to the nusinersen SmPC, for the reported complications in special populations. Risdiplam has been well tolerated in patients exposed to date, including 465 paediatric and adult patients exposed to risdiplam for up to 3 years in studies FIREFISH, SUNFISH and JEWELFISH. Potential risks identified from nonclinical safety findings were not observed in any patient, and no drug-related AEs have led to withdrawal from treatment in any patient. The COMP considered that improved safety could not be considered documented for the justification of significant benefit, in the absence of a quantitative comparison across the entire safety profile of the two compared products.

Lastly, a major contribution to patient care was examined, on the basis of daily oral administration with risdiplam, versus IT administration every 4 months with nusinersen. Several aspects are discussed in this regard that can be grouped in three categories: 1) therapy would not require healthcare unit visits or hospitalization with all the associated procedural complexities and such advantages become apparent in situations such as the current COVID-19 pandemic; 2) therapy would be appropriate for populations ineligible for IT treatment (e.g., patients with severe scoliosis and spine surgery precluding intrathecal administration, and those with intolerance to nusinersen) and 3) a burden/preference argument was put forward.

The sponsor cited a number of publications (Haché et al. 2016; Pane et al. 2018; Bortolani et al. 2019; Sansone et al. 2019; Stolte et al. 2018), suggesting that, as many as 2%-3% of lumbar puncture procedures may fail to deliver nusinersen and as many as 6%-8% of SMA patients may not be able to receive nusinersen given the complexities of scoliosis. In an SMA Europe survey (EUPESMA-2019), 11% of respondents (106/962) indicated that the patient was unable to initiate nusinersen therapy secondary to scoliosis or spinal fusion (Gusset 2020). The COMP remained sceptical with regards to the actual number of patients for whom it is not possible to administer nusinersen, and the absence of data in ineligible patients who went on to be successfully treated with Risdiplam. Nevertheless, an alternative option for ineligible patients was acknowledged, in line with the observations from the case from JEWELFISH study referred to above.

Finally, with regards to the treatment burden argument, it was reported that 15 patients (20%) in the JEWELFISH study cited the inconvenience of the treatment, patient preference, or caregiver preference as the primary reason for switching from nusinersen to risdiplam. These data support the results of a preference study conducted in the United Kingdom in 2019, which was specifically designed to quantify caregiver and patient preferences for SMA treatment attributes and showed that caregivers were 2.9 times more likely to choose an oral solution administered once daily over an intrathecal injection every 4 months, with all other factors being equal, and adult patients were 2.0 times more likely to choose the oral treatment (Lo et al. 2020). The recent SMA Europe survey (EUPESMA-2019) also demonstrated that patients are more ready to accept treatment through oral administration (91.0%) compared to intrathecal (63.1%) or intravenous (84.4%) administration (Gusset 2020). In evaluation of this point the COMP referred to the Protocol Assistance received by the sponsor and considered that merely increased preference would not suffice unless the clinical consequences can be documented. For example, PRO-driven comparisons would be helpful in documenting this claim which was not available at this point in time.

In evaluation of the submitted justifications the COMP concluded that the product has effects in patients with more than 3 copies of SMN2, thereby targeting a broader population compared to

Zolgensma, as also reflected in the agreed CHMP indication. The product also has a clinically relevant advantage of improved efficacy versus nusinersen (Spinraza), on the basis of an indirect matching-adjusted indirect comparison, that reported improved effects on survival and motor function outcomes in Type 1 patients.

4. COMP position adopted on 02 March 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of spinal muscular atrophy (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.4 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to muscle wasting, weakness, failure to thrive, pulmonary and orthopaedic complications;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that risdiplam may be of potential significant benefit to those affected by the orphan condition still holds. The proposed product targets a broader population than *onasemnogene abeparvovec* and is an oral formulation. Risdiplam is an alternative treatment for patients not eligible for intrathecal administration. Moreover, the sponsor has provided a matching-adjusted indirect comparison supporting improved survival in type 1 patients compared to nusinersen. The COMP considered that this constitutes a clinically relevant advantage.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Evrysdi (risdiplam) for treatment of spinal muscular atrophy (EU/3/19/2145) is not removed from the Community Register of Orphan Medicinal Products.