27 March 2025
EMA/130688/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Evrysdi

International non-proprietary name: Risdiplam

Procedure No. EMEA/H/C/005145/X/0024/G

Note

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

Table of contents

List of abbreviations

AI	Acceptable intake
CHMP	Committee for Medicinal Products for Human use
CQA	Critical quality attribute
EC	European Commission
HPLC	High performance liquid chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
KF	Karl Fischer titration
LC-HRMS/MS	Liquid chromatography – high resolution mass spectrometry/mass spectrometry
MAH	Marketing authorisation holder
MO	Major objections
NIR(S)	Near infrared (spectroscopy)
PDE	Permitted daily exposure
Ph. Eur.	European Pharmacopoeia
QTPP	Quality target product profile
RH	Relative humidity
RMSEP	Root mean square error prediction
RTRT	Real time release testing
SmPC	Summary of product characteristics
TOST	Two one-sided tests
UDU	Uniformity of dosage units
UHPLC	Ultra-high performance liquid chromatography
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

Roche Registration GmbH submitted on 22 April 2024 a group of variation(s) consisting of extensions of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	II

Type II variation (C.I.4) to update sections 4.2 and 5.2 of the SmPC in order to update the recommended method of administration based on the food effect results from study BP42066; this is a phase 1, open-label, multiperiod crossover study to investigate the safety, food effect, bioavailability, and bioequivalence of oral doses of two different formulations of risdiplam in healthy subjects. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes to the Product Information and to align the Package Leaflets of both formulations.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/00086/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/00086/2023 was completed. The PDCO issued an opinion on compliance for the PIP P/00086/2023.

With the current submission, the applicant requested the inclusion of the PIP compliance statement in the Marketing Authorisation. It is confirmed the compliance of all studies in the agreed paediatric investigation plan whose results have been assessed in the initial marketing authorisation, which was granted on 26 March 2021, within post-authorisation measures and type II variations and are duly reflected in the Evrysdi product information for both oral solution and film-coated tablets. In conclusion, the PIP compliance statement can be included in the Marketing Authorisation.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

N/A

1.5. Scientific advice

The MAH did not seek Scientific advice at the CHMP.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Fátima Ventura

The application was received by the EMA on	22 April 2024
The procedure started on	23 May 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 August 2024
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	19 September 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	14 January 2025
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the MAH on	30 January 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Evrysdi on	27 March 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by the progressive loss of proximal motor neurons leading to muscle weakness beginning in infancy.

2.1.2. Epidemiology

SMA is the leading genetic cause of mortality in infants and young children, with an incidence of 1 in approximately 11,000 live births, and a carrier frequency estimated at between 1 in 50 and 1 in 70 live births.

2.1.3. Management

There are three products specific for the treatment of SMA: nusinersen, risdiplam and onasemnogene abeparvovoec. These may be used to delay disease progression, on top of best medical care.

2.2. About the product

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

2.3. The development programme/compliance with guidance/scientific advice

This application provides data from Study BP42066, which assessed the bioequivalence of the risdiplam film-coated tablet versus the currently marketed powder for oral solution, to support the marketing authorisation for the film-coated tablet.

Risdiplam powder is constituted to and administered as an oral solution, which provides the required flexibility for the mg/kg dosing regimen in the paediatric setting. However, all patients ≥ 2 years of age with a body weight of ≥ 20 kg receive a flat dose of 5 mg. The risdiplam oral solution must be constituted from the powder to the solution by a pharmacist, and for a dose of 5 mg, a volume of 6.6 mL must be drawn up in an oral syringe by the patient or his/her caregiver every day. The risdiplam film-coated tablet formulation was developed to provide an option to patients with ≥ 20 kg body weight to either use the current oral solution or the new tablet. The tablet, which can be swallowed or dispersed in water to be administered as a dispersion, will significantly simplify the daily administration procedures.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

GMP compliance has been ensured during the manufacturing of the new pharmaceutical form (film-coated tablets).

GCP

The study BP42066 has been conducted under GCP.

2.5. Quality aspects

2.5.1. Introduction

This line extension concerns the addition of a new dosage form, film-coated tablet, developed to provide an additional option to patients with ≥20 kg body weight to either use the authorised oral solution or the new tablet formulation. The tablet can be swallowed or dispersed in water to be administered as a dispersion, which is intended to simplify daily administration.

The finished product is presented as film-coated tablets containing 5 mg risdiplam as active substance.

Other ingredients are:

Tablet cores: microcrystalline cellulose (E460), mannitol (E421), tartaric acid (E334), silica colloidal anhydrous (E 551), crospovidone, sodium stearyl fumarate and strawberry flavour.

White film-coating: polyvinyl alcohol, macrogol 3350 (E1521), titanium dioxide (E171) and talc.

Yellow film-coating: polyvinyl alcohol, macrogol 3350 (E1521), titanium dioxide (E171), talc and iron oxide yellow (E553b).

The product is available in aluminium/aluminium perforated unit dose blisters.

2.5.2. Active Substance

The active substance used in this new formulation is the same as that used in the already marketed powder for oral solution formulation. No further information was provided.

2.5.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is presented as film-coated tablets containing 5 mg risdiplam as active substance. Tablets are pale yellow, round and curved with "EVR" debossed on one side. The core tablets are coated with a white base layer followed by a second yellow layer of film-coating.

The tablet composition complies with the state of the art for solid dosage forms. With the exception of the film coating mixtures and strawberry flavour which are controlled according to acceptable in-house reference standards, all excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.5.1 of this report. The qualitative composition of the strawberry flavour has been presented. The function of each excipient is explained and compatibility with the active substance was demonstrated.

The development goals were outlined in the provided quality target product profile (QTPP). The tablet was developed to fulfil the needs of the patient population as a convenient alternative to the existing powder for oral solution formulation. The tablet needed to have a fast dissolution profile to achieve bioequivalence with the oral solution. The tablet can be swallowed whole or dispersed in water for ease of administration to children or to patients with dysphagia. Although the tablet does not always meet the Ph. Eur. monograph disintegration requirements for dispersible tablets, the disintegration time is still considered short enough to allow patients to disperse the tablet in water for convenience. Bioequivalence was demonstrated *in vivo* between the oral solution, dispersed and whole tablets.

The active substance is a stable crystalline solid routinely isolated as form A. It is milled to reduce particle size which ensures content uniformity during formulation. It exhibits pH-dependent solubility in aqueous media, being most soluble at acidic pH.

The proposed tablet dissolution method is well developed and described. The discriminating power of the dissolution method was demonstrated by evaluating samples manufactured with different active substance particle sizes and different compressions forces during tableting. Discriminatory power was also evaluated for samples stored under stressed temperature and humidity conditions.

A quality by design approach was adopted for development of the manufacturing process. Guided by an initial risk assessment, appropriate univariate/multivariate studies were conducted to evaluate the significance of process parameters on the quality and performance of the tablet formulation. The following critical quality attributes (CQAs) were identified as being potentially impacted by the finished product manufacturing process variables and were, therefore, investigated in development studies: appearance, content, uniformity of dosage units (UDU), dissolution, degradation products, and water content.

The compatibility of the finished product with different types of drinking water was assessed by monitoring risdiplam content and degradation products. The active substance is susceptible to degradation in the presence of chlorine, and a dispersion of the film-coated tablet in chlorinated drinking water exhibited increased amounts of degradation products over time. As tap water may contain chlorine, depending on regional practice, the use of bottled drinking water was recommended by the MAH. However, some bottled water may also contain chlorine. Furthermore, instructions to use non-chlorinated water may be difficult to comply with for healthcare professionals and patients as information on chlorine content is not readily available. Considering the degradation profile, defining a ten-minute window for administration was seen as the best way to ensure the safety of the medicine. Furthermore, it was also observed that the tablets dispersed on water are sensitive to light. The product information (SmPC section 4.2 and package leaflet) explains how to handle the dispersed tablets, including the instructions "*if Evrysdi is dispersed in water, take it immediately. Evrysdi must not be dispersed in any liquid other than water. Discard the prepared mixture if it is not used within 10 minutes of adding water. Do not expose the prepared mixture to sunlight*." This is considered acceptable by CHMP.

The primary packaging is aluminium/aluminium perforated unit dose blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured at F. Hoffmann-La Roche Ltd., Wurmisweg, 4303 Kaiseraugst, Switzerland. Satisfactory GMP documentation has been provided.

The manufacturing process consists of four main steps: blending, compression, film-coating and packaging. The process is considered to be a standard manufacturing process.

Critical process parameters are clearly stated in the dossier and acceptable ranges have been defined. Data from three production scale batches indicates that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. A formal validation protocol has been provided and is considered acceptable.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including description, identity (NIR, UHPLC, UV), content (NIR, UHPLC), degradation products (UHPLC), *N*-nitrosorisdiplam (LC-HRMS/MS), water content (KF), dissolution (HPLC), uniformity of dosage units (Ph. Eur., content uniformity by NIR), and microbial limits (Ph. Eur.).

The limits for degradants are set in line with ICH guidance and are justified based on the batch and stability data.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data from three production scale batches was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective permitted daily exposure (PDE). Based on the risk assessment and the presented batch data, control of elemental impurities in the finished product is not necessary.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). *N*-nitrosorisdiplam was detected at levels below the acceptable intake (AI) and the applicant proposed that no controls were needed. However, some batches contained *N*-nitrosorisdiplam above 10% of the AI. As such, the CHMP raised a major objection (MO)

requesting the test to be added to the release and stability specifications. In response, the applicant proposed to apply skip-testing, considering that no batches contained *N*-nitrosorisdiplam exceeding 30% of the AI. This is in line with published guidance and was considered acceptable.

The applicant has developed a near infrared spectroscopy (NIRS) procedure for testing identity, content and content uniformity of the tablet cores and a real-time release testing (RTRT) approach was proposed. A UHPLC reference method was also developed. The NIRS model was developed using suitable samples at both lab and commercial scale and using different batches of active substance and excipients. Samples were included in independent calibration and validation sets as per the guidance. However, based on the initially submitted dossier, the CHMP identified issues with the development and validation of the NIRS method and considered that there was insufficient data available to demonstrate equivalence of the UHPLC and NIRS methods, resulting in a MO. In response, the applicant provided further equivalence data from an additional six productions scale batches from two campaigns, including batches manufactured with different sources of microcrystalline cellulose and crospovidone, analysed by UHPLC and NIRS. Comparability of range and mean was evaluated statistically by means of a two one-sided test (TOST) approach. The accuracy of the two methods was evaluated using bias and root mean square error prediction (RMSEP). The applicant explained the approach to be used for on-going monitoring of the NIRS procedure throughout its lifecycle, including model maintenance and dealing with spectral outliers. The CHMP considered the additional data was sufficient to demonstrate equivalence between the UHPLC and NIRS analytical procedures and the RTRT process is endorsed. The lifecycle management approach is also considered acceptable.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results are provided for three production scale batches and two clinical batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through a combination of traditional final product release testing and real time release.

Stability of the product

Stability data from three production scale batches of finished product stored for up to 24 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The stability batches are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to the shelf-life specification. The analytical procedures used are stability indicating based on the results of forced degradation studies. All measured parameters remained within specification throughout the testing period. Observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC. The CHMP considered that the proposed wider shelf-life specifications for degradants were not justified considering that only minor degradation is observed based on the data provided. However, the applicant argued that further batches would be needed before tightening the limits. This was accepted with a recommendation to reassess the shelf-life limits for degradants once release and stability data from a substantial number of batches become available.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The finished product is photostable. An open dish study showed that the tablets take up water over time leading to discolouration.

Based on available stability data, the proposed shelf-life of 3 years without specific temperature storage conditions as stated in the SmPC (sections 6.3 and 6.4) is acceptable. Tablets should be stored in the original package in order to protect from moisture.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.5.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

Two major objections were raised within the procedure. In relation to the NIRS method for RTRT, the applicant provided further batch data and statistical analysis to demonstrate equivalence between the UHPLC and NIRS methods. The lifecycle management strategy for model maintenance and on-going monitoring was clearly explained. The applicant added a limit for *N*-nitrosorisdiplam to the finished product specification to resolve the second MO.

In addition, the quality of water to be used for optional dispersion of tablets was agreed and clear administration instructions have been included in the product information.

At the time of the CHMP opinion, there was a minor unresolved quality issue having no impact on the Benefit/Risk ratio of the product, which pertains to reassessing the shelf-life limits for degradants. This point is put forward and agreed as recommendations for future quality development.

2.5.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.5.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The MAH should reassess the shelf-life limits for degradants once release and stability data from a substantial number of batches become available.

2.6. Non-clinical aspects

2.6.1. Introduction

The non-clinical profile of Evrysdi was extensively characterised during the MAA and no changes have emerged since the original approval that require a discussion as part of this application.

The discussion of the impact of the current submission on the environment is presented below.

2.6.2. Ecotoxicity/environmental risk assessment

Evrysdi film-coated tablets contain 5 mg of Risdiplam, an active substance indicated for the treatment of spinal muscular atrophy (SMA). The aim of developing a new pharmaceutical form associated with a new strength was to improve the patient experience by simplifying the administration, handling, and storage, and the maximum daily dose of 5 mg was maintained.

A justification for not submitting an updated Environmental Risk Assessment (ERA) of Everysdi (Risdiplam) 5 mg, film-coated tablet, an extension application to introduce a new formulation was based on the fact that Risdiplam was first registered in the European Union by the present MAH, in 2021, with a Phase I ERA, according to the G*uideline on the Environmental Risk Assessment of Medicinal Products for Human Use* (EMEA/CHMP/SWP/4447/00 corr 2, 2006.

A summary of the ERA Phase I assessment for the Evrysdi 5 mg, film-coated tablet was submitted. Nevertheless, all relevant information including the study reports to confirm their compliance should be given. As requested, the MAH has provided an updated ERA. The OECD 107 Partition Coefficient (1-Octanol/Water) shake-flask study was performed following Good Laboratory Practice (GLP) standards. The ion-corrected log Dow values for diflunisal at pH levels 5, 7, and 9 are recorded as 0.69, 2.37, and 2.63, respectively. Therefore, a screening for PBT of diflunisal will not be required.

Relevant endpoints, methods used, and study results are summarised in Table 5.

Table 1: Summary of main study results

Substance (INN/Invented Name): Risdiplam			
CAS-number: 1825352-65-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	0.69 pH=5.0 2.37 pH=7.0 2.63 pH=9.0	Potential PBT (**N**)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	0.69 pH=5.0 2.37 pH=7.0 2.63 pH=9.0	**Not B**
	BCF	< 3 (pH 7.0)	**Not B**
PBT-statement:	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$refined	0.0009	µg/L	<0.01 threshold

			Phase II environmental fate and effects analysis is not needed
Other concerns (e.g. chemical class)			N

2.6.3. Discussion on non-clinical aspects

The experimental log Dow values at all environmentally relevant pHs were determined using the OECD Guideline 107 shake flask method. At pH 5, pH 7, and pH 9, log Dow values of 0.69, 2.37 and 2.63 were found, respectively, and are below the action limit of 4.5. So, no further assessment for persistence, bioaccumulation and toxicity should be performed.

The MAH performed a GLP-compliant OECD 107 study in 2021. The results were reported in the Environmental Risk Assessment (ERA) report and communicated to EMA in 2021. The ion-corrected log Dow values for diflunisal at pH levels 5, 7, and 9 are recorded as 0.69, 2.37, and 2.63, respectively. Therefore, a screening for PBT of diflunisal will not be required.

Refined PECsurfacewater has been determined based on refined Fpen value, based on European disease prevalence data for the sought indication(s), according to the Questions and Answers document on Guideline EMA/CHMP/SWP/44609/2010, Rev.1, 2016. After Fpen refinement, the Refined PECsurfacewater value was 0.00009 µg/L, far below 0.01 µg/L. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 2, 2006, if a PECsurfacewater value is below 0.01 µg/L, a Phase II environmental fate and effect analysis is not required.

As per Questions and answers on the *Guideline on the environmental risk assessment of medicinal products for human use* (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016) document, "*Prevalence data should be as recent as possible, preferably not older than 5 years. The usefulness of older data has to be justified by the applicant".*

In an updated ERA report according to the revised EMA ERA Guidance of 2024, the prevalence reported in a recent study from Italy (Mercuri et al., 2023, https://doi.org/10.1212/WNL.0000000000201654) is used to refine the PECSW. The prevalence of SMA in the whole population is used. Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder affecting approximately 1:10,000 live births, with a reported carrier frequency of 1:41 in Europe and 1:51 worldwide (Verhaart et al., 2017a; Wirth et al., 2020). Since SMA is a relatively rare condition, studies of its prevalence and incidence are challenging. The MAH cites a prevalence of 2.12 cases per 100,000 based on a recent Italian study (2023). The refined PECsurfacewater value is below the action limit of 0.01 µg/L, and a phase II environmental fate and effects analysis is not required. The evaluation of the ERA can be concluded in Phase I.

The updated ERA report according to the revised EMA ERA Guidance of 2024 was provided.

The SmPC and PL contain sufficient information regarding precautionary and safety measures to reduce environmental risk.

Considering the above data, Evrysdi 5 mg, film-coated tablets approval is not expected to pose a significant environmental risk.

2.6.4. Conclusion on the non-clinical aspects

From the non-clinical point of view this line extension is approvable.

2.6.5. Introduction

GCP aspects

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

This application provides data from Study BP42066, which assessed the bioequivalence of the risdiplam film-coated tablet versus the currently marketed powder for oral solution, to support the marketing authorization for the film-coated tablet.

The pharmacokinetic (PK) properties of risdiplam administered as an oral solution have been well characterized in healthy subjects and in SMA patients, as described in the marketing authorization.

Table 2. Tabular overview of clinical studies

Study identifier	Study design	Population (incl number of subjects, healthy vs patient and gender ratio)	Dosing regimen	Main PK parameters
BP42066	A Phase I, Open-label, Multiperiod Crossover Study to Investigate the Safety, Food Effect, Bioavailability, and Bioequivalence of Oral Doses of Two Different Formulations in Healthy Subjects	Part 1 (healthy subjects) Cohort A: 12 (9M/3F) Cohort B: 13 (13M) Cohort C: 15 (12M/3F) Cohort D: 14 (11M/3F) Cohort E: 28 (25M/3F) Part 2 (healthy subjects) Group 1: 25 (21M/4F) Group 2: 24 (22M/2F)	Single dose 5 mg	C_{max} AUC T_{max} $T_{1/2}$ F_{rel}

2.6.6. Clinical pharmacology

2.6.6.1. Pharmacokinetics

Absorption

Absorption of risdiplam following oral administration has been characterized in the original dossier resulting in the approval of Evrysdi 0.75 mg/mL powder for oral solution. Given that a new film coated tablet formulation was developed, absorption characteristics of risdiplam were updated based on results from study BP42066.

Study BP42066 was a randomized, performed in two parts, single oral dose, crossover study to investigate the relative bioavailability and bioequivalence of two different formulations of risdiplam 5 mg (risdiplam/F21 and risdiplam/F22 film coated tablets) *versus* the current risdiplam formulation (powder for constitution to an oral solution) in healthy male and female subjects. The effect of food on these two film coated tablets and the current oral solution was studied, as well as the effect of omeprazole on the film coated tablets in part 1. Following part 1, F21 film coated tablet formulation was selected to proceed to part 2. In part 2 bioequivalence assessment and a food effect evaluation were conducted with the selected film coated tablet formulation administered as whole (swallowed) (group 1) and dispersed in water (group 2).

Regarding the already approved powder for oral solution formulation, results obtained for Part 1 (cohorts A, B, E) and Part 2 (Group 1 and Group 2) for the pharmacokinetic parameters C_{max} and t_{max} are summarised in Table 7 below following administration on fasting state conditions:

Table 3: Powder for oral solution formulation - Pharmacokinetic parameters C_{max} and t_{max} of cohorts A,B,E and groups 1, 2 (fasting state conditions)

	n	Cmax (ng/mL)	tmax (h)
Part 1 - Cohort A	12	30.4	2.5 (1.5-6.0)
Part 1 - Cohort B	15	23.3	4.0 (3.0-4.0)
Part 1 - Cohort E	27	22.1	4.0 (1.5-8.0)
Part 2 - Group 1	24	26.3	3.3 (1.5-5.0)
Part 2 - Group 2	23	20.5	3.5 (1.5-4.5)

The MAH has revised the wording of section 5.2 (Absorption) of the corresponding SmPC, specifying the described absorption characteristics to powder for oral solution formulation as below:

«Risdiplam was rapidly absorbed in the fasted state with a plasma t_{max} ranging from 1 to 5 hours after powder for oral solution administration.»

Regarding film-coated tablet F21 formulation administered as a whole tablet (swallowed), results obtained for Part 1 (cohorts A and C) and Part 2 (Group 1) for the pharmacokinetic parameters C_{max} and t_{max} are summarized in the table below following administration on fasting state conditions:

Table 4: Film-coated tablet F21 formulation administered as a whole tablet (swallowed) - Pharmacokinetic parameters C_{max} and t_{max} of cohorts A,C and group 1 (fasting state conditions)

	n	Cmax (ng/mL)	tmax (h)
Part 1 - Cohort A	12	28.6	3.0 (2.0-4.0)
Part 1 - Cohort C	15	28.0	3.0 (2.0-4.0)
Part 2 - Group 1	24	26.9	3.5 (2.0-4.5)

Regarding film-coated tablet F21 formulation administered as dispersed in water, results obtained for Part 1 (cohort A) and Part 2 (Group 2) for the pharmacokinetic parameters C_{max} and t_{max} are summarize in Table 9 below following administration on fasting state conditions:

Table 5: Film-coated tablet F21 formulation administered as dispersed in water - Pharmacokinetic parameters C_{max} and t_{max} of cohort A and group 2 (fasting state conditions)

	n	Cmax (ng/mL)	tmax (h)
Part 1 - Cohort A	12	28.9	3.5 (1.5-5.0)
Part 2 - Group 2	22	21.5	4.0 (2.0-4.1)

For film-coated tablets, the MAH proposes the following wording to the item "Absorption" in section 5.2 of the SmPC, which is supported by results from study BP42066:

«Risdiplam was rapidly absorbed in the fasted state with a plasma t_{max} ranging from 2 to 4.5 hours after oral administration of the film-coated tablet or the prepared dispersion.»

Bioavailability

The relative bioavailability of F21 Tablet swallowed and dispersed in water on fasting state conditions was assessed in Part 1 – cohort A. It can be concluded that in comparison to oral solution, F21 tablet formulation shows the same amount absorbed, as assessed by AUC, following its administration as whole tablet or dispersed in water, with a relative bioavailability of 1.09 and 1.02, respectively.

Bioequivalence

Bioequivalence between the F21 tablet as whole tablet (swallowed) or dispersed in water and the oral solution was demonstrated following administration in both fasted and fed state conditions.

For film-coated tablets, the MAH proposes the following wording to the item "Absorption" in section 5.2 of the SmPC, which is supported by results from study BP42066 and accepted by the Rapporteur:

«Risdiplam exposure after administration of the film-coated tablet or the prepared dispersion was bioequivalent to the oral solution.»

Effect of Food

Results from part 2 indicated that there was no clinically relevant impact of food on the PK parameters of risdiplam administered as F21 tablet formulation as whole or dispersed in water. Moreover, it was observed no clinically relevant impact of food on the PK parameters of risdiplam administered as oral solution.

For oral solution, the MAH proposes the following wording to the item "Absorption" in section 5.2 of the SmPC, which is supported by results from study BP42066:

«Based on data in 47 healthy subjects, food (high--fat, high calorie breakfast) had no relevant effect on the exposure of risdiplam. In the clinical studies, risdiplam was administered with a morning meal or after breast feeding.»

For the film coated tablets, the MAH proposes the following wording to the item "Absorption" in section 5.2 of the SmPC, which is supported by results from study BP42066:

«Food (high-fat, high calorie breakfast) had no relevant effect on the exposure of risdiplam. In the clinical studies, risdiplam was administered with a morning meal or after breast feeding.»

Distribution

No additional data was submitted regarding distribution of risdiplam.

The distribution properties of risdiplam have been assessed in the original submission (oral solution) and are described in the approved SmPC. The proposed SmPC for film coated tablets contains the same wording:

«Risdiplam distributes evenly to all parts of the body, including the central nervous system (CNS) by crossing the blood brain barrier, and thereby leading to SMN protein increase in the CNS and throughout the body. Concentrations of risdiplam in plasma and SMN protein in blood reflect its distribution and pharmacodynamic effects in tissues such as brain and muscle.

The population pharmacokinetic 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, without any binding to alpha-1 acid glycoprotein, with a free fraction of 11%.»

Elimination

No additional data was submitted regarding elimination and biotransformation of risdiplam.

The elimination properties of risdiplam have been assessed in the original submission (oral solution) and are described in the approved SmPC. The proposed SmPC for film coated tablets contains the same wording:

«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 (MDR1).

Approximately 53% of the dose (14% unchanged risdiplam) was excreted in the faeces and 28% in urine (8% unchanged risdiplam). 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.»

The biotransformation properties of risdiplam have been assessed in the original submission (oral solution) and are described in the approved SmPC. The proposed SmPC for film coated tablets contains the same wording:

«Risdiplam is primarily metabolized by FMO1 and FMO3, and also by CYPs 1A1, 2J2, 3A4 and 3A7.

Co-administration of 200 mg itraconazole twice daily, a strong CYP3A inhibitor, with a single oral dose of 6 mg risdiplam showed no clinically relevant effect on the PK of risdiplam (11% increase in AUC, 9% decrease in C_{max}).»

Dose proportionality and time dependencies

No additional data was submitted regarding dose proportionality and dose dependencies.

Special populations

No additional data was submitted regarding special populations (impaired renal and hepatic functions, elderly and paediatric populations). In study BP42066 only healthy subjects aged 21 to 55 years old were enrolled.

Pharmacokinetic interaction studies

No additional data was submitted regarding in vitro and in silico data to assess pharmacokinetic interactions.

Nevertheless, the effect of an antacid (omeprazole) on the absorption of risdiplam following administration of F21 tablet formulation (whole tablet) was assessed through Part 1 – cohort C in study BP42066.

The exposure to risdiplam (AUCs and C_{max}) was similar for the F21 tablet swallowed after coadministration with omeprazole and the F21 tablet swallowed alone, indicating that the bioavailability of F21 tablet swallowed in the fasted condition was not affected by the coadministration of omeprazole. Such conclusion was included in the proposed section 4.5 of the SmPC for Evrysdi 5 mg film-coated tablets.

2.6.6.2. Pharmacodynamics

Not applicable.

2.6.7. Discussion on clinical pharmacology

Risdiplam was developed as a 5 mg film-coated tablet to be swallowed whole as a tablet or dispersed in a small amount of bottled water prior to administration (section 2.1 of the Clinical Overview). The absorption of risdiplam following its administration as a whole tablet or dispersed in water, in both fasting and fed state conditions, has been characterized. .

In study BP42066 it was concluded that the exposure to risdiplam (AUCs and C_{max}) was similar for the F21 tablet swallowed after coadministration with omeprazole and the F21 tablet swallowed alone, indicating that the bioavailability of F21 tablet swallowed in the fasted condition was not affected by the coadministration of omeprazole. Such conclusion is now reflected in the proposed section 4.5 of the SmPC for Evrysdi 5 mg film-coated tablets.

The paediatric PBPK model of risdiplam previously developed for the population ≥2 months old was successfully adapted to the extended population ≥16 days old by estimating in vivo FMO3 ontogeny by Mech-PPK modelling using 13,230 plasma concentration data of risdiplam collected from subjects 16 days to 61

years old. The updated paediatric PBPK model can simulate risdiplam PK in neonates and infants with consideration of concurrent changes in physiology such as FMO3, CYPs 3A4/7 and albumin abundances, organ size and blood flow. The information currently included in SmPC section 5.2 (PK properties) sufficiently describe the results of the studies performed.

No relevant food effect was observed for the 5 mg film coated tablet administered as a whole tablet or for the oral solution of risdiplam. Moreover, bioequivalence between the film coated tablet and the oral solution was also demonstrated in the tested administration conditions, bridging clinical efficacy and safety from phase III studies to the film-coated tablet.

2.6.8. Conclusions on clinical pharmacology

Risdiplam was developed as a 5 mg film-coated tablet to be swallowed whole as a tablet or dispersed in a small amount of bottled water prior to administration. The clinical pharmacokinetic section of this application is based on data from the Phase 1 study BP42066. Generally, the characterization of absorption of risdiplam following its administration as a whole tablet or dispersed in water, in both fasting and fed state conditions, is adequate. Section 4.5 (Interactions) duly reflect the results from Part 1 cohort C found in study BP42066.

2.6.9. Clinical efficacy

The efficacy of risdiplam has been established in prior clinical trials submitted as part of the original marketing application for the powder for oral solution.

No new data is provided in this submission.

2.6.10. Clinical safety

This type II variation pertains the analysis of the Study BP42066. Only the safety aspects of the study and its impact on the overall safety of risdiplam are discussed.

2.6.10.1. Patient exposure

Risdiplam (Evrysdi®), also known as RO7034067, is the first orally administered small molecule survival of motor neuron 2 (*SMN2*) splicing modifier developed to treat spinal muscular atrophy (SMA). Risdiplam was approved in August 2020 in the United States (U.S.) and in March 2021 in the European Union (E.U.) for treatment of SMA. Risdiplam targets the underlying molecular deficiency in SMA and promotes the inclusion of exon 7 to generate full length *SMN2* messenger RNA to increase the production of functional survival of motor neuron (SMN) protein.

Study BP42066 corresponds to the administration of single oral doses of the currently approved oral solution of risdiplam and two new tablet formulations in healthy subjects. The safety data presented includes a total of 131 subjects who received at least one dose of risdiplam during the study, up to the date of the last scheduled procedure for the study (28 January 2023).

Study BP42066 was a randomized, open-label, multi-period crossover Phase I study in two parts evaluating the safety, food effect, bioavailability, and bioequivalence of oral doses of two different formulations of risdiplam in healthy subjects. The study was designed to have up to three parts; however, the Sponsor decided not to proceed with Part 3, as the bioequivalence objective of the study was met in Part 2. Two different formulations of risdiplam 5 mg (F21 dispersible tablet and F22 dispersible tablet) were compared to the currently approved risdiplam oral solution formulation.

During the conduct of Study BP42066, the tablet nomenclature was considered by the Sponsor as "dispersible tablet". However, the designation was later changed by the Sponsor to "film-coated tablet". Therefore, "film-coated tablet" is considered synonymous with "dispersible tablet" within the context of this variation.

Part 1 of the study assessed the bioavailability of the two tablet formulations versus the approved oral solution of risdiplam. The study also assessed whether the solubility and bioavailability of the tablets were impacted by a change in the stomach pH after co-administration of the proton pump inhibitor (PPI) omeprazole. Part 2 of the study assessed the bioequivalence of the formulation selected based on Part 1 data versus the approved oral solution of risdiplam, as well as the effect of food on the oral solution and the tablet.

Table 6 presents an overview of Study BP42066 contributing to the safety evaluation.

Treatment Regimens

The investigational medicinal products (IMPs) for Study BP42066 were risdiplam 5 mg oral solution (powder for oral solution, 0.75 mg/mL of risdiplam once reconstituted) and two different formulations of 5 mg risdiplam tablets (risdiplam/F21 tablet and risdiplam/F22 tablet). Both tablets could either be dispersed in water and ingested as a suspension or swallowed as a whole tablet. Omeprazole oral capsule (40 mg) was a non-IMP for this study.

Throughout the study, risdiplam was administered at the therapeutic dose (5 mg) for SMA patients with a body weight ≥ 20 kg, as defined in the Evrysdi U.S. Prescribing Information. Treatments were assigned either in a fixed sequence or randomly, as described in the CSR for Study BP42066.

Study Populations

Healthy male and female subjects 18 to 55 years of age, with a body mass index (BMI) of 18.0 to 32.0 kg/m^2 were included in the study. Enrollment of the same subject in more than one cohort or group was not permitted regardless of the study part.

Study BP42066, Report 1128161, Section 9.6.1.2.

Overall Design Features

Study BP42066 was a randomized, open-label, multi-period crossover Phase I study evaluating the safety, food effect, bioavailability, and bioequivalence of oral doses of two different tablet formulations of risdiplam in healthy subjects compared to the currently approved risdiplam powder for constitution to oral solution formulation. The study was designed to have up to three parts. Per protocol, the Sponsor made the decision on 20 July 2023 not to proceed with Part 3 of the study, as the bioequivalence objective of the study was met in Part 2.

Demographic and Other Characteristics of the Study Population

All subjects satisfied the inclusion and exclusion criteria prior to entry into the study. There were no findings in the medical history of clinical concern for any subject. In addition, there were no baseline signs or symptoms of clinical concern prior to dosing for any subject.

Table 6: Summary of Studies Contributing to Safety Evaluation

Study Number	**Study Design**	**Population**	**Number of Subjects Evaluable for Safety**	**Dose, Route, and Regimen**
BP42066	Phase I, randomized, open-label, multi-center, multi-period crossover study. **Part 1:** **Cohort A** and **Cohort B** = 5-way crossover, partial randomization **Cohort C** and **Cohort D** = 2-period fixed sequence **Cohort E** = 2-way crossover, full randomization **Part 2:** fully randomized 4-period cross-over	Healthy male and female subjects aged 18 to 55 years, with a BMI of 18.0 to 32.0 kg/m^2	A total of 131 subjects were enrolled in the study. **Part 1:** A total of 82 subjects were enrolled into five cohorts: **Cohort A** = 12 **Cohort B** = 13 **Cohort C** = 15 **Cohort D** = 14 **Cohort E** = 28 **Part 2:** A total of 49 subjects enrolled into two groups: **Group 1** = 25 **Group 2** = 24	**IMP Treatment:** Risdiplam powder for constitution to oral solution, 5 mg oral single dose Risdiplam tablet F21, 5 mg oral single dose Risdiplam tablet F22, 5 mg oral single dose **Non-IMP Treatment:** Omeprazole 40 mg oral capsule Treatments were assigned either in a fixed sequence or randomly

BMI = body mass index; IMP = investigational medicinal product.

2.6.10.2. Adverse events

Overall, the administration of a single 5 mg oral dose of risdiplam in different forms was well tolerated by the healthy adult subjects in this study.

An event of blood pressure increase and hypertension was observed in Part 2 of Study BP42066, with the oral solution (fed) and F21 tablet dispersed in water (fed) formulation, respectively, for the same subject (1/24, around 4% of total population). In both cases a drug causal relationship was established. Hypertension is currently not listed in section 4.8 of the SmPC nor was it reported among the ADRs in the original EPAR, implying absent or negligible incidence. A review of the frequency of this event was conducted to evaluate the need for an update of the relevant section of the SmPC upon RfSI. The patient on which an event of high blood pressure / hypertension was reported was on previous anti-hypertensive medication, and the baseline

BP levels were even higher than later on. Also, from the 4 risdiplam CTs, there were only 4 mild to moderate episodes of high BP, none of which resulted in risdiplam dose modification and resolved spontaneously.

No deaths, serious adverse events (SAEs), or nonserious adverse events of special interest (NSAESIs) were reported in any part of the study. There were 17 treatment emergent adverse events (TEAEs) reported in 13 subjects in Part 1 and 18 TEAEs reported in 12 subjects in Part 2 (25 subjects with 35 TEAEs, overall), 6 of which were assessed as treatment-related by the investigator. Six subjects were discontinued from the study due to an AE.

All TEAEs resolved by the end of the study, except 1 TEAE of suspected coronavirus disease (COVID-19) with an unknown outcome.

Adverse Events Related to Treatment

Six TEAEs in total were assessed as treatment-related (3 in Part 1: rash maculo-papular [F21 tablet swallowed, fasted], headache [oral solution, fasted], headache [oral solution, fed]; 3 in Part 2: blood pressure increased [oral solution, fed] and hypertension for the same subject [F21 tablet dispersed in water, fed], and headache [F21 tablet dispersed in water, fasted]).

Adverse Events by Intensity

Apart from 6 moderate TEAEs (3 in Part 1 [rash maculo-papular, pharyngitis, and rhinitis]; 3 in Part 2 [headache, vomiting, dental caries]), all TEAEs reported in this study were mild in severity.

2.6.10.3. Serious adverse events, deaths, and other significant events

No deaths or other serious adverse events have been reported in the study.

2.6.10.4. Laboratory findings

There were no treatment-related or formulation-related trends in the mean or individual subject serum biochemistry, hematology, or urinalysis data during Part 1 or Part 2 of Study BP42066. No abnormal findings were reported as TEAEs.

Hematology and chemistry

There was no hematology trends reported in this study.

Other Safety Evaluations

There were no trends in vital signs, electrocardiography, or taste assessment data, nor clinically significant findings from the physical examination, apart from an erythematous papular eruption reported as a TEAE (rash maculo-papular; Cohort C; 1 subject after administration of F21 tablet swallowed [fasted]), a raised erythema patch reported as a TEAE (eczema nummular; Cohort D; 1 subject after administration of omeprazole 40 mg), a vesicular eruption with crusting reported as a TEAE (oral herpes; Group 1; 1 subject after administration of oral solution [fasted]), and one subject with a TEAE of blood pressure increase followed by a TEAE of hypertension (both related; Group 2).

2.6.10.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.10.6. Safety in special populations

Not applicable.

2.6.10.7. Immunological events

An erythematous papular eruption reported as a TEAE (rash maculo-papular; Cohort C; 1 subject after administration of F21 tablet swallowed [fasted]), a raised erythema patch reported as a TEAE (eczema nummular; Cohort D; 1 subject after administration of omeprazole 40 mg), a vesicular eruption with crusting reported as a TEAE (oral herpes; Group 1; 1 subject after administration of oral solution [fasted]), and one subject with a TEAE of blood pressure increase followed by a TEAE of hypertension (both related; Group 2).

2.6.10.8. Safety related to drug-drug interactions and other interactions

Drug Interactions

The impact of the PPI omeprazole on the F21 and F22 tablets was assessed in this study. The bioavailability of the 5 mg F21 tablet swallowed in fasted condition was not affected by the coadministration of omeprazole. For the 5 mg F22 tablet swallowed in fasted state, the maximum concentration observed (C_{max}) of risdiplam was lower after coadministration with omeprazole. As omeprazole, which induces a change in stomach pH, led to a greater impact on the absorption rate of risdiplam for the F22 tablet, the F21 tablet formulation was selected for the bioequivalence assessment conducted in Part 2 of this study.

No relevant food effect was observed for both tablet formulations and the oral solution.

2.6.10.9. Discontinuation due to adverse events

Adverse Events That Led to Discontinuation from Treatment or Study

Six subjects (3 in Part 1, and 3 in Part 2) discontinued from the study due to an AE, which were all assessed as not related to the IMP except for 1 TEAE of moderate rash maculo-papular after administration of the F21 tablet swallowed, fasted (Cohort C, Part 1). None of the AEs leading to discontinuation in any part of the study were considered to impact the known safety profile of risdiplam.

Adverse Events that led to Dose Modification

No AEs that led to dose modification were reported in this study.

Adverse Events of Special Interest

Neither serious adverse events of special interest (AESIs) nor NSAESIs were reported in any part of the study.

2.6.10.10. Post marketing experience

The new tablet formulation of risdiplam is not marketed in any country; therefore, no post marketing data are available for the tablet.

Risdiplam as powder for oral solution is currently approved in over 100 international markets (including U.S. and E.U.) for the treatment of SMA. Since the international birth date (07 August 2020) through 6 August 2023 (data lock point for the Periodic Benefit-Risk Evaluation Report [PBRER] 1122884), an estimated cumulative total of 10,885 patients have received risdiplam from marketing experience (European Economic Area n = 3,597; rest of the world n = 4,128; U.S. = 2,513). Exposure was similar between sexes (male n = 5,119; female n = 5,119; unknown n = 0). The information that became available did not alter the known benefit-risk profile of risdiplam and the benefit-risk profile of risdiplam in the authorized indication remains favorable.

2.6.11. Discussion on clinical safety

There were no new adverse events or safety concerns regarding the new formulation.

The only aspect that must be highlighted is that the tablet or tablet mixture should not be used to treat children with a nasogastric (NG-tube) or gastrostomy tube (G-tube). This is reflected in SmPC section 4.2 to make it clear for the prescriber.

2.6.12. Conclusions on clinical safety

No new adverse events have been identified. The observed AEs are in line with what has been identified / described in SmPC

2.7. Pharmacovigilance

2.7.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.7.2. Periodic Safety Update Reports submission requirements

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

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disorder characterized by the progressive loss of spinal motor neurons leading to muscle weakness and is the leading genetic cause of mortality in infants and young children. SMA is caused by a homozygous deletion (95% of cases) or mutation of the Survival of Motor Neuron 1 (SMN1) gene on chromosome 5q (locus 5q13) which encodes SMN, 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. Due to a translationally synonymous C→T mutation at nucleotide 6 in exon 7, the SMN2 mRNA undergoes alternative splicing that excludes exon 7 from 85%-90% of mature SMN2 transcripts, which produces an unstable SMNΔ7 protein that is rapidly degraded. Accordingly, full-length SMN2 mRNA is generated in only 10-15% of splicing events. Since SMA patients only have the SMN2 gene, their SMN protein levels are significantly decreased.

3.1.2. Available therapies and unmet medical need

There are currently three authorised medicinal products for SMA: nusinersen, onasemnogene abeparvovec and risdiplam.

Risdiplam was approved in August 2020 in the United States (U.S.) and in March 2021 in the European Union (E.U.) for treatment of SMA. Risdiplam targets the underlying molecular deficiency in SMA and promotes the inclusion of exon 7 to generate full length *SMN2* messenger RNA to increase the production of functional survival of motor neuron (SMN) protein.

3.1.3. Main clinical studies

The clinical development for the risdiplam tablets consisted of one Phase I, open-label, multi-period crossover study to investigate the safety, food effect, bioavailability and bioequivalence of two different tablet formulations in healthy subjects (Study BP42066).

The study was planned to consist of up to three parts. The objectives for Part 1 were:

- to assess the relative bioavailability of two new dispersible tablet formulations (F21 and F22) of risdiplam compared to the currently marketed risdiplam formulation (powder for oral solution) in healthy subjects after single oral dose administration of 5 mg risdiplam;
- to assess the effect of food on the bioavailability of the two tablet formulations and the oral solution; and
- to assess the effect of omeprazole on the bioavailability of the two tablet formulations.

The objective of Part 2 and 3 was to assess the bioequivalence of the selected risdiplam tablet formulation versus the oral solution. As the bioequivalence objective was met in Part 2 of the study, the decision was made to not proceed with Part 3.

The primary PK parameters for the assessment of bioequivalence were the maximum observed plasma concentration (C_{max}), the area under the plasma concentration-time curve (AUC) from time zero to the time of the last quantifiable concentration (AUC_{0-t}), and the AUC from time zero to extrapolated infinity ($AUC_{0-\infty}$). Bioequivalence was considered established if the 90% confidence intervals (CIs) of the geometric least squares means (GLSMs) were within 80.00%-125.00%.

The safety objective for this study was to evaluate the safety and tolerability of risdiplam in healthy subjects. Safety assessments included adverse events (AEs), clinical laboratory assessments, ECG, vital signs, and physical examination.

3.2. Favourable effects

No new efficacy data has been provided.

The only potential favourable effect (theoretical) of this new formulation is the easiness of transport and administration, particularly for older children and adults without swallowing difficulty.

3.3. Uncertainties and limitations about favourable effects

The above potential advantage is theoretical. Individual patients may prefer the solution rather than the tablet formulation.

3.4. Unfavourable effects

The adverse event profile identified in the healthy volunteers of the study is in line with what has been described with the liquid formulation and already known for risdiplam.

3.5. Uncertainties and limitations about unfavourable effects

No new uncertainties on safety issues emerged with this pharmacokinetic study in healthy volunteers.

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

Assuming that the new solid formulation is equivalent to the oral solution and may be easier to transport and administer in older children and adults without the need for tube feeding, the efficacy is similar to the presently approved formulation.

No new safety issues have emerged in the bioequivalence study.

3.6.2. Balance of benefits and risks

Given the potential benefit of easiness to administer, store and transport, and the identical safety profile to the oral formulation, the balance remains positive.

3.6.3. Additional considerations on the benefit-risk balance

Not applicable.

3.7. Conclusions

The overall benefit/risk balance of Evrysdi is positive, subject to the conditions stated in section Recommendations.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety, the CHMP considers by consensus that the benefit-risk balance of Evrysdi new pharmaceutical form is favourable in the following indication(s):

Evrysdi is indicated for the treatment of 5q spinal muscular atrophy (SMA) in patients with a clinical diagnosis of SMA Type 1, Type 2 or Type 3 or with one to four *SMN2* copies.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Evrysdi subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/00086/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variation to the terms of the marketing authorisation, concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, IIIA and IIIB

Type II variation (C.I.4) to update sections 4.2 and 5.2 of the SmPC in order to update the recommended method of administration based on the food effect results from study BP42066; this is a phase 1, open-label, multiperiod crossover study to investigate the safety, food effect, bioavailability, and bioequivalence of oral doses of two different formulations of risdiplam in healthy subjects. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor changes to the Product Information and to align the Package Leaflets of both formulations.