12 May 2026
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Itvisma (onasemnogene abeparvovec)
Treatment of spinal muscular atrophy
EU/3/15/1509

Sponsor: Novartis Europharm Limited

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)	Adeno-associated viral vector serotype 9 containing the human *SMN* gene
Other name(s)	-
International Non-Proprietary Name	Onasemnogene abeparvovec
Tradename	Itvisma
Orphan condition	Treatment of spinal muscular atrophy
Sponsor's details:	Novartis Europharm Limited Vista Building Elmpark Merrion Road Dublin 4 D04 A9N6 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	AveXis EU Ltd
COMP opinion	13 May 2015
EC decision	19 June 2015
EC registration number	EU/3/15/1509
Post-designation procedural history	
Transfer of sponsorship / sponsor's name change	- Transfer from AveXis EU Ltd to Avexis Netherlands B.V. – EC decision of 27 September 2018. - 2nd Transfer from Avexis Netherlands B.V. to AveXis EU Limited - EC decision of 26 September 2019. - Name change from AveXis EU Limited to Novartis Gene Therapies EU Limited – EC letter 9 December 2020. - 3rd Transfer from Novartis Gene Therapies EU Limited to Novartis Europharm Limited – EC decision of 18 July 2022.
COMP opinion on review of orphan designation at the time of marketing authorisation	1 April 2020 (Zolgensma)
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Emmely de Vries / Attila Sebe
Applicant	Novartis Europharm Limited
Application submission	29 April 2025
Procedure start	22 May 2025
Procedure number	EMA/H/C/006498 duplicate MAA to: Zolgensma Union Register of medicinal products - Public health - European Commission The scope of this opinion does not include Zolgensma as far as it concerns the orphan designation for that product.
Invented name	Itvisma

Proposed therapeutic indication	Itvisma is indicated for the treatment of 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene in patients 2 years of age and older. Further information can be found in the European public assessment report (EPAR) on the Agency's website Itvisma | European Medicines Agency (EMA)
CHMP opinion	23 April 2026
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Fernando Mendez Hermida
Sponsor's report submission	5 November 2025
COMP discussion and adoption of list of questions	14-16 April 2026
Oral explanation	11 May 2026
COMP opinion	12 May 2026

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 designation in 2015 was based on the following grounds:

"Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 9 containing the human *SMN* gene was considered justified based on preclinical data in a valid in vivo model of the condition, where administration of the product resulted in expression of the missing protein and improved motor function and survival;
- the condition is life-threatening and chronically debilitating due to muscle wasting, weakness, failure to thrive, pulmonary and orthopaedic complications;
- the condition was estimated to be affecting less than 0.4 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing adeno-associated viral vector serotype 9 containing the human *SMN* gene as an orphan medicinal product for the orphan indication: treatment of spinal muscular atrophy".

2.2. Review of orphan medicinal product designation at the time of Zolgensma marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2020 was based on the following grounds:

"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 less than 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 of treatment of the condition have been authorised in the European Union, the assumption that Zolgensma may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor has presented an indirect comparison versus nusinersen, supporting an improvement in survival or time to permanent ventilation in treated patients with type I disease. The Committee considers 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 Zolgensma, adeno-associated viral vector serotype 9 containing the human *SMN* gene, onasemnogene abeparvovec, EU/3/15/1509 for treatment of spinal muscular atrophy is not removed from the Community Register of Orphan Medicinal Products".

3. Review of criteria for orphan designation at the time of Itvisma 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

SMA is an autosomal-recessive neuromuscular disease characterized by irreversible and progressive motor neuron loss, leading to progressive muscle atrophy and weakness, and subsequent paralysis and early death in the most severe cases. Other symptoms are amongst others scoliosis, difficulties with breathing and swallowing, failure to thrive and tremors (tongue fasciculations).

The most common form of SMA results from bi-allelic mutations to the Survival Motor Neuron 1 (SMN1) gene on chromosome 5q13 (5q SMA); of these 5q SMA cases, 95% are due to bi-allelic deletions, with the remainder being hemizygous deletions with a loss of function mutation on the other chromosome. The lack of SMN protein leads to motor neurons loss in the anterior horn of the spinal cord and brain stem nuclei.

The severity of the disease is mainly influenced by the number of copies of the SMN2 gene. SMN2 produces only ~10-15% functional SMN protein, so higher SMN2 copy numbers generally result in milder SMA symptoms and slower progression.

In 1991, an international consortium on spinal muscular atrophy sponsored by the Muscular Dystrophy Association (MDA) formalized a classification scheme for the different phenotypes of SMA. This classification highlighted 5 types of SMA based on age of onset, the highest level of motor function (non-sitting, sitting, walking) and SMN2 copy numbers. Subsequent modifications included a type 0 for patients with prenatal onset and a type 4 for adult-onset cases, see Table 1 below (after Arnold et al (2015), Spinal muscular atrophy: Diagnosis and management in a new therapeutic era. Muscle Nerve, 51: 157-167; Nishio H, et al., Int J Mol Sci. 2023 Jul 26;24(15)).

Currently, also other functional classification system are used, into functional classification based on the individual's maximum motor function achieve only: (a) 'Non-sitters' with individuals who are unable to sit independently and may require support for trunk control, (b) 'Sitters' with individuals who can sit independently but are unable to walk and (c) 'Walkers' with individuals who demonstrate the ability to walk independently.

Table 1. Classification of SMA (Arnold et al., 2015)

Table 1. Classification of SMA.

Type	Onset	Function	Median Survival	*SMN2* Copy Number in *SMN1*-Deleted Patients
0	Prenatal	Respiratory failure at birth	Weeks	1
I	0–6 months	Never sit	<1 years	2–3
II	<18 months	Sit	>25 years	3
III	>18 months	Stand or ambulatory	adult	3–4
IV	>30 years	Ambulatory	adult	≥4

Adapted from the original by Arnold et al. [11].

The diagnosis is made based on genetic screening. In many member states, neonatal screening is applied routinely.

The approved therapeutic indication "***Itvisma*** *is indicated for the treatment of 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene in patients 2 years of age and older"* falls within the scope of the designated orphan condition "treatment of spinal muscular atrophy".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

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

The COMP noted that authorized disease modifying SMA treatments had a major positive impact on morbidity and mortality. However, despite these treatments being very effective, the responses may be incomplete, and SMA is still considered a seriously debilitating and life-threatening condition.

Number of people affected or at risk

The sponsor has proposed a complete prevalence estimate of SMA in the EU of 0.375 per 10,000 people.

This estimate is similar to the prevalence accepted by the COMP at the time of granting of orphan drug designation (ODD) for onasemnogene abeparvovec in 2015 (EU/3/15/1509) and at the time of Orphan Maintenance Assessment for Zolgensma in 2020, i.e. SMA was estimated to affect less than 0.4 in 10,000 people in the European Union (EU).

The sponsor conducted a comprehensive literature review and calculated the weighted complete prevalence of SMA in EU per 10,000 people, by using the most recent population statistics. Population size on 1 January 2024 of each respective country is reported by Eurostat (Eurostat 2025). For countries without a prevalence estimate, the prevalence estimated by Sarv et al (2021) was used as a reference, which was the highest, country-level prevalence estimate identified in the literature. Verhaart et al (2017) estimated the incidence of genetically confirmed SMA in Europe using data from genetic laboratories, the TREAT-NMD Global SMA Patient Registry, and the Care and Trial Site Registry (CTSR). Data were collected from 122 laboratories across 27 European countries, but sufficient coverage (>80%) for incidence calculations was achieved in 18 countries, highlighting variability in registry participation and patient access to care.

While most studies are on the prevalence in neonates only, two additional references include epidemiologic estimates pertaining to the total population including adults:

- Population point-prevalence: Norway 0.37/10,000 (children and adults, 2020), using hospital records and genetic registries (Muller et al 2021);
- Primary-care database Italy: 0.51/10,000 using broad case definitions, 0.112/10,000 when restricted to "certain" cases (Maggi et al 2023).

The complete prevalence rate of SMA in EU was estimated at 0.375 per 10,000 people. Results are listed in Table 2.

Table 2. Primary analysis: Countries without prevalence estimate assumed the highest country-level prevalence

Country	Reference to input data	Prevalence per 10,000 people	Population in 2024	Weighted prevalence
Belgium	Verhaart et al (2017)	0.156	11,817,096	0.004049084
Bulgaria	Verhaart et al (2017)	0.083	6,445,481	0.001175046
Czechia	Verhaart et al (2017)	0.117	10,900,555	0.002801276
Denmark	Verhaart et al (2017)	0.411	5,961,249	0.005381465
Germany	Vill et al (2021)	1.45	83,456,045	0.265245348
Estonia	Sarv et al (2021)	1.207	1,374,687	0.003644454
Ireland	Lefter et al (2017)	0.110	5,351,681	0.001293017
Greece	Kekou et al (2020)	0.15	10,400,720	0.0034267
Spain	Verhaart et al (2017)	0.030	48,619,695	0.003203723
France	Verhaart et al (2017)	0.030	68,467,362	0.004511555

Country	Reference to input data	Prevalence per 10,000 people	Population in 2024	Weighted prevalence
Croatia	Drausnik et al (2019)	0.93	3,861,967	0.007888837
Italy	Coratti et al (2023)	0.212	58,971,230	0.027459808
Cyprus	Assumed*	1.207	966,365	0.002561946
Latvia	Assumed*	1.207	1,871,882	0.004962576
Lithuania	Verhaart et al (2017)	0.031	2,885,891	0.0001965
Luxembourg	Assumed*	1.207	672,050	0.001781683
Hungary	Verhaart et al (2017)	0.086	9,584,627	0.001810486
Malta	Assumed*	1.207	563,443	0.001493753
Netherlands	Verhaart et al (2017)	0.123	17,942,942	0.004847527
Austria	Verhaart et al (2017)	0.040	9,158,750	0.00080467
Poland	Verhaart et al (2017)	0.088	36,620,970	0.007078381
Portugal	Machado et al (2024)	0.371	10,639,726	0.008670134
Romania	Verhaart et al (2017)	0.013	19,067,576	0.000544453
Slovenia	Verhaart et al (2017)	0.164	2,123,949	0.000765084
Slovakia	Verhaart et al (2017)	0.024	5,424,687	0.000285961
Finland	Verhaart et al (2017)	0.064	5,603,851	0.000787749
Sweden	Verhaart et al (2017)	0.062	10,551,707	0.001436931
Iceland	Assumed*	1.207	383,567	0.001016881
Liechtenstein	Assumed*	1.207	40,015	0.000106084
Norway	Husebye et al (2020)	0.442	5,550,217	0.005388324
Overall Europe			455,279,983	
Overall Europe prevalence per 10,000 persons				**0.374619436**

*Assumed prevalence corresponds to (Sarv et al 2021) as the highest country-level prevalence identified in the literature

Based on the sponsors prevalence calculations, the COMP accepted a prevalence estimate of approximately 0.4 in 10,000 persons in the EU, similar to previously accepted values for this condition.

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 currently three medicinal products authorized in the EU for the treatment of spinal muscular atrophy (SMA), the two SMN2 splicing modulators Spinraza (nusinersen) and Evrysdi (risdiplam) as well as the gene therapy product Zolgensma (onasemnogene abeparvovec). Considering that Itvisma (onasemnogene abeparvovec) is a duplicate marketing authorization of the same active substance as Zolgensma and thus covered by the same orphan designation (EU/3/15/1509), Zolgensma is excluded from the selection of satisfactory methods in the context of this procedure. In this respect, the scope of this opinion does not include Zolgensma as far as it concerns the orphan designation for that product.

At time of orphan maintenance review, satisfactory methods are identified based on a comparative evaluation of the target patient populations, as per the SmPC, of the new orphan medicinal product vis a vis the authorized therapies. Based on this initial analysis and considering the respective overlap of study populations as covered by the therapeutic indications/SmPC's, the identified satisfactory methods for Itvisma were Spinraza and Evrysdi (Table 3). As regards the latter, the COMP noted the specific mention of SMA types and *SMN2* copy numbers in the Evrysdi 4.1 indication wording, while this is not applied for the Itvisma indication, albeit that the use of Itvisma is restricted to patients above 2 years of age. The COMP considers that the specific wording in the Evrysdi indication of "…..or with one to four *SMN2* copies" would in principle also comprise patients with SMA type 4. The Sponsor is asked to discuss the overlap of the target populations as defined by the therapeutic indications/SmPC of Itvisma and Evrysdi.

Table 3. Relevant approved treatments for Spinal Muscular Atrophy and satisfactory methods for Itvisma

Medicinal Product	**Authorized Indication (4.1 SmPC)**	**Satisfactory Method for Itvisma**
Spinraza® (nusinersen) **Intrathecal/every 4 months** (SMN2 splicing modulator)	Treatment of 5q SMA.	**Yes**
Evrysdi® (risdiplam) **Oral/daily** (SMN2 splicing modulator)	Treatment of 5q 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.	**Yes (see list of questions)**

Conclusion:

In order to better inform the final decision on the selection of satisfactory methods in the context of this procedure, the COMP adopted a question. The COMP views in principle both Spinraza and Evrysdi as satisfactory methods for Itvisma due to the overlap in the target patient populations. However, the sponsor is invited to share their views and discuss the overlap of the target populations as defined by the therapeutic indications/SmPC of Itvisma and Evrysdi.

Significant benefit

The sponsor provided a general discussion, arguing that despite effective authorized therapies for SMA, significant limitations and an unmet need remain for a broad patient population living with SMA, considering that Zolgensma is indicated only for use in younger patients. Nusinersen (intrathecal administration once every 4 months) and risdiplam (oral administration once daily) require chronic administration in order to sustain effectiveness. According to the sponsor, there is a need for an effective, one-time gene replacement therapy option for patients with SMA at various ages and motor function levels.

However, the exact significant benefit claim of Itvisma over relevant satisfactory methods is not clear. The significant benefit could be based on a clinically relevant advantage regarding efficacy, safety or a major contribution to patient care.

However, at time of orphan maintenance review any claims (in accordance with Article 3(1)(b) of the EU Orphan Regulation) made by the sponsor are expected to be substantiated by comparative quantitative data, and these data were not provided.

Furthermore, the sponsor is reminded that to be regarded as making a major contribution to patient care (MCPC), it should be demonstrated that Itvisma is at least equivalent in terms of efficacy, safety and benefit/risk balance as compared with relevant satisfactory method(s). Furthermore, comparative quantitative data would be expected which demonstrates that Itvisma represents a benefit to patients as compared to relevant satisfactory method(s), such as an improvement in the quality of life.

In addition to the data from the pivotal trial STEER, also data from the Phase 3 Study 12302 (STRENGTH) in patients switching from authorized SMA targeted therapies to Itvisma might be of interest to support a possible significant benefit over relevant satisfactory methods.

Reference is made to the Commission notice on the application of Articles 3, 5 and 7 of the EU Orphan Regulation (2016/C 424/03)

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN

The COMP adopted a question on significant benefit.

4. COMP list of issues

Satisfactory Methods

In order to establish relevant satisfactory methods, the sponsor is invited to discuss the relevance of Evrysdi in this context. This should include a comparison of target patient populations of Itvisma and Evrysdi.

Significant benefit

The sponsor is invited to further substantiate the significant benefit of Itvisma vis a vis relevant satisfactory method(s).

The sponsor is reminded that to be regarded as making a major contribution to patient care (MCPC), Itvisma should at least be equivalent in terms of efficacy, safety and benefit/risk balance as compared with relevant satisfactory method(s). Furthermore, quantitative data would be expected which demonstrates that Itvisma represents a benefit to patients as compared to relevant satisfactory method(s), e.g. reduced administration burden.

Reference is made to the Commission notice on the application of Articles 3, 5 and 7 of the EU Orphan Regulation (2016/C 424/03).

https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=OJ:JOC_2016_424_R_0003&from=EN

Comments on sponsor's response to the COMP list of issues

The Sponsor responded to the COMP's list of question in writing and during an oral hearing. The main data and discussion points as well as the COMP's conclusion are summarized below.

Evrysdi (risdiplam) as a satisfactory method

The sponsor addressed the question on the overlap of the therapeutic indications between risdiplam (Evrysdi) and Itvisma as described in section 4.1 of the SmPC of both products, in order to establish whether Evrysdi is a 'satisfactory method' for the entirety of the target population as approved for Itvisma. Evrysdi is indicated for 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, whereas Itvisma is indicated for patients 2 years of age and older with 5q SMA and a bi-allelic mutation in the SMN1 gene. Accordingly, the overlap in population comprises patients aged 2 years and above, which falls within both label definitions, and who have a clinical diagnosis of SMA type 1-3 or 1-4 copies of SMN2 (see Table 4 below).

Table 4. Target population defined by the therapeutic indications of Itvisma and Evrysdi

	Itvisma (onasemnogene abeparvovec)	**Evrysdi (risdiplam)**
Indication (section 4.1 of respective SmPC's)	Treatment of 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene in patients 2 years of age and older	Treatment of 5q 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
Population included in both indications; complete overlap	**≥2 years** with 5q SMA with a clinical diagnosis of SMA Type 1–3 or SMN2 copy criteria	
Population included in the one indication: not overlapping	adult-onset SMA (Type 4) >4 copies of SMN2	2 months to < 2 years

Based on the respective indication wordings (4.1 of respective SmPC's), there is no complete overlap in the SMA target patient populations (Table 4). The target population indicated for Itvisma from 2 years of age and older (children from age 2, adolescents and adults) covers a heterogenous population, symptomatic or pre-symptomatic, treatment-naive or treatment experienced, as demonstrated in the OAV101B clinical program and several subgroup analyses. The risdiplam indication does not cover such adult-onset SMA population with clinical diagnosis (i.e. Type 4), rather patients with later-childhood-onset SMA with clinical diagnosis and pre-symptomatic SMA patients with one to four copies of SMN2. The sponsor considers that the specific wording of the indication of risdiplam "…*or with one to four SMN2 copies*" refers exclusively to pre-symptomatic SMA and does not include individuals with symptomatic SMA. It is noted that the standard assays, as also used in the pivotal trial of Itvisma, cannot reliably distinguish between individuals with 4 or more SMN2 copies.

The COMP concluded that based on the respective indication wordings, there is no complete overlap in the SMA target patient populations, regarding patients with symptomatic adult-onset SMA (type 4). Therefore, Evrysdi was not considered to be a satisfactory method for the purpose of this procedure. Consequently, the scope of the significant benefit discussion is limited to Spinraza.

Significant benefit versus Spinraza (nusinersen)

Significant benefit of Itvisma based on a major contribution to patient care

The significant benefit of Itvisma is based on a major contribution to patient care (MCPC) relative to nusinersen as it only requires a one-time administration rather than ongoing chronic lumbar puncture treatment every 4 months with nusinersen. The sponsor considers that Itvisma has at least equivalent

efficacy, safety and benefit/risk balance as nusinersen, based on several indirect comparisons (ICs) summarized below.

Pivotal evidence for the approval of Itvisma is derived from a randomized double-blind, sham-controlled pivotal Phase 3 study, B12301 that has demonstrated the efficacy and safety of one-time administration of OAV101B in SMA patients. The clinical study randomized a total of 136 treatment-naïve patients aged 2 to <18 years in a 3:2 ratio with 126 patients receiving either OAV101B (n=75) or Sham (n=51). 122 patients (72 who received OAV101B, and 50 who received Sham) completed the 52-week Period 1. Study B12301 met its primary objective showing a statistically significant difference between OAV101B arm vs Sham arm on change from baseline in Hammersmith Functional Motor Scale – Expanded (HFMSE) total score to end of Period 1 in the overall study population (2 to <18 years of age).

CHERISH was a Phase 3 double blind, sham-controlled trial evaluating intrathecal nusinersen in 126 children with later onset SMA (symptom onset >6 months). Participants were randomized 2:1 to nusinersen or sham procedure, with a treatment duration of 15 months. Key eligibility criteria included age of 2 to 12 years, and HMFSE score at screening above 10 points. The study enrolled 126 patients (84 nusinersen, and 42 control) with 16% of the participants 6 years of age or older, and no patients above age 9 enrolled. Participants were younger overall with a median age of 4.0 (range 2 – 9 years) in the nusinersen group and 3.0 years (range 2–7 years) in the sham control group, compared to the B12301 study, in which the mean age was 5.71 years (range 2.0-16.5) in the OAV101 group and 5.70 years (range 2.0-14.1) in the sham group.

The sponsor points out that the B12301 study included a broader patient population in terms of age, baseline HFMSE scores, and disease duration. The CHERISH pivotal study enrolled more restrictive later-onset patients in term of age and clinical characteristics. A comprehensive comparison of baseline characteristics has not been provided.

According to the sponsor, the comparative evidence suggests that Itvisma provides similar clinical benefit when compared with Spinraza:

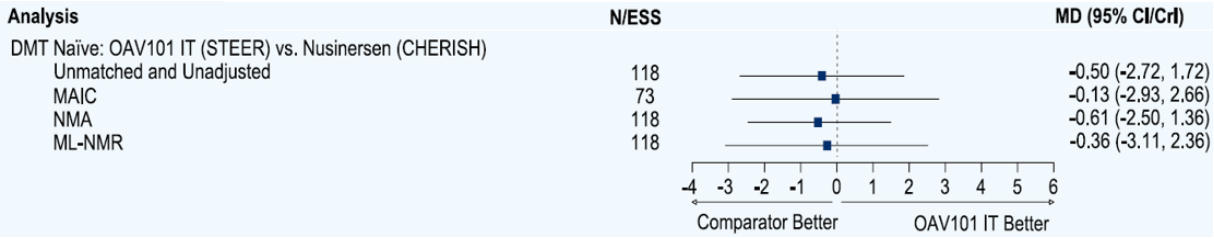
- CHERISH Phase 3 study of intrathecal nusinersen in 126 children with later-onset SMA, over 15 months enrolled a relatively narrow population, including patients aged 2 to 9 years with HFMSE >10 at screening, thereby selecting a younger and higher-functioning cohort.
- Nusinersen showed a least-squares mean change from baseline of 3.35 points in the nusinersen group versus 0.24 points in the sham group, corresponding to a difference of 3.11 points at 12 months (95% CI 1.51 to 4.71; P < 0.001). Improvements were also observed on RULM, a secondary endpoint.
- Significant HFMSE baseline imbalances (2.5 HFMSE points) were identified in CHERISH that favored the treatment arm and may have inflated the treatment effect, because better functioning children were allocated to active at baseline, stratification only accounted for age at screening (B12301 stratification accounted for age at screening and baseline HFMSE).
- CHERISH enrolled a younger population than B12301 and excluded lower-functioning patients through an HFMSE >10 entry criterion, whereas B12301 included a broader and more heterogeneous population across age and baseline motor function.
- Similar change from baseline was observed in B12301 at 12 months despite approximately 25% of enrolled participants had an HFMSE score below 10 at study entry, a population ineligible for CHERISH. Collectively, these design and population differences limit the validity and interpretability of cross-trial comparisons with B12301.

According to the sponsor, anchored Matching Adjusted Indirect Comparison (MAIC) analyses showed that OAV101B (Itvisma) provided comparable improvements in change from baseline (CFB) in HFMSE score to nusinersen (Spinraza) (mean difference [MD] [95% CI]: -0.13 [-2.93, 2.66]; Table 5). The change from baseline (CFB) in HFMSE analyses comparing Itvisma to nusinersen (Spinraza) did not produce statistically significant estimates, the point estimate even indicates a numerically unfavourable outcome for Itvisma. Of note, the published minimal clinically important difference (MCID) threshold for improvement is 1.46, established for Type 2 disease-modifying therapy (DMT)-naïve patients. While the indirect analyses suggest comparable outcomes according to the sponsor, these results carry considerable uncertainty. Additional caution is warranted in interpreting such analyses, which are supportive but not definitive evidence of equivalence. A comprehensive comparison of all relevant baseline variables (used or not in the weighting) between the unadjusted B12301 trial, the adjusted B12301 trial and the CHERISH trial has not been provided. Moreover, as the B12301 enrolled a broader population as compared to the CHERISH trial and IPD were available for B12301, patients from B12301 who would not have qualified for the CHERISH trial have been excluded before MAIC adjustment. The number of patients excluded from the analysis has not been provided.

Additional responder analyses for achieving ≥0-point CFB in HFMSE demonstrated similar results to overall CFB in HFMSE score in comparisons to nusinersen (Spinraza) (relative risk [RR] [95% CI]: 0.85 [0.58, 1.25]; Table 5).

Further, the sponsor claims that OAV101B (Itvisma) provided comparable improvements in CFB in Revised Upper Limb Module (RULM) score to nusinersen (Spinraza) (MD [95% CI]: -1.15 [-3.32, 1.01]; Table 5). The CFB in RULM analyses comparing OAV101B (Itvisma) to nusinersen (Spinraza) did not produce statistically significant estimates. Of note, the published MCID threshold is 2.0 for RULM, established for Type 2 and 3 disease-modifying therapy-naïve patients.

Figure 1. Summary of ITC (indirect trial comparisons) efficacy results for SMA disease-modifying therapy-naïve patients (OAV101 vs Nusinersen); Primary outcome HFMSE



According to the sponsor, consistent findings were observed in the multilevel network meta-regression (ML-NMR) analysis of motor function outcomes (CFB in HFMSE and RULM). In the ML-NMR analyses, OAV101B (Itvisma) was shown to provide comparable improvements in CFB in HFMSE score to nusinersen (Spinraza) (MD [95% credible interval {CrI}]: -0.36 [-3.11, 2.36]; Table 5). Similarly, responder analyses for achieving ≥0-point CFB in HFMSE demonstrated comparable results to nusinersen (Spinraza) (RR [95% CI]: 0.91 [0.80, 1.08]; Table 5). Moreover, the sponsor believes that OAV101B (Itvisma) provided comparable improvements in CFB in RULM score to nusinersen (Spinraza) (MD [95% CrI]: -1.51 [-3.58, 0.52]; Table 5). All point estimates were below the published MCID threshold of 2.0 for RULM, established for Type 2 and 3 DMT-naïve patients and the RULM differences (∼−1 to −1.5 points) were small and not statistically significant.

Finally, the sponsor reported that MAIC analyses demonstrated comparable safety outcomes between OAV101B (Itvisma) and nusinersen (Spinraza) with respect to the frequency of treatment emergent adverse events (TEAEs), (Number of patient (N) or Effective Sample Size (ESS) [%]: 45 [98.2%] for OAV101B vs. 30 [90.5%] for sham; 84 [92.06%] for nusinersen vs. 42 [95.2%] for sham; Table 5)

and serious treatment-emergent adverse events (STEAEs) (N or ESS [%]: 45 [24.0%] for OAV101B vs. 30 [29.2%] for sham; 84 [15.3%] for nusinersen vs. 42 [23.6%] for sham; Table 5). According to the sponsor, consistent findings were observed in the ML-NMR safety analyses when comparing the frequency of TEAEs between OAV101B (Itvisma) (% [95% CrI]: 98 [93, 100] for OAV101B vs. 90 [81, 96] for sham; Table 5) and nusinersen (Spinraza) (% [95% CrI]: 90 [30, 99] for nusinersen vs. 90 [81, 96] for sham control; Table 5).

Table 5. Summary of ITC efficacy and safety results for SMA disease-modifying therapy-naïve patients

Outcome	**Measure**	**MAIC Primary Analysis**		**ML-NMR Primary Analysis**	
OAV101B (Itvisma) [STEER] vs. nusinersen (Spinraza) [CHERISH]					
CFB HFMSE	MD (95% CI/CrI)	-0.13 (-2.93, 2.66)		-0.36 (-3.11, 2.36)	
≥0-point CFB HFMSE	RR (95% CI/CrI)	0.85 (0.58, 1.25)		0.91 (0.80, 1.08)	
CFB RULM	MD (95% CI/CrI)	-1.15 (-3.32, 1.01)		-1.51 (-3.58, 0.52)	
TEAE	MAIC: N or ESS (%) ML-NMR: % (95% CrI)	STEER	OAV101B: 45 (98.2) Sham: 30 (90.5)	STEER	OAV101 IT: 98 (93, 100) Sham: 90 (81, 96)
		CHERISH	Nusinersen: 84 (92.06) Sham: 42 (95.2)	CHERISH	Nusinsersen: 90 (30, 99) Sham: 90 (81, 96)
STEAE	MAIC: N or ESS (%)	STEER	OAV101B: 45 (24.0) Sham: 30 (29.2)	NA	
		CHERISH	Nusinersen: 84 (15.3) Sham: 42 (23.6)		

Abbreviations: CFB, change from baseline; CI, confidence interval; CrI, credible interval; DMT, disease modifying therapy; ESS, effective sample size; HFMSE, Hammersmith Functional Motor Scale – Expanded;; ITC, indirect treatment comparison; MAIC, matching-adjusted indirect comparison; MD, mean difference; ML-NMR, multilevel network meta-regression; n, number of patients; NR, not reported; OAV101B, onasemnogene abeparvovec intrathecal; RR, risk ratio; RULM, Revised Upper Limb Module; SAP, statistical analysis plan; STEAE, serious treatment-emergent adverse events; TEAE, treatment-emergent adverse events; TEM, treatment-effect modifier.

The sponsor further points out that long-term follow-up data from the SHINE study with nusinersen (median of follow-up of 6.8 years), show that while improvements in motor function were maintained for the first 4 years of treatment, a gradual decrease in motor functions observed thereafter with reduction below baseline levels 5 years after initiation of treatment (Finkel et al 2024).

Supportive data for Itvisma from the COAV101B12302 study (STRENGTH) in treatment-experienced patients were also provided by the sponsor. COAV101B12302 is an open-label single arm, multi-centre study designed to characterize the safety and tolerability of OAV101B in patients with SMA age 2 to < 18 years of age who have discontinued treatment with nusinersen or risdiplam. The study included 27 treatment-experienced participants with SMA who were able to sit but had never been able to walk independently prior to enrolment. The mean age was 7.4 years (range 2.4 to 17.7 years). All participants had received prior SMN-targeted treatment: 77.8% had received nusinersen (mean duration of 4.3 years; range 1.86 to 6.18 years), 14.8% had received risdiplam (mean duration of 3.0 years; range 0.39 to 6.28 years), and 7.4% had received both treatments. The population was heterogenous in terms of motor function level at baseline, based on HFMSE total scores ranging from 2.0 to 46.5 (mean 24.31). The mean change from baseline to Week 52 in HFMSE total score was 0.17

(range -5.5 to 7.5), and the LSM change from baseline to Week 52 was 1.05 (95% CI: -0.21 to 2.32), indicative of overall stabilization of motor function in the overall study population. The importance of stabilization of motor function and caregiver experience is supported by one survey study (N = 822) in which most participants (97%) responded to indicate that stabilization was crucial and considered as therapeutic progress, with 81% considering it as major progress (Rouault et al 2017).

In support of the MCPC claim the sponsor points out that real-world evidence indicates that adherence and persistence with Spinraza may be suboptimal in routine clinical practice. In a retrospective US real-world study, 41% of patients were adherent at 56 weeks and 39% at 104 weeks, while persistence declined to 55% at 2 years (Fox et al. 2023). These findings are consistent with the treatment burden associated with repeated intrathecal administration, including the need for lumbar punctures, treatment in specialized clinical settings, and logistical coordination of travel and scheduling. These barriers may contribute to missed doses and discontinuation, particularly among patients with limited mobility or access to care. In addition, loss of efficacy was also an important reason for discontinuation. Similar observations are reported in European patient populations. During the Oral Explanation the known risks of repeated lumbar puncture were described generally, and specifically, in the context of SMA patients, the risks associated with an anesthetic procedure in patients with severe scoliosis.

Available evidence further suggests that reduced adherence to Spinraza may adversely affect maintenance of treatment benefit. In a prospective EU study from the Croatian National Referral Centre for Neuromuscular Disorders, adults with SMA type 3 who missed scheduled doses reported worsening in function and energy, consistent with a wearing-off effect when dosing was delayed (Hančević Mirea et al. 2025). Similar observations were reported from Germany, where patients and clinicians described declines in energy and performance prior to the next scheduled dose, with improvement following treatment resumption, supporting the clinical importance of maintaining regular dosing (Elbracht et al. 2025). Additional quantitative support from US real-world evidence shows that reduced adherence to Spinraza is associated with clinically relevant harm. Nonadherent patients experience increased rates of SMA-related comorbidities, including feeding difficulties, respiratory anomalies, and progressive muscle weakness (Gauthier-Loiselle et al., 2021). Furthermore, healthcare resource utilization is significantly higher among patients who miss doses or discontinue treatment, supporting the broader clinical consequences of nonadherence.

<u>COMP conclusion on the significant benefit claim of Itvisma vis a vis Spinraza (nusinersen) based on a major contribution to patient care</u>

To substantiate a claim of major contribution to patient care, applicants are expected to provide evidence demonstrating that the medicinal product offers efficacy and safety that are at least equivalent to existing authorised treatments. Where direct comparative data are not available, indirect treatment comparisons (ITCs) may be considered, provided methodological limitations are adequately addressed.

As a general comment, in addition to the cross-trial comparison (B12301 vs CHERISH), the applicant provided the indirect treatment comparison results. However, the lack of prespecified criteria for non-inferiority/superiority, the insufficient description and justification of the models and the incomplete reporting of the results hampered the assessment of the indirect comparisons. Furthermore, no detailed eligibility criteria and baseline characteristics tables by trial have been presented, which hampered the interpretation of the naïve side-by-side comparisons.

For Spinraza, it was unclear from the written responses at what timepoint change from baseline is measured in the indirect comparisons, as the primary endpoint in the CHERISH trial (Spinraza) was

measured at month 15, while it was month 12 in the B12301 trial. It is not clear if the timepoints been aligned for the indirect comparisons. During the Oral Explanation, it has been clarified that month 12 data for Spinraza from the publication was presented in the written response and that analyses were conducted on month 12 data for both trials.

With respect to treatment effect modifiers (TEMs), the sponsors response indicates that expert clinical input has been considered. However, the list of (the most important) TEMs was not provided in the written responses. It appears as if a range of models have been run but it is not clear which sets of TEMs have been used and which ones have finally been included in the primary analysis. During the oral explanation, it was clarified that the highest-ranked TEMs in descending order were age at screening, highest motor milestone ever achieved prior to treatment initiation, baseline HFMSE score and SMN2 copy number. It was also clarified that TEMs were added to the model until the pre-specified threshold of ESS ≥40 was met.

The applicant clarified during the Oral Explanation that the Effective Sample Size was reduced for OAV101IT vs. nusinersen, ESS was 71/118=60.2% for the first two TEMs, and adding a third TEM led to 21/118=17.8%.The applicant has not attempted to include further TEMs in the MAICs in view of the above results. The results suggest that the underlying assumptions for a MAIC may not hold and that the model may not reliably estimate the treatment effects. No information on the weights was provided but given the massive ESS reductions it seems unlikely that the weights are closely centred around 1.

Neither for the MAIC nor for the ML-NMR, the applicant has described the modelling approach. It is not clear what the primary model was, what the underlying assumptions were and if these were met or not.

During the Oral Explanation, the applicant clarified that MAIC was the primary analysis, and ML NMR was used as a supportive analysis using a Bayesian approach with a flat prior (without further details on the choice of the prior). It remains unclear if underlying assumptions have been checked. The applicant also noted that no additional sensitivity analyses (e.g. different choices for the prior) have been conducted and that prior-data conflict has not been further investigated, therefore analyses versus Spinraza remained associated with uncertainty. The COMP also took note that the point estimates for 4 different methodological approaches are numerically in favor of Spinraza, as compared to Itvisma . Furthermore, the respective confidence intervals are very wide with the lower bounds of approximately -3, which contributes to the uncertainty and indicate that Itvisma's superiority over Spinraza cannot be concluded. A formal non-inferiority margin was not pre-specified.

In the written response, the applicant stated that indirect safety comparisons to safety endpoints proved challenging "*Most models failed to meet standard diagnostic thresholds, including convergence, presence of divergent transitions, low ESS (bulk/tail ESS), and/or produced imprecise estimates (unreasonably wide posterior distributions).*" It is not clear from the sparse reporting if similar challenges have been encountered for the efficacy analyses. During the Oral Explanation, the applicant reiterated that caution is warranted in the interpretation of the indirect comparisons. Residual uncertainty remains due to cross trial differences. Not all treatment effect modifiers could be adjusted. The sponsor also emphasized again that the CHERISH data shows a trend towards effect in younger and better functioning patients in the treatment arm, favouring nusinersen and is not correctable by MAIC. Furthermore, the sponsor reiterated that the MAIC compares the generally broader STEER population to narrower CHERISH eligibility profile.

Overall, from a methodological perspective, the applicant has not provided convincing responses for the requested quantitative analyses. Insufficient description and justification of the models and incomplete reporting of the results add considerable uncertainty. The drastic decline of ESS in the

MAICs and the limited information provided for the ML-NMR suggest that indirect comparisons may not provide reliable estimates.

COMP conclusion on the significant benefit claim of Itvisma vis a vis Spinraza (nusinersen) based on a clinically relevant advantage

The COMP noted that non-adherence to nusinersen (Spinraza) has been reported in the literature; such non-adherence may reduce treatment effectiveness and could be associated with less favourable clinical outcomes. Accordingly, the COMP also considered whether a significant benefit claim for Itvisma could be established for specific patient subgroups, such as patients who are irresponsive/intolerant or ineligible for treatment with Spinraza. The sponsors supportive data from the open-label, single-arm COAV101B12302 study (STRENGTH) was evaluated in this regard. The study included 27 treatment-experienced participants with SMA who had received prior SMN-targeted treatment, including Spinraza, before switching to treatment with Itvisma.

Caregivers reported a substantial burden at baseline. At study exit, caregiver-perceived changes in SMA symptoms/problems were multidirectional, with caregivers reporting improvement (70%), stabilization (45%), and worsening (60%) across different domains (more details of the baseline scores and outcomes were not available for assessment by the COMP). Improvements were most frequently described for gross motor function (50%) and muscle weakness (40%). Overall, 90% of caregivers reported satisfaction with treatment outcomes, 45.0% being "very satisfied" or "extremely satisfied" and 45.0% being either "a little satisfied" or "somewhat satisfied".

Interim data from the STRENGTH trial (patients switched from Spinraza/Evrysdi to Itvisma) indicated maintained motor function post-switching, albeit without a concurrent control group. During the meeting the Sponsor clarified that also a stabilisation of motor function is relevant for the non-ambulant patients included in the study, as maintaining the sitting performance is relevant for clinical outcomes such as scoliosis and vital functions.

It was discussed during the meeting whether Itvisma, which is also administered via the intrathecal route like Spinraza, could still be applied in patients where the administration of Spinraza is not feasible anatomically due to severe scoliosis. It was clarified that the patients in the trials were non-ambulant and had a high scoliosis score, but a single dose of Itvisma could still be administered. However, detailed information on the reasons for switching from Spinraza in the STRENGTH study was not available.

Apart from the limitation of this being a single-arm study, it was not clear whether these patients were/had become intolerant to treatment with Spinraza and whether they had benefitted from their prior therapy or not as this data was not collected as part of the study. Therefore, a significant benefit claim of Itvisma vis a vis Spinraza (nusinersen) based on a clinically relevant advantage in specific patient subgroups could not be established.

Long-term follow-up data indicate that treatment effects of nusinersen may decline after 4–6 years. The durability of the efficacy of Itvisma relative to nusinersen remains unknown. The Sponsor provided ≥10-year follow-up data for Zolgensma, which shares the same gene construct (onasemnogene abeparvovec) as Itvisma, from a small extension study in SMA type 1. All 10 patients treated at the commercial Zolgensma dose level survived without ventilatory support and achieved independent sitting; however, 7 out of 10 patients received concomitant nusinersen or risdiplam. Furthermore, no data or arguments were provided to what extent the effects of Zolgensma could be extrapolated to Itvisma, which maybe challenging given the different route of administration and different study and target populations of both products. Considering the above, these data do not allow conclusions regarding long-term durability of Itvisma nor support extrapolation.

Overall COMP conclusion

The scope of the significant benefit discussion was limited to Spinraza. Evrysdi was not considered a satisfactory method by the COMP as there is no complete overlap in the SMA patient populations, as covered by the respective wordings of the indication in section 4.1 of the SmPC of both products.

The data presented by the sponsor is not considered conclusive evidence for the purpose of supporting the significant benefit of Itvisma over Spinraza. Claims based on Major Contribution to Patient Care (MCPC) require demonstration of equivalent efficacy, safety and benefit/risk balance (reference is made to the Commission notice on the application of Articles 3, 5 and 7 of the EU Orphan Regulation (2016/C 424/03)). This requirement could not be established based on the data provided by the sponsor.

Furthermore, the data presented by the sponsor does not constitute sufficient evidence to support a significant benefit claim based on clinically relevant advantage of Itvisma in specific patient subgroups, such as patients who are irresponsive/intolerant or ineligible for treatment with Spinraza as discussed above.

Overall, the available data is subject to significant methodological limitations and uncertainty and does not support the establishment of significant benefit for Itvisma over Spinraza (nusinersen).

5. COMP position adopted on 12 May 2026

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 approximately 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;
- a satisfactory method for the treatment of the condition has been authorised in the European Union, and the assumption that Itvisma is of significant benefit to those affected by the orphan condition is not established. The sponsor could not establish a clinically relevant advantage over the authorised satisfactory method of treatment, Spinraza;
- neither could it be established that the effect of Itvisma was of equal efficacy to Spinraza. Hence, the claims of a major contribution to patient care could not be assessed.

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 are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The Committee for Orphan Medicinal Products has recommended that Itvisma (adeno-associated viral vector serotype 9 containing the human *SMN* gene, onasemnogene abeparvovec) for treatment of spinal muscular atrophy (EU/3/15/1509) does not meet the criteria for designation as set out in Article 3(1) of Regulation (EC) No 141/2000.