

Onasemnogene abeparvovec[§]: A Glance on One Slide

Indication:

- Treatment of 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the SMN1 gene in patients 2 years of age and older.
 - ✓ *Of note: the indication was modified during the regulatory process; the initial indication included patients 6 months of age and older*
 - ✓ *Administered as a single intrathecal (IT) injection directly into the spinal canal (as compared to IV-injection for Zolgensma®)*

Guidelines:

- European Consensus Statement Update 2024*:
 - ✓ 12 consensus statements
 - ✓ no comparative statements regarding the 3 available licensed medicines: Onasemnogene abeparvovec IV (Zolgensma®); Nusinersen (Spinrasa®); Risdiplam (Evrysdi®)

Clinical Data (RCT STEER**):

- P: 2 - < 18 years; treatment-naïve; able to sit; never walked independently
- I: One-Time intrathecal gene transfer therapy
- C: Sham injections
- O: Primary: HFMSE Score; Change from baseline; LSM difference 1.88 (95% Confidence Interval: 0.51-3.25; p=0.0074); Safety with similar incidences of AEs; SAEs, and AESI in both study groups
- S: Randomised, sham-controlled, multicenter, double-blind trial; Phase 3; n = 75: Onasemnogene abeparvovec; n = 51: Sham control

EPAR Balance of Benefits and Risks†:

- Efficacy on different functional measures across the entire 2 to <18 years age range demonstrated
- Extrapolation of the indication to patients with milder SMA forms than those included in the development program (type 3 and 4), as well as in adult patients, is considered justified from the efficacy and safety perspective
- Based on totality of available information for peripheral sensory neuropathy no specific risk factors are highlighted

Scoping & HTD Dossier:

Final Scoping: 6 populations; 12 PICOs (*original scoping: 7 populations; 14 PICOs*): the HTD discriminated across DMT naïve vs DMT experienced patients; primary endpoint outcomes

- Population 1: Full Claimed Indication
 - *PICO 1: C: DMT naïve: Nusinersen (anchored MAIC vs Nusinersen (CHERISH Trial): CFB HFMSE -0.13 (-2.93; 2.66); ns*
 - *PICO 2: C: DMT naïve: Risdiplam (anchored MAIC vs Risdiplam (Sunfish 2 Trial): CFB HFMSE 1.93 (-0.25; 4.10); ns*
 - *PICO 3: C: Best Supportive Care (STEER outcomes vs sham control): CFB HFMSE 1.88 (0.52; 3.25); p = 0.007*
 - *PICO 4: C: Onasemnogene abeparvovec i.v.; no evidence*
- Population 2: weight ≤ 13.5kg and ≤ 3 copies of SMN2 gene
 - *PICO 5: C: Onasemnogene abeparvovec i.v.; no evidence*
- Population 3: n/a due to change of indication; PICOs 6 & 7 obsolete
- Population 4: ≤ 4 copies of SMN2 gene
 - *PICO 8: C: Nusinersen; evidence see PICO 1*
 - *PICO 9: C: Risdiplam; evidence see PICO 2*
- Population 5: Non ambulant patients; ≤ 4 copies of SMN2 gene
 - *PICO 10: C: Nusinersen; evidence see PICO 1*
 - *PICO 11: C: Risdiplam; evidence see PICO 2*
- Population 6: ≥ 4 copies of SMN2 gene, type 3, type 4 or without a defined type
 - *PICO 12: C: Individualised treatment including Nusinersen, Risdiplam, Best supportive care; no evidence*
 - *PICO 13: C: Individualised treatment including Nusinersen, Risdiplam; no evidence*
- Population 7: ≥ 4 copies of SMN2 gene; no evidence provided
 - *PICO 14: C: Individualised treatment including Watchful Waiting & Best supportive care; no evidence*

HTD also provided comparative data (unanchored MAIC) for DMT experienced patients for PICOs 1,2

JCA: Case number JCA-MP-2024-12

Available evidence for full claimed indication is limited to subpopulation as defined by PICOs 8 – 11

Following HTD suggestion to discriminate DMT naïve vs DMT experienced patients

The assessors pointed to various uncertainties and limitations e.g.:

- Presented data for PICO 1,2,8-11 are no 'proof' of equivalence
- No comparative evidence available for patients that cannot sit or can walk independently
- Commented on various adjustment details and matching uncertainties of the ITCs
- Commented that the HTD declined to provide IPD
- Subgroups analysis in patients 2-5 years failed to reach significance of CFB HFMSE
- Suggested MCD of HFMSE (1.46) is challenged

§ Itivisma®; Marketing Authorization Holder: Novartis; * <https://www.sciencedirect.com/science/article/pii/S1090379824000874>; ** https://pmc.ncbi.nlm.nih.gov/articles/PMC12920101/pdf/41591_2025_Article_4103.pdf;

+ https://www.ema.europa.eu/en/documents/assessment-report/itivisma-epar-public-assessment-report_en.pdf; AE Adverse Event; AESI: Adverse Event of Special Interest; CI: Contraindication; DMT: Disease Modifying Therapy; EPAR: European Product Assessment Report; Hazard Ratio; HFMSE score (Hammersmith Functional Motor Scale Expanded score); HTD: Health Technology Developer; INV: Investigator; IO: Immunotherapy; IRF: independent review facility; i.v.: intravenous; LSM: Least Square Mean; OD: Orphan Designation; ITC: Indirect Treatment Comparison; MAIC: Matched Adjusted Indirect Comparison; MLNMR: Multi Level Network MetaRegression; SAE: Serious Adverse Event; SMA: spinal muscular atrophy

Onasemnogene abeparvovec: Topline Comments

- SMA is a rare condition (1 in 3'900 – 16'000 live births)
- Major therapeutic advances in recent years with 3 innovative medicines (Onasemnogene abeparvovec i.v., Nusinersen; Risdiplam) being introduced
- Onasemnogene abeparvovec intrathecal is a new application of the already established molecule
- The European Guidelines were published in 2024 and include 12 consensus statements; no algorithm is provided how to navigate across the various innovative treatment options
- The European Medicine Agency is confirming a positive benefit risk ratio and considers extrapolation of outcomes justified
- The HTD is suggesting comparable efficacy with Nusinersen and Risdiplam while claiming superiority versus best supportive care based on the RCT STEER
- Within EU HTA scoping 12 (originally 14) PICO schemes and 6 (originally 7) populations are separated; in such rare condition this seems inappropriate and overengineered; the core question is comparative evidence versus the three already available innovative medicines and versus Best Supportive Care
- EU HTA does not support extrapolation of outcomes
- Only 2 carers and one clinician were involved