Feasibility of Indirect Treatment Comparisons for OAV101 IT in Spinal Muscular Atrophy

SA26

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BACKGROUND

- Spinal muscular atrophy (SMA) is a rare and debilitating genetic disorder that primarily affects motor neurons in the spinal cord, with progressive degeneration of motor neurons leading to muscle atrophy and weakness.[1]
- Current approved treatments for SMA are intravenous onasemnogene abeparvovec (OAV101 IV), nusinersen, and risdiplam. These treatments have demonstrated significant efficacy in slowing disease progression.[2]
- Intrathecal onasemnogene abeparvovec (OAV101 IT) is a one-time gene-replacement therapy for SMA that is approved by the FDA and is currently undergoing European Union (EU) Joint Clinical Assessment (JCA).[3-5]
- As no head-to-head trials compare OAV101 IT with other disease modifying therapies (DMTs), indirect treatment comparisons (ITCs) are needed for OA101 IT health technology assessment (HTA), including JCA.
- An ITC feasibility assessment (FA) was conducted to inform appropriate ITC analyses for supporting market access activities of OAV101 IT.

OBJECTIVE

To assess the feasibility of ITCs of OAV101 IT versus other DMTs for SMA to support HTAs including the EU JCA.

RESEARCH QUESTION

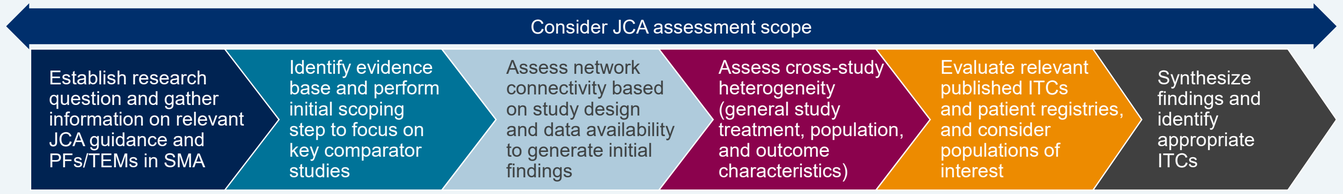
Given the characteristics of available OAV101 IT trials, what ITC approaches are appropriate:

- To compare OAV101 IT with the following approved DMTs or therapies currently in development for SMA?
  - OAV101 IV
  - Nusinersen
  - Risdiplam
  - Muscle enhancers/myostatin inhibitors: apitegromab, taldefgrobep alfa, GYM329, and NMD670
- For the treatment of symptomatic SMA patients aged 6 months of age to 18 years of age who can sit but not walk independently (i.e., OAV101 IT trial populations)?
- Based on efficacy, quality of life, and safety outcomes?
- To consider data from clinical trials, with real-world data as needed?

METHODS

- Relevant clinical trials and observational studies were identified via a systematic literature review (SLR) to inform the evidence base for the ITC FA.
- Studies were assessed qualitatively for network connectivity, outcome availability, and alignment with OAV101 IT trials based on pre-specified criteria. Cross-study heterogeneity was evaluated based on study design, population, and outcome characteristics, with consideration given to prognostic factors (PFs) and treatment effect modifiers (TEMs) in SMA (**Table 1**).
- JCA guidance was followed for each stage of the ITC FA (**Figure 1**).[6,7]

Figure 1: Overview of ITC Feasibility Assessment Methodology



RESULTS

To align with most SMA trials identified in the SLR, the feasibility of ITCs was considered for DMT-naïve and DMT-experienced populations. Conducting ITCs in a mixed SMA DMT-naïve/experienced population was not appropriate due to substantial cross-study heterogeneity related to prior DMT experience.

OAV101 IT vs. OAV101 IV

- ITC of OAV101 IT and OAV101 IV was deemed infeasible in both DMT-naïve and DMT-experienced populations due to limited sample size and insufficient overlap in the trial populations.[8,9]

OAV101 IT vs. nusinersen (DMT-naïve patients)

- Anchored matching-adjusted indirect comparison (MAIC) using clinical trial data from STEER[4] for OAV101 IT and CHERISH (NCT02292537)[10] for nusinersen was considered feasible in a DMT-naïve patient population aged ≥2 years (**Figure 2**).
- Multilevel network meta-regression (ML-NMR) using clinical trial data from STEER[4] for OAV101 IT, CHERISH[10] for nusinersen, and SUNFISH Part 2 (NCT02908685)[11] for risdiplam was considered feasible.

OAV101 IT vs. risdiplam (DMT-naïve patients)

- Anchored MAIC using clinical trial data from STEER[4] for OAV101 IT and SUNFISH Part 2[11] for risdiplam was considered feasible in a DMT-naïve patient population aged ≥2 years (**Figure 2**).
- ML-NMR using clinical trial data from STEER,[4] CHERISH,[10] and SUNFISH Part 2[11] (i.e., same analysis as for nusinersen) was considered feasible.

OAV101 IT vs. nusinersen or risdiplam (DMT-experienced patients)

- Unanchored MAIC using clinical trial data from STRENGTH[5] for OAV101 IT and the placebo arm from SAPPHIRE (NCT05156320)[12] for nusinersen or risdiplam was considered feasible in a DMT-experienced population ≥2 years for age-appropriate outcomes (e.g., HFMSE and RULM scores)(**Figure 2**).
- ITC using clinical data for patients previously treated with nusinersen or risdiplam independently was not feasible due to the small number of nusinersen-experienced or risdiplam-experienced patients in the considered trials.

Figure 2: Network Connectivity of SMA DMT Studies

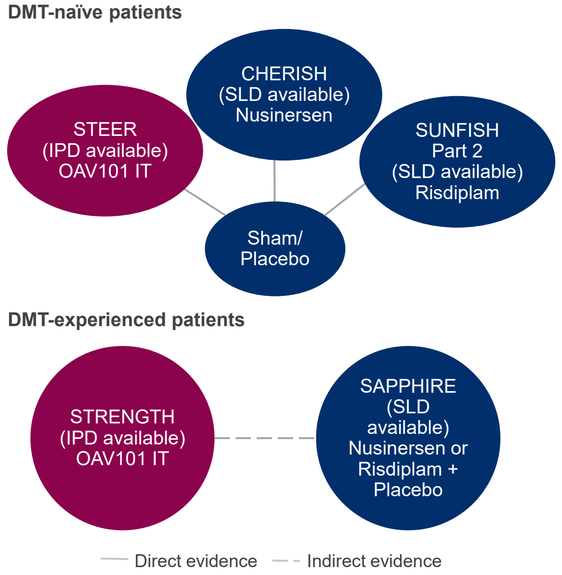


Table 1: Summary of Pre-specified Criteria for ITC Feasibility Assessment

Criteria
Study criteria to consider for an ITC with OAV101 IT
• Age at screening
• Symptomatic status
• Functional/ambulatory status
• Naivety to OAV101 IT
• Current or anticipated approval by the EMA
• Availability of baseline characteristics and outcome results
• Study design
Characteristics to consider for assessment of cross-study heterogeneity
• General study characteristics
• Study eligibility criteria
• Baseline patient characteristics
• Outcome characteristics (i.e., definitions, timepoints, and methods of reporting)
• Data availability

STRENGTHS & LIMITATIONS

Strengths:

- In accordance with JCA guidance, all trials identified by the SLR were considered in a structured FA to evaluate cross-trial heterogeneity, data availability, and evidence network connectivity.
- Observational studies were included in the FA; however, they were ultimately not considered for ITCs due to the availability of high-quality evidence sources (i.e., clinical trials) to inform the ITCs.

Limitations:

- ITCs could not be conducted for certain populations (e.g., patients aged >18 years) due to a lack of comparable study data across trials.

CONCLUSIONS

Comprehensive ITC feasibility assessments are necessary for informing evidence generation strategies across often wide-ranging populations and outcomes of interest to JCA and other HTAs.

Based on clinical evidence for SMA DMTs identified via SLR:

- An ITC of OAV101 IT versus OAV101 IV is not feasible.
- ITCs are feasible for OAV101 IT versus nusinersen and risdiplam in both DMT-naïve and DMT-experienced populations aged ≥2 years.

ABBREVIATIONS: DMT = disease modifying therapy; EMA = European Medicines Agency; EU = European Union; FA = feasibility assessment; FDA = Food & Drug Administration; HFMSE = Hammersmith Functional Motor Scale – Expanded; HTA = health technology assessment; IPD = individual patient data; IT = intrathecal; ITC = indirect treatment comparison; JCA = Joint Clinical Assessment; MAIC = matching-adjusted indirect comparison; OAV101 = onasemnogene abeparvovec; OAV101 IT = Intrathecal onasemnogene abeparvovec; OAV101 IV = intravenous onasemnogene abeparvovec; PF = prognostic factor; PICO = population, intervention, comparator, and outcome; RULM = Revised Upper Limb Module; SLD = summary-level data; SLR = systematic literature review; SMA = spinal muscular atrophy; TEM = treatment effect modifier.

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