ECKER ECKER

HTA58

Poster Download

Ecker T.[1], Le Mao J.[2], Prada M.[3], Lizán L.[4], Flenner F.[1], Brozek A.[1]
[1] Ecker + Ecker GmbH, Hamburg, Germany, [2] CEMKA, Bourg La Reine, France, [3] Intexo SB, Rome, RM, Italy, [4] Outcomes'10, Castellón de la Plana, Spain

Scoping Mock-Up: What Can We Learn From an EU-4 Experiment for EU HTA?

Objectives

Scoping defines each HTA institute's setting of the research question with its components **P**opulation, **I**ntervention, **C**ontrol, **O**utcomes (PICO). The scoping process will be key for the subsequent EU HTA. The future scoping process was simulated within our European network.

Methods

Mock-up was done for onasemnogene abeparvovec (Zolgensma®), as ATMPs are within the first wave of EU HTA. Gene therapies for rare diseases and thus most ATMPs pose special methodological challenges within HTA, and this was a widely discussed product launch. Scoping consists of two phases, survey and consolidation. Survey was done considering actual assessment as well as reimbursement restrictions of the respective countries. Written feedback from Italy, Spain, France, and Germany was checked for consistency and follow-up questions asked for clarification. Consolidation was performed by TE and AB.

Results

Assessment and reimbursement are not completely separate processes in all 4 countries. Germany was the only country for which the complete label was relevant for reimbursement. France excluded symptomatic patients with SMA type 3. Italy and Spain only included symptomatic patients with SMA type 1 and pre-symptomatic patients with up to 2 copies of the *SMN2* gene. For the symptomatic patients, Italy and Spain defined restrictions regarding weight and age. In addition, Spain also set an age restriction for the pre-symptomatic population.
Nusinersen was considered a relevant comparator in all countries at some point of the evaluation, whereas risdiplam was only considered by France during reassessment which occurred later. Initially, Germany did not define a comparator.
Not all outcomes have had the same relevance in every jurisdiction, but there seemed to be reasonable consensus.

EMA - Label

Zolgensma® is indicated for the treatment of:
- patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1, or
- patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene.

	Germany	France	Spain	Italy
Population	• a) 5q associated SMA type 1 • b) 5q-SMA type 2 and up to 3 *SMN2* copies • c) 5q-SMA type 3 and up to 3 *SMN2* copies • d) pre-symptomatic patients with up to 3 *SMN2* copies	• a) Patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1 and 2 or pre-symptomatic SMA, with up to 3 copies of the SMN2 gene • b) Patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 3	• a) Patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1 • b) Patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene	• a) Patients with 5q spinal muscular atrophy (SMA) with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA Type 1 • b) Patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene
Reimbursed	• All populations	• Only population a)	• Patients with pre-symptomatic 5q SMA with a bi-allelic mutation in the *SMN1* gene complying with additional clinical criteria	• Patients with SMA 5q with weight up to 13.5 kg and clinical diagnosis of SMA Type 1 and symptom onset in the first 6 months of life, • OR genetic diagnosis of SMA Type 1 (biallelic mutation in *SMN1* and up to 2 copies of *SMN2*)
Intervention	• Dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec as a single IV infusion (as per requirements in 4.2 of the SmPC)	• Dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec as a single IV infusion	• Dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec as a single IV infusion	• Dose of nominal 1.1 x 10^{14} vg/kg onasemnogene abeparvovec as a single IV infusion
Control	• a) Nusinersen • b) Nusinersen • c) Therapy of physician's choice (nusinersen or best supportive care) • d) Nusinersen	• In pre-symptomatic patients: Nusinersen • In patients with type 1 or 2 spinal muscular atrophy: Nusinersen and risdiplam	• Nusinersen* *funding is restricted for the treatment of patients diagnosed with 5q spinal muscular atrophy excluding patients belonging to types 0, IA, IV	• Nusinersen* *reimbursed in Italy for SMA type 1
Outcomes	• Mortality • Ventilatory support (different endpoints) • Reaching of motor milestones (different endpoints) • Bayley Scale • CHOP INTEND • Hospitalizations • Adverse events	• Ventilation free survival • Independent sitting • Maintenance of motor milestones • Adverse events	• Survival • Independence of ventilatory support • Sitting upright with head support for at least 30 seconds • Improvement in motor function and muscle strength • Bayley Scale • CHOP INTEND • Medro capacity	• Efficacy on clinically relevant outcomes or • Ability to reduce the risk of disabling or potentially fatal complications, or • Better risk/benefit ratio (R/B) than alternatives, or • Ability to avoid the use of high-risk clinical procedures

Conclusions

In summary, whereas intervention, control, and outcomes mostly converge, no two countries aligned on the assessment and reimbursed population. Interestingly, final assessment decisions seemed to be determined by the data and were to some extent independent of a predefined PICO scheme, but still led to different decisions regarding reimbursement. This might be caused by the rather special case of onasemnogene abeparvovec: It represents a gene therapy which addresses a high unmet medical need and has the potential to change the course of a life-threatening disease while being applied only once. Given that this will apply to many ATMPs, it remains unclear how expected synergies of a joint assessment can be achieved with PICOs varying to such a degree.

Note that the findings of this PICO mock-up are consistent with the outcome of the PICO exercise on tabelecleucel (Ebvallo®)[a].

References

[a] EUnetHTA21, 2023: PICO exercise II – tabelecleucel Ebvallo.
https://www.eunethta.eu/wp-content/uploads/2023/09/EUnetHTA-21-PICO-2-Deliverbale.pdf

Abbreviations

ATMP: advanced therapy medicinal products; Bayley Scale: Bayley Scales of infant development; CHOP INTEND: Children's Hospital of Philadelphia infant test of neuromuscular disorders; EU: European Union; HTA: health technology assessment; IV: intravenous; Medro capacity: ability to tolerate fluids and maintain weight according to age without requiring gastrostomy or other mechanical or non-oral nutritional support; PICO: patients, intervention, comparator, outcomes; SMA: spinal muscular atrophy; SMN: survival of motor neuron; SmPC: summary of product characteristics

Ecker + Ecker GmbH · Warburgstr. 50 · 20354 Hamburg · Germany
+49 (40) 41 330 81-0 · info@ecker-ecker.de · www.ecker-ecker.de