Understanding How Clinical Uncertainty is Scrutinised Across European HTA Appraisals of Gene Therapies, and Implications for Commercialisation in the JCA Era

HTA193

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Objective

To identify divergence in interpretation of clinical evidence for gene therapies across European Health Technology Assessment (HTA) bodies and assess implications for access in the Joint Clinical Assessment (JCA) era.

Background

- Gene therapies can be transformative for people with rare genetic conditions, representing a one-time, potentially curative treatment.
- However, challenges in clinical evidence generation makes it difficult to meet HTA evidentiary standards, compounding the commercialisation barriers that gene therapies already face in Europe due to high acquisition costs.
- With the EU JCA now applying to advanced therapy medicinal products, understanding how national HTA bodies have historically scrutinised clinical uncertainty is critical to anticipating how it will be handled in the JCA era.

Methods

- We reviewed European HTAs for four gene therapies launched within the past five years (atidarsagene autotemcel, valoctocogene roxaparvovec, onasemnogene abeparvovec, etranacogene dezaparvovec), selected based on availability of documentation across French (HAS), German (G-BA), Swedish (TLV/FINOSE) and Irish (NCPE/BeNeLuxA) HTA bodies.
- These bodies represent distinct HTA archetypes, selected to ensure coverage of both comparative effectiveness-driven and cost effectiveness-driven markets.

Results

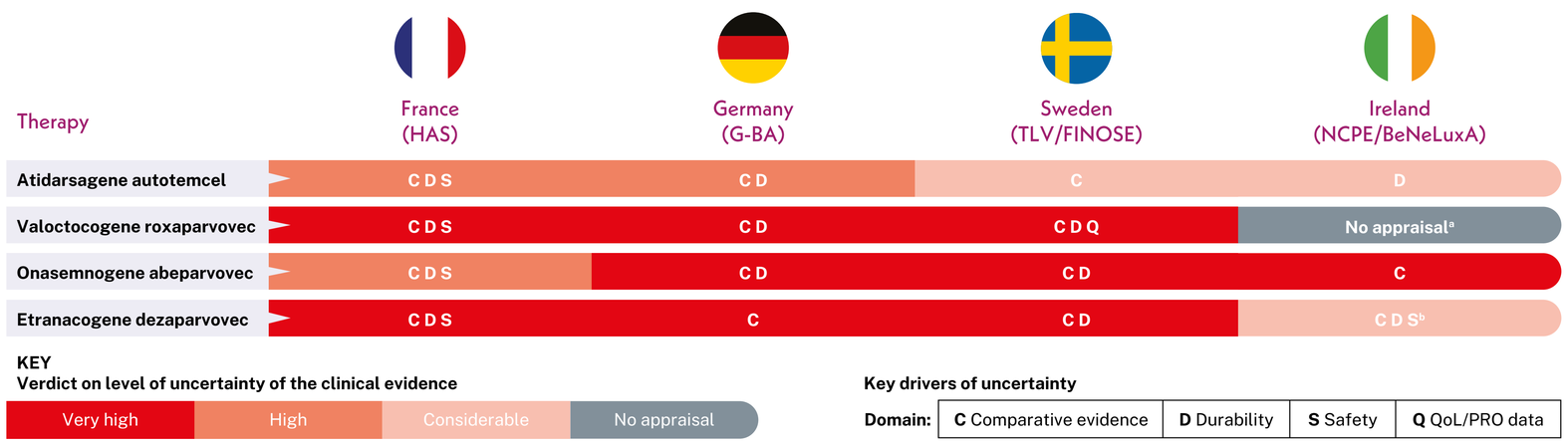
- Submitted evidence for all four therapies was derived from short-term, single-arm trials. Across the HTA value assessments, the key drivers of uncertainty that influenced HTA outcomes were consistent, with comparative evidence and durability of effect emerging as the two most influential (**Figure 1**):
  - HAS acknowledged the single-arm evidence but considered it insufficient to establish comparative benefit; uncertainty in safety data also influenced the value assessment outcome.
  - G-BA generally rejected indirect treatment comparisons (ITCs), making comparative efficacy the primary driver of uncertainty.
  - TLV/FINOSE and BeNeLuxA incorporated single-arm evidence directly into cost-effectiveness assessments, where durability assumptions were key model drivers and central to pricing and access decisions; uncertainty in the quality-of-life/patient-reported outcome data further influenced the outcome for TLV.
- Despite a common clinical evidence base, HTA value assessments for the same therapy ranged from "major added benefit" to "not recommended", demonstrating divergent national HTA body value frameworks and assessment methods (**Figure 2**).
- Negative or neutral value assessments did not prevent reimbursement, with pricing negotiations, managed-entry agreements and statutory orphan provisions determining reimbursement and patient access (**Figure 3**).

Conclusion

While evidence limitations were consistent across appraisals, differences in how local HTA frameworks handled this unresolved uncertainty drove divergent decision-making and access outcomes. Harmonised clinical evaluation under JCA is unlikely to eliminate these differences. Evidence generation planning for gene therapies should identify where uncertainty can feasibly be reduced, and where strong contextual justification or post-approval evidence generation is required, to support broad European access.

FIGURE 1

Analysis of the key drivers behind clinical uncertainty across appraisals of gene therapies



[a]No NCPE or BeNeLuxA assessment conducted for valoctocogene roxaparvovec. [b]No NCPE assessment for etranacogene dezaparvovec, BeNeLuxA report (July 2024) was used in the extraction instead.

FIGURE 2

Value assessment outcomes across HTA bodies

Product	Indication/subgroup	France (HAS)	Germany (G-BA)	Sweden (TLV/FINOSE)	Ireland (NCPE/BeNeLuxA)
Atidarsagene autotemcel	Asymptomatic late-infantile/ early-juvenile MLD	ASMR III – moderate added value[a]	Hint of major additional benefit	Recommended	Not recommended at submitted price
	Symptomatic early-juvenile MLD	ASMR IV – minor added value[a]	Hint of non-quantifiable additional benefit		
Valoctocogene roxaparvovec	Severe haemophilia A	ASMR V – no added value[a]	Hint of non-quantifiable additional benefit	No recommendation issued[b]	Not assessed[c]
Onasemnogene abeparvovec	Pre-symptomatic SMA with 1–2 *SMN2* copies	ASMR III – moderate added value[a]	Additional benefit not proven	Recommended	Not recommended at submitted price
	Pre-symptomatic SMA with 3 *SMN2* copies	ASMR V – no added value			
	SMA type 1	ASMR III – moderate added value[a]			
	SMA type 2	ASMR V – no added value		Not recommended	
	SMA type 3	Not recommended[d]			
Etranacogene dezaparvovec	Haemophilia B	ASMR IV – minor added value[a]	Additional benefit presumed[e]	Not recommended	Conditional positive recommendation

Major added benefit/ unqualified positive recommendation; Moderate added benefit; Minor or non-quantifiable added benefit; or conditional recommendation; No added benefit, not proven, or not recommended; Not assessed/ no submission

HAS grades actual clinical benefit (SMR) and added clinical benefit (ASMR I–V); the G-BA grades extent of added benefit together with a certainty qualifier ("hint", "indication", "proof"); the TLV/FINOSE and the NCPE developed a health-economic report, which is assessed by NT-rådet in Sweden which in turn issues reimbursement recommendations rather than graded added-benefit ratings. The grading system is indicative only – outcomes are not directly comparable. [a]Received SMR important rating. [b]No Swedish recommendation was issued because the manufacturer did not launch within the market. [c]No Irish appraisal has been published. [d]Received SMR insufficient rating. [e]Additional benefit presumed under the orphan drug exemption, rather than derived from comparative clinical evidence.

FIGURE 3

Reimbursement Outcomes Across Regions

Product	Indication/subgroup	France (HAS)	Germany (G-BA)	Sweden (TLV/FINOSE)	Ireland (NCPE/BeNeLuxA)
Atidarsagene autotemcel	Asymptomatic late-infantile/ early-juvenile MLD	Reimbursed	Reimbursed	Reimbursed	Not reimbursed
	Symptomatic early-juvenile MLD	Not reimbursed[a]			
Valoctocogene roxaparvovec	Severe haemophilia A	Not reimbursed (manufacturer withdrew)	Reimbursed	Manufacturer did not prioritise the market[b]	NA[c]
Onasemnogene abeparvovec	Pre-symptomatic SMA ≤3 *SMN2* copies	Reimbursed	Reimbursed	Reimbursed	Reimbursed
	SMA type 1				
	SMA type 2		Reimbursed in select subgroup[d]	Not reimbursed	Not reimbursed
	SMA type 3	Not reimbursed			
Etranacogene dezaparvovec	Haemophilia B	Reimbursed	Reimbursed[e]	Not reimbursed	Not reimbursed

Reimbursed – immediate/unrestricted access; Reimbursed – after price negotiation/managed access; Reimbursed in select subgroup; Not reimbursed/exceptional funding only; Not applicable – no submission/no data

[a]Reflects the original assessment, restricted to the asymptomatic late-infantile/early-juvenile population; reimbursement was extended to the symptomatic early-juvenile population following 2024 re-application. [b]No Swedish recommendation was issued because the manufacturer did not launch within the market. [c]No Irish appraisal has been published. [d]Reimbursed in patients who have up to 3 copies of *SMN2*. [e]Additional benefit presumed under the orphan drug exemption, rather than derived from comparative clinical evidence.

Abbreviations: HTA: Health Technology Assessment; **JCA:** Joint Clinical Assessment; **ITCs:** Indirect Treatment Comparisons; **MLD:** metachromatic leukodystrophy; **SMA:** spinal muscular atrophy; **MA:** Marketing Authorisation; **SMR:** service médical rendu; **ASMR:** amélioration du service médical rendu; **HAS:** Haute Autorité de Santé (French National Authority for Health); **G-BA:** Gemeinsamer Bundesausschuss (Federal Joint Committee, Germany); **TLV:** Tandvårds-och läkemedelsförmånsverket (Dental and Pharmaceutical Benefits Agency, Sweden); **FINOSE:** Finland, Norway, Sweden (joint HTA collaboration); **NCPE:** National Centre for Pharmacoeconomics (Ireland); **BeNeLuxA:** Belgium, Ireland, the Netherlands, Luxembourg, and Austria (collaborative HTA and pricing initiative); **QoL:** Quality-of-Life; **PROs:** Patient-Reported Outcomes.

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