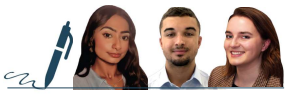
The HTA trends of recently approved gene therapies

HTA257



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Objective

Despite progress in the gene therapy landscape, manufactures faces challenges to demonstrate long-term safety and efficacy with robust clinical trials.

This study analyses HTA perceptions of gene therapies, focusing on trial design, safety / efficacy, costs, & potential learnings for emerging therapies.

Methods

Qualitative analyses were conducted from 24 publicly available HTA reports for recently approved gene therapies including, Zolgensma® (onasemnogene abeparvovec), Libmeldy™ (atidarsagene autotemcel), Zynteglo® (betibeglogene autotemcel), Upstaza™ (eladocagene exuparvovec) and Luxturna® (voretigene neparvovec), across EU4, England, and the US (ICER reports). While not legally binding, ICER's decision carries significant weighting in pricing and reimbursement decisions in the US.

HTA agencies' critique on 3 categories were considered:

1 Trial Design

Sample size, trial type, trial duration, patient population and limitations with indirect treatment comparisons

2 Safety & Efficacy

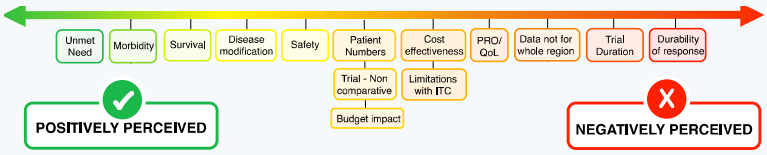
Safety, overall survival, morbidity endpoints, disease modification, patient reported outcomes and durability of response

3 Unmet needs & costs

Disease burden, cost-effectiveness, unmet need, cost-estimates and budget impact

Results

Ranking of different aspects of gene therapy HTA reviews across scope markets (illustrative)



Overview of HTA outcomes of gene therapies across scope markets*

Country	Therapy	HTA Outcome	Trial design	Safety & efficacy	Durability	Unmet need	BI / CE estimates
U.S	Zolgensma						
	Libmeldy						
	Zynteglo						
	Upstaza						
	Luxturna						
DE	Zolgensma						
	Libmeldy						
	Zynteglo						
	Upstaza						
	Luxturna						
FR	Zolgensma						
	Libmeldy	**					
	Zynteglo						
	Upstaza						
	Luxturna						
IT	Zolgensma						
	Libmeldy						
	Zynteglo						
	Upstaza						
	Luxturna						
ES	Zolgensma						
	Libmeldy						
	Zynteglo						
	Upstaza						
	Luxturna						
U.K	Zolgensma						
	Libmeldy						
	Zynteglo						
	Upstaza						
	Luxturna						

Positive HTA outcome for whole population/ coverage as per label | Moderate HTA outcome/ coverage for part of the patient population | Negative HTA outcome / no coverage | Not reviewed / no decision available | Not commented within the report

** HTA parameters were assigned ratings based on a three-point scale: **positive (acceptable), moderate (accepted with some concerns), or negative (unacceptable/major concerns).** ** The G-BA provided a **hint of significant added benefit rating** to for children with late (Late Infantile (LI)) or early childhood (Early Juvenile (EJ)) forms of metachromatic leukodystrophy (MLD) without clinical manifestation of the disease and a **hint of non-quantifiable added benefit** for Children with the EJ form of MLD with premature clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline*

Cross-Country Takeaways

Overall, safety and efficacy were well-received, with the U.K, U.S. and France showing greater acceptance. Yet, durability of effect was a major concern across all scope markets

HTA agencies, especially the G-BA and HAS scrutinized trial design:

- Despite this, positive HTA decisions were possible across markets.
- In some markets, this led to reimbursement without any restrictions (e.g., Luxturna® in both France & the UK; Upstaza™ in the UK)

The G-BA and HAS have consistently assigned lower HTA ratings to therapies, compared to other scope markets. However, it's worth noting that the G-BA and HAS are unique among HTAs in providing graded ratings, unlike NICE & ICER, which base their recommendations for reimbursement on cost-effectiveness

Key Insights Across in-scope Therapies

Libmeldy™ & Luxturna® outperformed other therapies with respect to their HTA outcomes. The high unmet need was recognized across markets due to absence of SoC at launch

Libmeldy™

The G-BA noted concerns on trial design, especially the historical comparison and trial duration. Despite concerns, the ITC was accepted based on robust safety and morbidity data; recognition that the disease course in siblings is similar

- Although the G-BA doesn't formally assess unmet need, the HTA report acknowledges that the disease severity and progression was considered
- The high unmet need coupled with robust safety and morbidity data likely led to the added benefit rating
- While Libmeldy™ received a positive reimbursement outcome in the UK, this was only possible after a decrease in the confidential net price

Luxturna®

Of the therapies assessed, Luxturna® was the only treatment to have a phase III RCT, likely supporting its favourable HTA outcomes

- NICE were the only agency who considered data from a Phase I, study, with a 7.5-year follow-up. No other country considered this, likely owing to uncertainties in the evidence due to lack of comparison and study design
- While Luxturna® was able to achieve positive outcomes in 5 out of 6 scope markets, it was perceived to have a negative HTA outcome in the U.S. due to its inability to meet acceptable cost-effectiveness thresholds

Zolgensma®, Libmeldy™ & Upstaza™ included natural history studies for their assessments. Despite HTA agencies' critique on these studies, they contributed to supporting HTA outcomes

Zolgensma®

- Natural history studies were used as a control to Zolgensma® for the economic model. This was highly scrutinized by HAS, AIFA and AEMPS, however it was accepted by NICE due to the rarity of the condition
- The ITC comparing Zolgensma® and Spinraza® caused significant concerns across markets, as patients in the comparator study were significantly older with longer disease durations .The G-BA and ICER determined the ITC could not be used to derive an additional benefit due to the high risk of bias

Upstaza™

- While an ASMR III and a non-quantifiable benefit rating was designated to Upstaza™, NICE is the only HTA body to date, to recommend Upstaza™ for reimbursement, without any population restrictions
- The G-BA and HAS both acknowledged an improvement in primary endpoints, however highlighted the lack of QoL data
- The significant unmet need in AADC and the absence of available SoC treatments appeared to be factors that steered NICE's positive HTA outcome.

Conclusion

The large heterogeneity in HTA outcomes highlights that there is no 'one size fits all approach' for HTA submissions. Certain markets have been more accepting of uncertainties on trial design compared to others. Nevertheless, robust safety and efficacy data, coupled with compelling cases of high unmet need, in countries where it's formally considered, appear to be strong influencing factors that can steer overall HTA outcomes.

Durability of effect is difficult to demonstrate

Durability of effect was highlighted as a major concern for all therapies across scope markets. Recent willingness by payers and manufacturers to leverage RWE and OBAs, as seen with gene therapies such as Roctavian™ (valoctocogene roxaparvovev) and Hemgenix® (etranacogene dezaparvovec), offer potential mitigation strategies. Despite this, successfully negotiating and implementing OBAs aren't always smooth sailing.

OBA's & RWE's influence can be crucial

BioMarin initially signed two OBAs for Roctavian in Germany but discontinued their efforts to pursue OBAs, due to insurer challenges and a reduced free-pricing period. As a result, Roctavian's uptake has been slower than expected owing to reimbursement dynamics. Monitoring the impacts of OBAs & RWE on therapy uptake is essential. Manufacturers can leverage these insights to proactively plan their HTA submissions, for a higher likelihood of positive outcomes.