Drivers of Access to Gene Therapies in Poland and Selected Central and Eastern Europe Countries

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Gene therapies show promise for rare diseases, but their availability in CEE countries is limited. Challenges in reimbursement include high costs, uncertain long-term benefits, and unresolved risk-sharing agreements underscoring difficulties in balancing patient access with budget constraints.

Objectives

- Gene therapies (GTx) are a "gamechanger" in many rare diseases where patients previously had limited or no treatment options.
- Since 2012, 12 single-administration non-oncological GTx have been approved in the US and Western Europe. However, outside those regions, adoption of GTx is often hindered by challenges such as limited financial resources and administrative capacity, and the absence of GTx-specific health technology assessment (HTA) methodologies.
- This research aimed to assess the availability of single-administration GTx and HTA decision drivers in selected CEE countries.

Methods

- In June 2024, we conducted a targeted review of HTA reports and access conditions of non-oncological single-administration GTx in Poland, Slovakia, Czech Republic, Lithuania, Estonia. HTA outcomes, date of publication, and drivers of HTA outcomes were extracted.
- We searched the following databases using both the trade names and international nonproprietary names: HTA and Tariffication Agency (AOTMiT) in Poland, National Institute for Value and Technologies in Healthcare (NIHO) in Slovakia, State Institute for Drug Control (SUKL) in Czech Republic, The State Medicines Control Service (VVKT) in Lithuania, and Health Insurance Fund (Tervisekassa) in Estonia.
- For comparison, HTA reports and access conditions in EU4 (France, Germany, Italy and Spain) and the UK were analyzed.

Results

- The review identified 11 HTA reports on 6 single-administration GTx (atidarsagene autotemcel, eladocagene exuparvovec, etranacogene dezaparvovec, onasemnogene abeparvovec, valoctocogene roxaparvovec, voretigene neparvovec).
- Onasemnogene abeparvovec was the only therapy assessed and reimbursed in all countries. All 6 GTx were assessed in Poland, 2 in Czech Republic, and 1 in Slovakia, Estonia and Lithuania each (Table 1).
- In addition, alipogene tiparvovec, betibeglogene autotemcel, and exagamglogene autotemcel were assessed in France, Germany and the UK, however, assessments for these drugs were not identified in CEE countries of interest. [47-55]
- Among the CEE countries in scope, the highest number of HTA assessments was identified in Poland; therefore, we reviewed in detail the HTA decision drivers through the Polish "Highly innovative health technologies" pathway (Table 2).
- The main drivers of HTA recommendations were: 1) innovative therapy leading to a significant improvement in the disease course; 2) rare disease; 3) efficacy demonstrated in clinical trials; and 4) positive reimbursement decision in other European countries. Raised concerns were associated with uncertainty around lifetime benefits and high costs.

Table 1. Overview of HTA Outcomes of Non-oncological Single-administration GTx in Selected CEE Countries

Therapy *Indication*	PL	CZ	SK	EST	LT	EU4 + UK
Atidarsagene autotemcel[1-8] *Metachromatic leukodystrophy*	✓	–	–	–	–	✓ FR (asymptomatic) ✓ DE, ESP, IT, UK ✗ FR (symptomatic)
Eladocagene exuparvovec[9-14] *Severe aromatic L-amino acid decarboxylase deficiency*	✗	–	–	–	–	✓ DE, FR, IT, UK ✓ ESP
Etranacogene dezaparvovec[15-18] *Severe hemophilia B*	✗	–	–	–	–	✓ DE ✓ ESP, FR, UK
Onasemnogene abeparvovec[19-34] *Spinal Muscular Atrophy*	✓	✓	✓ SMA1 ✓ presymptomatic	✓	✓	✓ DE ✓ FR (SMA 1 and 2 only), ESP, IT, UK ✗ FR (SMA 3)
Valoctocogene roxaparvovec[35-38] *Severe hemophilia A*	✗	–	–	–	–	✓ DE ✓ FR, ESP, IT, UK
Voretigene neparvovec[39-46] *Retinal dystrophy*	✓	✓	–	–	–	✓ DE, ESP ✓ FR, IT, UK

✓ Recommended for reimbursement; ✓ Recommended for reimbursement with conditions; ✗ Not recommended for reimbursement; – Not assessed.

- Although 3 therapies received positive HTA decisions in Poland (Table 1), only 1 (onasemnogene abeparvovec) was reimbursed by the National Health Fund.
  - The reimbursement process for voretigene neparvovec was suspended on March 22, 2022, at the Marketing Authorization Holder's (MAH) request to adjust the drug program terms. According to the local policy, the MAH has 3 years from the suspension date to resume the process; otherwise, the application will be withdrawn.[56]
  - Atidarsagene autotemcel was not reimbursed due to unsuccessful price negotiations between the MAH and the Economic Commission. Key issues included high cost of treatment (exceeding the costs in reference countries like Germany and Italy), lack of cost-effectiveness, and disagreement over risk-sharing schemes (clinical outcomes, target population). Additionally, its marketing authorization was conditional, and Poland lacked a certified medical center to administer the drug. [57]

Conclusion

The availability of GTx in selected CEE countries is limited. Considering there are 88 ongoing GTx phase 3 clinical trials, with 58 expected to be completed within the next 5 years,[58] the decision-makers will likely face even greater challenges to balance patient access and impact on public budgets.

Abbreviations: BSC, Best standard care; AU, Austria; AUS, Australia; BEL, Belgium; BR, Brazil; CA, Canada; CE, cost-effectiveness; CEE, Central and Eastern Europe; CHE, Switzerland; CZ, Czech Republic; DE, Germany; ESP, Spain; EST, Estonia; EU4, France, Germany, Italy & Spain; FR, France; GTx, Gene therapies; HTA, health technology assessment; IE, Ireland; ISR, Israel; IT, Italy; ITC, Indirect treatment comparison; JP, Japan; LT, Lithuania; NL, Netherlands; MAH, Marketing Authorization Holder; mo, months; OS, Overall survival; PE, pharmacoeconomic; PL, Poland; QAT, Qatar; QoL, Quality of life; RCT, Randomized controlled trial; SE, Sweden; SK, Slovakia; SMA, Spinal Muscular Atrophy; SmPC, Summary of Product Characteristics; UK, United Kingdom;

Table 2. Drivers of HTA Decisions in Selected CEE Countries

Therapy	Clinical efficacy & safety	Costs	Orphan drug or rare disease	Innovativeness	Reimbursement decisions from other countries	Unmet need
Atidarsagene autotemcel[1-8]	✓ Strength of the benefit/risk profile (PL) ✓ Relevance of study primary endpoint (PL) ✓ Low risk to bias (PL) ✓ Recognized clinical benefit (FR, DE, IT, UK) ✗ Study design limitations (lack of control arm, short follow-up, small sample size) (PL, IT) ✗ Uncertainties around the extent of QoL benefits, and long-term treatment effect (UK)	✗ High uncertainty of long-term CE (PL) ✗ Uncertainty of target population estimation (PL) ✓ Cost-effective (UK)	~ Orphan status (PL) ✓ Orphan status (DE)	✓ Innovative status recognized (PL)	~ Positive decisions in FR, DE, UK (PL)	✓ Disease severity (PL, DE) ✓ Lack of available treatment options (PL, FR, IT, UK)
Eladocagene exuparvovec[9-14]	✓ Strength of the benefit/risk profile (PL) ✓ Low risk to bias (PL) ✗ Study design limitations (single-arm studies, small sample size, higher dose than in SmPC in 5/26 patients, short follow-up, historical control) (PL) ✗ Lack of data on QoL, comparative data on mortality, non-motor outcomes, and long-term safety profile (FR, DE, IT, UK) ✗ High risk of bias associated with the single-arm study design and small sample size (FR, DE, IT, UK)	-	~ Orphan status (PL)	-	~ Positive decisions in FR, DE (PL)	✓ Disease severity (PL, FR, DE, IT, UK) ✓ Lack of available treatment options (PL, FR, DE, IT, UK)
Etranacogene dezaparvovec[15-18]	✓ Strength of the benefit/risk profile (PL) ✓ Recognized clinical benefit (FR, DE, IT, UK) ✓ Low risk to bias (PL) ✗ Study design limitations (single-arm study, small sample size, short follow-up) (PL) ✗ Lack of long-term data (PL, FR, DE, UK, IT) ✗ Poor quality ITC (FR, DE, IT, UK)	✓ Potentially cost-effective therapy (PL) ✗ High uncertainty of long-term CE (PL) ✗ Lack of CE (FR)	~ Orphan status (PL) ✓ Orphan status (DE)	-	~ Positive decision in DE (PL)	✗ Unmet need not recognized (PL)
Onasemnogene abeparvovec[19-34]	✓ Strength of the benefit/risk profile (PL) ✓ Recognized clinical benefit vs historical control (EST, UK, DE, FR, IT, LT, PL) ✓ Relevance of study primary endpoint (PL) ✓ Low risk to bias (PL) ✗ Low quality of evidence (IT) ✗ Study design limitations (lack of active comparator, small sample size, surrogate endpoints) (PL, EST, SK) ✗ Lack of long-term data (PL, SK, LT, EST) ✗ Limitations of ITC methodology (differences in study population and endpoints definition) (EST, DE, SK) ✗ Lack of direct comparison vs nursinersen; no added benefit vs BSC and nursinersen in ITC (LT)	✓ Acceptable cost of treatment (PL) ✓ Budget impact (PL) ✓ Number of life years gained estimated in CE (EST) ✗ Uncertainty of CE estimates (PL, SK) ✗ Lack of CE in patients aged >6 mo (SK) ✗ Inappropriate presentation of CE results (LT) ✗ Lack of CE vs BSC (EST) ✗ High uncertainty of CE results (EST)	✓ Orphan status (PL, DE)	✓ Innovative status recognized (PL)	~ Positive decisions in FR, DE, AU, BR, CZ, ISR, JP, QAT, SK, CHE, IT (PL) ✓ Decisions in IE, CA, UK, NL, DE, FR, NL (SK) ✓ Decisions in NL/BEL, UK, SE, CA, AUS (EST) ✓ Decisions in UK, CA, IE, SE, NL (LT)	✓ Disease severity (PL, UK, FR, IT) ✓ Insufficient efficacy of available treatment options (PL) ✓ Limited therapeutic options (UK, FR, IT)
Valoctocogene roxaparvovec[35-38]	✓ Low risk to bias (PL) ✗ Study design limitations (single-arm studies, short follow-up, small sample size, lack of OS and QoL endpoints) (PL) ✗ Uncertainties around safety and efficacy data (FR, DE)	✓ Expected to reduce costs over a lifetime time horizon (PL) ✗ High uncertainty of long-term CE (PL)	~ Orphan status (PL) ✓ Orphan status (DE)	-	~ Positive decisions in FR, DE (PL)	✗ Unmet need not recognized (PL) ✓ First GTx in indication (FR)
Voretigene neparvovec[39-46]	✓ Recognized clinical benefit (PL) ✓ Acceptable safety profile (PL) ✓ Low risk to bias (RCT, blinded) (PL, UK) ✗ Study design limitations (study endpoints, short follow-up) (PL, DE)	✓ Cost-effective vs BSC (UK)	~ Orphan status (PL) ✓ Orphan status (DE) ✓ Rare disease (PL) ✓ Ultra-rare disease (UK, FR)	✓ Innovative status recognized (PL)	✓ Positive decisions in FR, DE, UK, CA, NL (PL)	✓ Disease severity (PL) ✓ Lack of available treatment options (PL, UK, FR)

✓ Positive impact on HTA outcome; ~ Neutral impact on HTA outcome; ✗ Negative impact on HTA outcome.

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