Review of HTA evaluations for gene therapies and their future implications in Europe

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Background and objective

GTs are breakthrough treatments targeting serious diseases with high unmet medical needs. Since the approval of the first GT, several experts have published papers on the need for HTA frameworks that are adapted to GTs and consider their specificities (1-5). However, no innovative frameworks specific to GTs have been adopted by HTA bodies to date.

The objective of this study was to review HTA outcomes for GTs in France, England, and Germany to present the challenges that must be overcome in the rapidly evolving GT landscape.

Methods

GTs approved and withdrawn in ECs by 16 June 2023 were identified from the EMA and MHRA websites (6-7). Available HTA reports were extracted from the websites of HTA bodies (NICE, G-BA, and HAS) and analysed (8-10).

Results

Twenty GTs were identified, among which 4 were withdrawn upon the manufacturers' request after HTA assessments; 1 was not yet approved (Table 1). For the approved GTs, a total of 56 HTA reports were identified (NICE, 15; HAS, 21; G-BA, 20) (Table 1). Additionally, we identified 11 early access reports in France (not presented in the current review).

Table 1. List of approved/withdrawn GTs with date of EMA MA or withdrawn date and summary of HTA outcomes

Brand name (INN)	Status/indication (short)	HAS/France (n=21[b])	G-BA/Germany (n=20)	NICE/England (n=15)
Glybera® (alipogene tiparvovec)	**Withdrawn** October 2017 Familial lipoprotein lipase deficiency	**November 2015** SMR: Not reimbursed	**May 2015** Non-quantifiable AB	Not assessed
Imlygic® (talimogene laherparepvec)	**Approved** December 2015 Unresectable melanoma	Not assessed	**December 2016** AB not proven	**September 2016** Reimbursed with MAA (PAS)
Strimvelis® (autologous CD34+ enriched cell fraction[a])	**Approved** May 2016 Severe combined immunodeficiency	Not assessed	Not assessed	**February 2018** Reimbursed
Kymriah® (tisagenlecleucel)	**Approved** August 2018 R/R DLBCL R/R B-cell ALL	**December 2018 (ALL)** SMR: Important, ASMR: III	**March 2019 (ALL)** Non-quantifiable AB	**December 2018 (ALL)** Reimbursed with MAA (CDF)
		March 2021 (ALL, reassessment) SMR: Important, ASMR: III	**September 2020 (ALL, reassessment)** Non-quantifiable AB	Not assessed
		December 2018 (DLBCL) SMR: Important, ASMR: IV	**March 2019 (DLBCL)** Non-quantifiable AB	**March 2019 (DLBCL)** Reimbursed with MAA (CDF)
		March 2021 (DLBCL, reassessment) SMR: Important, ASMR: IV	**September 2020 (DLBCL, reassessment)** Non-quantifiable AB	Suspended
	Approved April 2022 R/R FL	**December 2022** SMR: Important, ASMR: V	**December 2022** Non-quantifiable AB	Not assessed
Yescarta® (axicabtagene ciloleucel)	**Approved** June 2022 R/R FL	**January 2023** SMR: Important, ASMR: V	*In development (December 2023)*	**June 2023** Not reimbursed
	Approved October 2022 R/R DLBCL and high-grade B-cell lymphoma	**February 2023** SMR: Important, ASMR: III	*In development (December 2023)*	**June 2023** Reimbursed with MAA (CDF)
	Approved August 2018 R/R DLBCL and PMLBCL	**December 2018** SMR: Important, ASMR: III	**May 2019** Non-quantifiable AB	**February 2023** Reimbursed with MAA (PAS)
		March 2021 (reassessment) SMR: Important, ASMR: III	**November 2022 (reassessment)** Non-quantifiable AB	*No reassessment*
Luxturna® (voretigene neparvovec)	**Approved** November 2018 Vision loss	**April 2019** SMR: Important; ASMR: II	**October 2019** Hint of considerable AB	**October 2019** Reimbursed with MAA (PAS)
			September 2022 (reassessment) Hint of considerable AB	
Zynteglo® (betibeglogene autotemcel)	**Withdrawn** March 2022 Transfusion-dependent β thalassaemia	**March 2020** SMR: Important, ASMR: III	**May 2020** Non-quantifiable AB	**February 2021** Not reimbursed (draft guidance)/discontinued
Tecartus® (brexucabtagene autoleucel)	**Approved** May 2020 R/R mantle cell lymphoma	**April 2021** SMR: Important, ASMR: III	**August 2021** Non-quantifiable AB	**February 2021** Reimbursed with MAA (CDF)
	Approved September 2022 R/R ALL	**February 2023** SMR: Important, ASMR: V	**March 2023** Non-quantifiable AB	**June 2023** Reimbursed with MAA (CDF)
Zolgensma® (onasemnogene abeparvovec)	**Approved** December 2020 conditional approval switched to full MA in 2022 Spinal muscular atrophy	**December 2020** SMR: Important, ASMR: III/V	**November 2021** AB not proven	**July 2021** Reimbursed with MAA (PAS)
		September 2021 (reassessment) SMR: Important, ASMR: III/IV	*No reassessment*	*No reassessment*
		May 2023 (reassessment) SMR: Important, ASMR: III	*No reassessment*	**April 2023 (reassessment)** Reimbursed with MAA(PAS)
Libmeldy® (autologous CD34+ cells encoding ARSA gene)	**Approved** December 2020 Metachromatic leukodystrophy	**April 2021** SMR: Important, ASMR: III	**November 2021** Hint of a major/non-quantifiable AB	**March 2022** Reimbursed with MAA (PAS)
Skysona® (elivaldogene autotemcel)	**Withdrawn** November 2021 Early cerebral adrenoleukodystrophy	*Not assessed*	*Not assessed*	*Discontinued*
Abecma® (idecabtagene vicleucel)	**Approved** August 2021 R/R multiple myeloma	**December 2021** SMR: Important, ASMR: V	**June 2022** Non-quantifiable AB	*Not assessed*
Breyanzi® (lisocabtagene maraleucel)	**Approved** April 2022 R/R DLBCL, PMLBCL, and FL grade 3B after 2 or more lines	***August 2022*** *Early access*	*Not assessed*	*Suspended*
	Approved March 2023 R/R DLBCL, PMLBCL, and FL grade 3B after 1st line	*Not assessed*	**April 2023** AB not proven	*Not assessed*
Carvykti® (ciltacabtagene autoleucel)	**Approved** May 2022 R/R multiple myeloma	**November 2022** SMR: Important, ASMR: V	*In development*	*Application withdrawn*
Upstaza® (eladocagene exuparvovec)	**Approved** July 2022 Aromatic L amino acid decarboxylase deficiency	**December 2022** SMR: Important, ASMR: III	**February 2023** Non-quantifiable AB	**April 2023** Reimbursed with MAA (PAS)
Roctavian® (valoctocogene roxaparvovec)	**Approved** August 2022 Haemophilia A	*In development*	**March 2023** Non-quantifiable AB	*Not assessed*
Ebvallo® (tabelecleucel)	**Approved** December 2022 R/R Epstein-Barr virus PTLD	*In development*	*In development*	*Suspended*
Hemgenix® (etranacogene dezaparvovec)	**Approved** February 2023 Haemophilia B	***May 2023*** *Early access*	*In development*	*In development*
Lumevoq® (lenadogene nolparvovec)	**Withdrawn** April 2023 Loss of vision	*Not assessed*	*Not assessed*	*Suspended*
Adstiladrin® (nadofaragene firadenovec-vncg)	**Not yet approved by EMA** Malignant bladder neoplasms	*Not assessed*	*Not assessed*	*Not assessed*

Colour coding

Positive decision: HAS: SMR, major to mild; ASMR, major (I) to non-existent (V); G-BA: AB, major to non-quantifiable

Positive decision with restrictions on indication

Negative decision: HAS: SMR: insufficient; G-BA: no AB

Abbreviations: AB, added benefit; ALL, acute lymphocytic leukaemia; ASMR, clinical added value; CDF, Cancer Drugs Fund; DLBCL, diffuse large B-cell lymphoma; EU, European Union; EC, European countries; EMA, European Medicines Agency; FL, follicular lymphoma; GT, gene therapy; G-BA, Gemeinsamer Bundesausschuss; HAS, Haute Autorité de Santé; HTA, health technology assessment; HTAB, health technology assessment body; INN, international nonproprietary names; MA, marketing authorisation; MAA, managed access agreement; MHRA, Medicines and Healthcare products Regulatory Agency; NICE, National Institute for Health and Care Excellence; OD, orphan drug; PAS, patient access scheme; PTLD, positive post-transplant lymphoproliferative disease; PMLBCL, primary mediastinal large B-cell lymphoma; R/R, relapsed/refractory; SMR, clinical value

[a]Contains CD34+ cells transduced with a retroviral vector that encodes for the human ADA cDNA sequence
[b]Early access decisions not counted

England

In England, all assessed GTs were reimbursed within their label indication (n=8) or restricted indication (n=2). Three GTs (Yescarta®, Tecartus®, and Kymriah®) were funded via the CDF during the collection of long-term data, and financial schemes were agreed for most GTs to address cost-effectiveness issues. For Zynteglo®, draft guidance was issued with a negative recommendation.

France

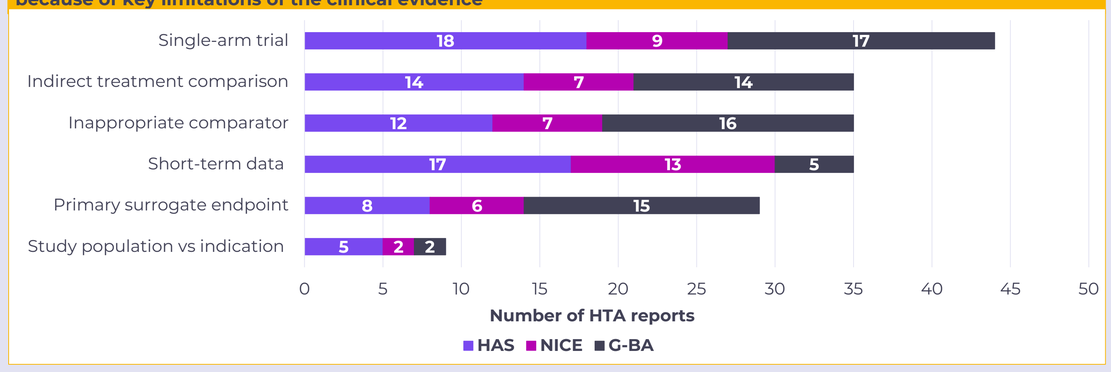
Despite the quality of the evidence being criticised, 10 of 11 assessed GTs were recommended for reimbursement in France with different clinical (added) value levels. Only Glybera® was rejected before its MA withdrawal. The indication recommended for reimbursement was restricted in 4 cases (Zolgensma®, Libmeldy®, Kymriah, and Tecartus) because of the lack of clinical data in the excluded subpopulations. A reassessment after 1 year was requested for most GTs because of the existence of only short-term data at the time of assessment.

Germany

Two GTs (Imlygic® and Breyanzi®) were assessed via the standard process with no proven added benefit (AB) because of inappropriate comparator use. Ten GTs benefited from the OD pathway, 2 OD-GTs showed a considerable/major AB (Luxturna®, Libmeldy), and 8 OD-GTs showed a non-quantifiable AB (Yescarta, Upstaza®, Tecartus, Roctavian®, Kymriah, Abecma®, Zynteglo®, and Glybera). Two products were reassessed after exceeding the revenue threshold—Yescarta, with ongoing assessment recommended, and Zolgensma, with no proven AB.

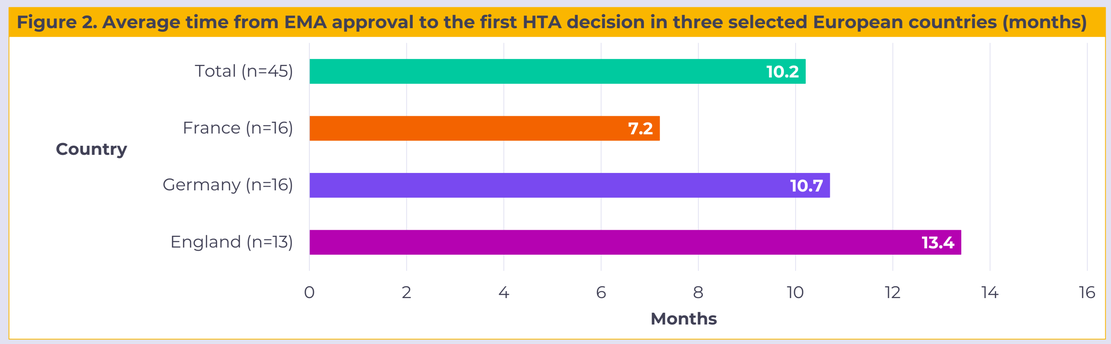
- Considerable challenges persist in the HTA of GTs, mainly stemming from the clinical evidence for GTs being criticised by HTABs in France, England, and Germany (Figure 1)
- The most common limitations raised by HAS, NICE, and G-BA were related to the presence of a single-arm trial design in 13 GTs. Of all the GTs, pivotal evidence based on randomised clinical trials was only provided for 6. Other important issues were the methodologic limitations of indirect treatment comparisons and the selection of inappropriate comparators
- HAS and NICE most frequently commented on the short-term efficacy and safety data, and the G-BA criticised the primary surrogate endpoint (e.g., the high risk of bias in the primary outcome, which is not considered relevant to patients)

Figure 1. Number of HTA reports in France (HAS), England (NICE), and Germany (G-BA) criticised by HTA bodies because of key limitations of the clinical evidence



- Further evidence was requested for 31 of 56 reports (e.g., long-term follow-up, a prospective study from relevant registers, or the setting up of a relevant register).
- For 3 products (Kymriah, Yescarta, and Zolgensma), HAS and G-BA expressed concerns during the reassessment regarding the lack of additional data requested from the first assessment. This implies that some uncertainties in the clinical evidence persist. However, these concerns did not affect the reassessment, and the HTBs requested that steps be taken to address these uncertainties in the next re-evaluation.
- The average time from MA to the first HTA decision for the 3 countries combined was 10.2 months (Figure 2).

Figure 2. Average time from EMA approval to the first HTA decision in three selected European countries (months)



Conclusions

- Although HTA agencies have not adopted specific frameworks, they have used existing pathways to tackle various challenges and ensure patient access to GTs at the national level
- Overall, GTs were recommended with some variations between countries, with decisions taking <11 months on average, leveraging managed entry agreements and/or indication restrictions in France and England, and the OD pathway in Germany
- The key decision drivers and limitations identified in this analysis reflect the general approach that HTABs are taking during the evaluation of pharmaceutical products; however, greater flexibility is observed in some cases
- The need for additional evidence is a prominent aspect of HTA requirements, appearing in more than half of the reports (31 of 56). These findings emphasise the evolving landscape of evidence requirements in the evaluation of advanced therapies, ensuring that patient safety and treatment efficacy remain paramount in the decision-making process
- With GTs included in the first wave of joint clinical assessments, the possibility of implementing a dedicated and streamlined GT framework remains to be assessed and the potential implications of EU regulation in the United Kingdom must be investigated further

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