HTA bodies acceptance of Indirect Treatment Comparisons for Gene Therapies in US, England and Wales, France and Germany

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Introduction

- Gene therapies (GTs) often lack comparators in their pivotal clinical trials when they first seek market access, especially when targeting rare diseases where only symptomatic treatment exists. Furthermore, rare diseases represent a challenge in terms of patient population and clinical trial sample size.
- As health technology assessment (HTA) bodies have published specific recommendations for indirect treatment comparisons (ITCs)[1,2,3], GT manufacturers resorted to single-arm trials and developed ITCs for HTA.
- With 381 ongoing trials (57 Phase III), the GT landscape is growing, with many GTs expected to see market access within a short period between one another[4]; thus, understanding the role of ITCs HTA and its inclusion in GT evidence packages is critical for GT developers.

Objective

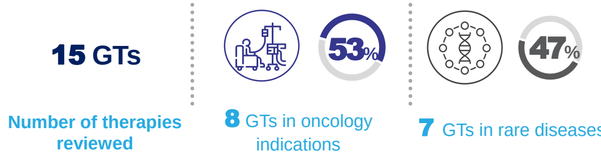
- To understand HTA bodies' evidence requirements for ITCs for GTs.
- Identify key drivers and limitations.

Methods

- The countries in scope were the US, England and Wales, France, and Germany.
- Official regulatory websites were reviewed to identify GTs with marketing authorization between January 1st, 2018 to January 1st, 2023. GTs without at least one report available from ICER, NICE, G-BA or HAS were excluded from this review.
- HTA bodies' feedback on ITCs was extracted from publicly available reports. Additional information was extracted such as type of evidence presented for HTA, key drivers and limitations of ITCs, and HTA outcome.
- A breakdown of the feedback by HTA body was conducted to identify country-specific requirements and key insights for ITC submission

Results

Figure 1. Overview of the GTs included in this review



Results (Continued)

Search results

- Fifteen approved GTs were identified in the countries of scope. Of these, 8 GTs are approved in oncology indications including 6 CAR-T therapies, and 7 GTs are approved in rare diseases. Two GTs have not been approved in the US. All 15 GTs submitted a pivotal open-label single-arm trial.
- In total, 14 GTs had HTA reports, and one was approved but had not been assessed by any HTA of scope. A total of 48 reports were extracted, which include reports for different indications of the same GTs, reassessments, and early access appraisals (for France only). ITCs were discussed in 71% (34) HTA reports for 9 GTs.
- G-BA had the most assessments including an ITC (12), followed by HAS (11) and NICE (4). ICER did not include an ITC with any of the GTs of interest.

Table 1. GTs approved in the US, England and Wales, Germany and France, with at least one available report from either ICER, NICE, G-BA or HAS

Abecma®	Luxturna®
Adstiladrin®	Roctavian® (not approved in the US)
Breyanzi®	Skysona®
Carvykti®	Tecartus®
Hemgenix®	Yescarta®
Imlygic®	Zolgensma®
Kymriah®	Zynteglo®
Libmeldy® (not approved in the US)	

Table 2. Breakdown of GTs and indications with reports per country/HTA body

Country (HTA body)	GTs with ≥1 report	Indications with ≥1 report	Indications with an ITC
US (ICER)	10	12	0
England, Wales (NICE)	7	8	4
Germany (G-BA)	8	13	12
France (HAS)	9	14	11

Key findings by country

ICER noted several limitations of ITCs: all GTs pivotal trials had a single-arm design, there were key differences in patient population baseline characteristics, differences in inclusion/exclusion criteria, differences in outcomes assessed, and a lack of patient-level data. ICER acknowledged in some cases the lack of control group for reasons of both ethics and feasibility, as per US FDA guidance.

In England and Wales, only Tecartus®, Kymriah® and Imlygic® were assessed with an ITC. NICE highlighted the following limitations: differences among populations, notably in terms of key prognosis factors that could not be adjusted for, and baseline characteristics considered as effect modifiers in oncology indications. Despite these limitations and inherent uncertainties, most ITCs were considered appropriate for decision-making, except for Imlygic®. For this, NICE concluded there was no methodologically valid way of comparing it to relevant therapies.

Results (Continued)

G-BA did not use ITCs for decision-making when a) important differences across patient populations in terms of prognosis factors (notably treatment history) could not be adjusted for, and b) when there was no systematic assessment of potential confounders and effect modifiers. Other major limitations include high rates of missing data on key outcomes and the absence of bridge comparator. For example, in Roctavian®'s case, G-BA noted additional limitations such as a high difference of sample size when comparing retrospective data versus prospective data, too short period of time for data collection that may result in distortions due to extrapolations, and a mismatch in the timing of patient-reported outcome collection. More generally, the use of early phase studies was also noted as an important limitation.

HAS made similar comments to ICER, NICE and G-BA overall, and criticized the post-hoc nature of ITCs. HAS also criticized heterogeneity in the way key outcomes have been measured such as overall response rate and progression-free survival for Yescarta® and, more generally, the use of small trials, which limited the effective sample size. For Kymriah®, HAS noted a significant mismatch between the periods of time between two studies, which introduced uncertainty given the expected evolution of the standard of care.

Discussion

Country-specific insights

The absence of ITCs in the US can be explained by several factors. Manufacturers are not required to submit evidence to ICER for reimbursement. Furthermore, as manufacturers are more likely to target the US as the first market to launch their GT, conducting ITCs may not be identified as a priority for US launch; rather, they may be postponed for the European launch.

There are limited England and Wales-specific insights given the few GTs and indications assessed by NICE. Furthermore, the GTs assessed had either no comparator available in England and Wales, such as Libmeldy® and Luxturna® or the available comparator was not deemed as relevant, as in the case of Zolgensma®, as Spinraza® is not routinely commissioned for use in the NHS.

G-BA provided detailed insights into their assessment of ITCs. Using as an example Libmeldy® for "children with late infantile or early juvenile forms of metachromatic leukodystrophy without clinical manifestations of the disease", G-BA accepted the use of a cohort of siblings given their comparable clinical course. Libmeldy® was granted a hint of a major additional benefit. G-BA noted the ITC as the driver of this outcome. This was the most successful HTA outcome in Germany as all other GTs were granted a hint of a non-quantifiable additional benefit.

Discussion (Continued)

G-BA also highlighted the importance of identifying relevant prognostic factors and confounders in oncology indications. This has been the case for Kymriah®, where G-BA noted differences between JULIET (Kymriah®'s pivotal study) and ZUMA-1 (a phase I Yescarta® study) on the time between leukapheresis and infusion with the CAR-T cell product, as well as the bridge chemotherapy performed during this period. G-BA ended up not using this ITC for decision-making. This observation could be especially relevant for manufacturers of ex-vivo GTs in oncology indications.

HAS called out the lack of a comparative arm for Kymriah® as they considered that a comparator arm with SoC in JULIET was feasible. HAS made similar comments to G-BA regarding the differences in treatment course in JULIET and ZUMA-1. HAS also noted key differences on the types of lymphoma included in the trials and the percentage of patients retreated. This last point is particularly relevant for GT manufacturers given that GTs remain a relatively new and innovative mechanism of action. HTA bodies have yet to be convinced of the long-term benefits of GTs and therefore, HTA bodies are compelled to request additional evidence on the need for retreatment with either the same GT or another follow-up treatment. Furthermore, from 2023 onwards HAS decided to conduct an economic evaluation for all Advanced Therapy Medicinal Product, regardless of turnover, to mitigate long-term uncertainty[5].

Conclusions

- HTA bodies consistently noted important limitations to ITCs submitted by GT manufacturers. There were few cases where ITCs were deemed well-managed and suitable for decision-making.
- Key insights show that ITCs most often lack adjustment for key confounding factors, and studies used must align with HTA bodies perception of robustness which include published phase III studies with adequate sample size. Real-world evidence (registries, long-term follow-up studies, early access program data) may be leveraged but require an exhaustive collection of key data points.
- The growing number of GT launches will raise concerns for HTA bodies, as such therapies will likely be tied to a high price tag and significant budget impact in the context of already constrained health care systems.
- With the upcoming new EU HTA Regulation, this review provides an overview of future evidence requirements given the significant G-BA insights extracted and the German influence on EU methods.

Abbreviations: G-BA: Gemeinsamer Bundesausschuss; HAS: Haute Autorité de Santé; ICER: Institute for Clinical and Economic Review; NICE: National Institute for Health and Care Excellence

References (full references can be provided upon request)

1. ICER Gene Therapy White Paper 2017
2. NICE HTA guidelines 2022
3. HAS ITC guidelines 2009
4. ARM clinical trials 2023
5. HAS College decision 2022

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