Single Arm Trials and External Control Arms as Pivotal Evidence for ATMPs in HTA Submissions in Germany, France and the UK: A Targeted Review

HTA255

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INTRODUCTION

The gold standard for clinical evidence submitted to health technology assessment (HTA) bodies across Europe are randomised controlled trials (RCTs), so that the comparative clinical benefit can be established. However, developing treatments for rare diseases, such as advanced therapy medicinal products (ATMPs), often poses methodological and ethical challenges to the conduct of RCTs. To overcome those challenges, developers may conduct single-arm trials (SATs); this often requires indirect treatment comparison with external controls to demonstrate comparative efficacy and safety. HTA bodies develop their own methodological guidelines and / or decision criteria to determine the acceptability of this evidence.

OBJECTIVE

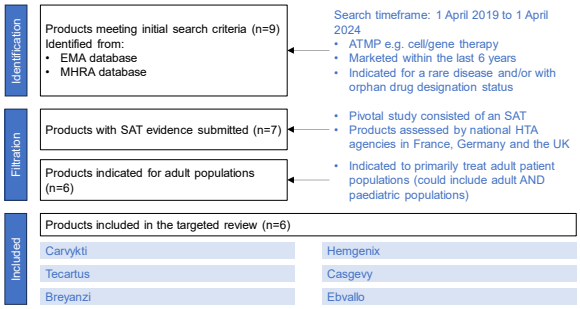
To understand, from a national HTA body perspective, the acceptability of pivotal evidence based on SATs with/without external control arms (ECAs) in HTA submissions for ATMPs in rare diseases in France, Germany, and the UK.

METHOD

Eligible medicinal products were identified via the EMA and MHRA websites, and relevant HTA reports were retrieved from national HTA body websites in France (HAS), Germany (G-BA) and the UK (NICE). The search focused on ATMPs marketed between April 2019 and April 2024, indicated for rare diseases in adult populations. Products were further filtered and selected if pivotal evidence was driven by SATs (with/without ECAs).

The flowchart presented in Figure 1 outlines the selection process for ATMPs included in the targeted review.

Figure 1: A PRISMA-like flowchart for the selection of analogues for the targeted review.



RESULTS

Guidelines and Methods Guides

In 2023 HAS published a position paper on the use of uncontrolled trials as pivotal studies[1]. Under exceptional circumstances, the paper recommends external comparisons to balance the need for rapid access for patients to drugs with evidential uncertainties i.e., SAT results are more likely to be accepted for review if submitted with an indirect comparison with an ECA.

There is no specific methods guidance for SATs or ECAs. SATs are not favoured. In exceptional circumstances, the G-BA will review an ITC, where the methodology is robust and the comparator is appropriate.

The NICE strategy plan 2021-2026 aims to integrate RWD into the evaluation process to resolve evidence gaps and drive forward patient access to innovations[2]. This strategy provides the potential for non-RCT evidence to be accepted for review.

Analogue Analysis

Six analogues were identified to investigate the research question: Breyanzi, Carvykti, Casgevy, Ebvallo, Hemgenix, and Tecartus. SAT study designs were similar; participant numbers ranged from n = 3 (Hemgenix) to n = 345 (Breyanzi). Analogue analysis was limited in the UK as several submissions remained 'work-in-progress' at the time of the research. An ECA was not submitted with the SAT for Casgevy in any of the three markets studied.

Of note, in addition to the SAT-generated data, submissions for Breyanzi and Carvykti also included data from RCTs. This may have influenced the final HTA outcome.

Tables 1a and 1b summarise key criticisms of SAT design and ECA methodologies employed. Table 2 outlines the HTA outcomes for the analogue case studies. Sources of ECA data and types of indirect comparison methodologies employed at HTA are summarised in Table 3.

While all three of the HTA bodies were willing to accept submissions utilising evidence from SATs and ECAs, they were not a driving force towards achieving favourable reimbursement status. Of the 17 submissions that reached completion, all achieved some level of recommendation for reimbursement. However, the committee's perception of the SAT and ERC designs was largely negative, especially from HAS and G-BA. Specifically, the G-BA were reluctant to consider ITC data derived from ECA use. NICE was more receptive of the SAT designs utilised in the submissions for Hemgenix and Tecartus; however, the ECA designs were viewed less favourably.

Table 1a: Key themes raised by HTA of SAT pivotal studies for six analogues; HTA conducted by HAS, G-BA and NICE

SAT design	Breyanzi	Carvykti	Casgevy	Ebvallo	Hemgenix	Tecartus
No ACT comparison	DE	FR	DE	DE	DE	FR, UK
Uncertainty due to inadequate data	FR	DE	DE, UK	DE, FR	FR	DE, UK
Limited case numbers / Inappropriate populations	FR		DE, UK	DE	UK	FR
Viewed as descriptive only	FR			FR		
High risk of bias					DE, UK	

ACT: active comparator therapy; SAT: single arm trial

Table 1b: HTA perspectives on ECA methodology and evidence submitted across six analogues; HTA conducted by HAS, G-BA and NICE.

ECA methodology	Breyanzi	Carvykti	Casgevy	Ebvallo	Hemgenix	Tecartus
Unsuitable AIC	DE					UK
Comparability issues	DE	DE			DE, UK	DE, UK
High risk of bias				DE, FR	FR	DE, FR
Questionable validity of method		FR		FR		FR, UK
Insufficient ECA structure	DE, FR	FR		DE	DE, FR	DE, FR
Not submitted			DE, UK			

AIC: adjusted indirect comparison, ACT: active comparator therapy; ECA: external control arm,

Table 2: HTA outcomes and HTA body's opinions of six analogue assessments

Drug		HTA outcome	Opinion on: SAT design	Opinion on: ECA design
Germany[5]	Breyanzi	Considerable added benefit (DLBCL, HGBCL, PMBCL, FL3B relapsed within 12 months or refractory to first-line)		
		No added benefit (DLBCL, HGBCL, PMBCL, FL3B relapsed within 12 months or refractory to two or more lines of systemic therapy)		
	Carvykti	Non-quantifiable added benefit		
	Casgevy	Discontinued consultation		*
	Ebvallo	Non-quantifiable added benefit		
	Hemgenix	Non-quantifiable added benefit		
	Tecartus	Non-quantifiable added benefit (R/R MCL after two or more lines of systemic therapy including BTKi)		
		Non-quantifiable added benefit (R/R ALL)		
France[6]	Breyanzi	ASMR III		
	Carvykti	ASMR V		
	Casgevy	Early Access		*
	Ebvallo	ASMR IV		
	Hemgenix	ASMR IV		
	Tecartus	ASMR III (R/R MCL after two or more lines of systemic therapy including BTKi)		
		ASMR V (R/R ALL)		
UK[7]	Breyanzi	Not submitted	*	*
	Carvykti	Submission withdrawn	*	
	Casgevy	HTA in development		
	Ebvallo	Not submitted	*	
	Hemgenix	Recommended; IMF MAA		
	Tecartus	Recommended; CDF MAA (R/R MCL after two or more lines of systemic therapy including BTKi)		
		Recommended; CDF MAA (R/R ALL)		

Key: Positive, Mixed, Negative, No comment given / not submitted*, Head-to-head Phase 3 data submitted

Table 3: Evidence and methodologies submitted to HTA bodies

		HAS	G-BA	NICE
Source of ECA	Individual arms of comparator retrospective/prospective studies (historical controls)	Breyanzi (2), Carvykti, Ebvallo, Hemgenix, Tecartus (R/R)	Breyanzi (1), Breyanzi (2), Carvykti, Ebvallo, Hemgenix	Tecartus (ALL)
	Data from chart review / real world study	Ebvallo, Hemgenix	Ebvallo, Hemgenix	
	Meta-analysis of ECA studies	Tecartus (R/R)	Tecartus (R/R)	
	Synthetic control arms from clinical SLR	Tecartus (ALL)	Tecartus (ALL)	
Methods used for indirect comparison	Matched comparison (without bridge comparator)	Carvykti	Breyanzi (1), Breyanzi (2), Carvykti, Ebvallo, Hemgenix	
	Matching adjusted indirect comparison (unanchored)	Tecartus (R/R), Tecartus (ALL)		Hemgenix, Tecartus (ALL)
	Propensity score weighting method (inverse)	Ebvallo, Hemgenix	Hemgenix	Hemgenix
	Cox model with adjustment for patient characteristics / combined with propensity score	Tecartus (R/R)		
	Naïve unadjusted comparison		Carvykti	Tecartus (ALL)

Key: Breyanzi (indication 1), Breyanzi (indication 2), Carvykti, Ebvallo, Hemgenix, Tecartus (R/R), Tecartus (ALL)

ECA: external control arm; SLR, systematic literature review

DISCUSSION

Overall, submitting SATs as pivotal studies is limited in driving a positive HTA outcome. SAT results are often viewed as purely descriptive, posing challenges for drawing conclusions about the quantification of the added benefit of an intervention compared to standard care. When a company prepares and submits an ECA, it must ensure that the evidence submitted, and studies included in the indirect comparison or meta-analysis are of high quality, with a high degree of comparability between patient populations, study designs, patient-relevant data, and confounders.

A recent reflection paper from the EMA[3] acknowledges that evidence from single-arm trials may be suitable in certain regulatory circumstances, although it does not specify the requirements. The draft EC Joint Clinical Assessment (JCA)[4] indicates that while SATs are acceptable for HTA, they may not be enough to allow an estimation of the relative treatment effect.

Of the 3 HTA bodies analysed, NICE were the most likely to positively receive non-RCT evidence as part of a submission. The G-BA were less receptive and placed particular emphasis on robust ITC design using appropriate comparators reflective of current disease management.

CONCLUSIONS

This analysis reveals the cautious acceptance of data generated via SAT by three key European HTA bodies. However, there is a lack of alignment between these bodies on how such studies should be designed, and the resulting data utilised.

SATs and ECAs are accepted when:

- The ECA is well defined before initiation of the SAT, and the data collected are recent enough to reflect current disease management
- There is clear justification why a direct comparison is unfeasible, or direct comparative data are unavailable
- The study design matches that of an RCT as closely as possible
- The patient groups are comparable
- The risk of bias has been addressed systematically

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AIC: adjusted indirect comparison, ACT: active comparator therapy, ASMR: clinical added value (amélioration du service médical rendu), ATMP: advanced therapy medicinal product, CDF: Cancer Drugs Fund, ECA: external control arm, EC: European Commission, EMA: European Medicines Agency, ERG: Evidence Review Group, G-BA: Federal Joint Committee (Gemeinsamer Bundesausschuss), HAS: French National Authority for Health (Haute Autorité de Santé), HTA: health technology assessment, IMF: Innovative Medicines Fund, JCA: Joint Clinical Assessment, MAA: managed access agreement, MAIC: matching adjusted indirect comparison, MHRA: Medicines and Healthcare Products Regulatory Agency, NICE: National Institute for Health and Care Excellence, RCT: randomised controlled trial, RWD: real-world data, SAT: single arm trial.