OPEN HEALTH

Bridging the Gap: Evidence Challenges for Advanced and Orphan Therapies in the EU HTA Landscape

Insights from a multi-country HTA comparison of oncology ATMPs and OMPs in the JCA era

By Shruti Pandey, Victoria Brennan, Amrita Sandhu, and Emanuele Arcà

www.openhealthgroup.com

Bridging the Gap: Evidence Challenges for Advanced and Orphan Therapies in the EU HTA Landscape

Insights from a multi-country HTA comparison of oncology ATMPs and OMPs in the JCA era

Introduction

Advanced therapy medicinal products (ATMPs) and orphan medicinal products (OMPs) are at the forefront of innovation, offering hope to patients with rare, life-threatening, or previously untreatable conditions. This is particularly evident in the oncology field, where there is a significant burden of unmet clinical need that has sparked rapid scientific innovation from manufacturers. This has, in turn, led to strategic focus from regulators and health technology assessment (HTA) bodies. While these therapies promise transformative outcomes, their evaluation under Europe's new HTA systems is anything but straightforward.

With the rollout of the **EU HTA Regulation (HTAR)** and its centerpiece, the **Joint Clinical Assessment (JCA)** process, Europe is entering a new era of cross-border collaboration on HTA. The JCA aims to harmonize clinical evidence requirements across Member States, streamlining access and reducing duplication. EU HTAR and JCA were introduced in January 2025 for ATMPs and OMPs in oncology. Their scope will expand to include all ATMPs and OMPs by January 2028. When assessing advanced or orphan therapies, the EU HTA regulation permits the use of methods such as surrogate endpoints and data from single arm trials. However, each individual Member State makes the ultimate decision regarding the relevance and acceptability of these methodologies. This creates uncertainty for both developers and payers, as evidence deemed sufficient for EU-level assessment may not meet national HTA expectations.

This **whitepaper** presents the results of a recent study that explored the current state of national HTA evaluations for advanced and orphan therapies. The paper focuses on alignment and divergence in evidence expectations and considers how the JCA might reshape the landscape for developers, regulators, and, ultimately, patients.

Key Questions:

Our study aimed to address four key questions:

- **How are ATMPs and OMPs in oncology currently assessed across the EU?**
- **What types of evidence are considered most relevant in HTA evaluations?**
- **What types of evidence are most frequently challenged in HTA evaluations?**
- **What are the implications of heterogeneous national evidence requirements for the JCA and its goal of harmonizing HTA processes across Europe?**

Our study focused on therapies approved between **July 2019 and July 2024**, with a specific focus on **rare oncology indications, where unmet need is high and generating robust evidence remains particularly challenging due to small patient populations, disease heterogeneity in terms of causes, symptoms, and treatment responses, and limited natural history data.**

Countries:

Countries were selected based on their active participation in HTAs, evaluated by the number of HTAs completed and their influence within EU-level discussions on the JCA. The following countries and their respective HTA bodies were included in the study:

- Germany: Gemeinsamer Bundesausschuss (G-BA)
- France: Haute Autorité de Santé (HAS)
- Spain: Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)
- Denmark: Danish Medicines Council (DMC)
- Belgium: Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV)
- The Netherlands: Zorginstituut Nederland (ZIN)

This selection of countries provides a balanced snapshot of Europe's HTA landscape, ranging from early access systems, such as that in Germany, to those that emphasize clinical added value, such as the French system, and the collaborative frameworks seen in the Beneluxa Initiative. This diversity allows for meaningful insights into how ATMPs and OMPs are currently assessed and what this might mean for future alignment under the JCA.

The HTA process in each of these national systems was analyzed across five evidence domains, reflecting the range of data often included within HTAs:

- **Trial data:** We examined how each HTA body assessed pivotal clinical trial design, endpoints, comparators, and statistical robustness, particularly in the context of small patient populations and single-arm studies that are common in rare oncology.
- **Real-world evidence (RWE):** We explored the extent to which real-world data (e.g., registry data, data from observational studies, post-marketing data) were considered credible or sufficient to complement or compensate for limited trial data.
- **Indirect treatment comparisons (ITCs):** Where head-to-head data were lacking, we assessed how HTA bodies handled indirect comparisons, including network meta-analyses and other modeling techniques, and whether the data were accepted or viewed critically.
- **Patient-centered outcomes (PCO)/Quality of life (QoL):** We reviewed how patient-reported outcomes, QoL measures, and other patient-centric evidence were valued, or questioned, within each appraisal.
- **Societal values and preferences:** Finally, we looked at whether broader societal considerations, such as ethics, caregiver burden, or disease severity, were factored into decision-making and how consistently this was done across jurisdictions.

Products:

To examine how companies structure clinical evidence packages in alignment with evolving EU HTAR guidance and explore potential differences in evidence presentation strategies across Member States, we selected a number of products recently submitted for assessment in the countries of interest. We conducted a targeted review of ATMPs and OMPs that had received European Medicines Agency (EMA) marketing authorization within the past five years to identify relevant products. This search yielded a total of 75 active non-oncology and oncology products.

Given the prioritization of oncology indications within the JCA under the EU HTAR, we focused exclusively on oncology-related therapies (n = 30). From this subset, eight products were selected for evaluation.

- Spexotras and Finlee for glioma[2,3]
- Talvey and Carvykti for multiple myeloma[4,5]
- Kimmtrak for uveal melanoma[6]
- Tepkinly for diffuse large B-cell lymphoma[7]
- Lunsumio for follicular lymphoma[8]
- Scemblix for chronic myeloid leukemia[9].

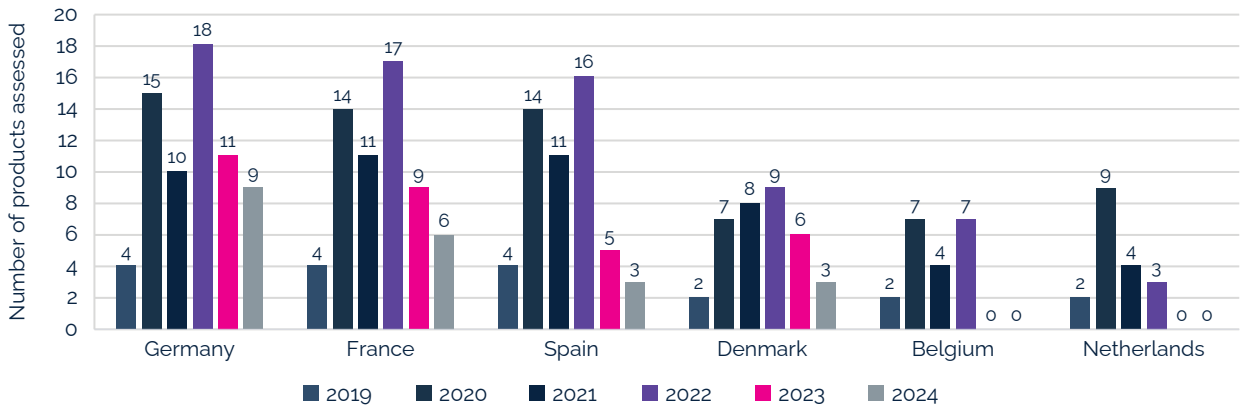
These products were selected as being among the most commonly assessed orphan oncology products across the six countries of interest for which the most recent national assessment, or re-assessment, was publicly available.

Results

1. Europe's HTA Hotspots

Figure 1 illustrates the volume of assessments, by country and year, for the six countries of interest. **Germany** has the most HTA evaluations, due to its legislation for early assessment, followed by **France** and then **Spain**.

Figure 1. Number of products assessed in each country by year



2. A Patchwork of Evidence Acceptance

Table 1 summarizes the divergence in evidence expectations and decision-making across the six countries of interest. In summary:

- **Trial data:** Randomized controlled trials (RCTs) continue to be the gold standard across Europe. However, when RCTs are impractical — particularly in the case of rare cancers — **France, Germany, and the Netherlands** have accepted single-arm trials.
- **RWE:** The role of RWE varied significantly. **France, Denmark, and the Netherlands** have allowed registry and other real-world data to validate target populations. In contrast, **Belgium and Spain** showed little or no evidence of RWE influencing their assessments.
- **ITCs: France, Denmark, Belgium**, and **the Netherlands** have accepted ITCs to contextualize efficacy, provided methodologies are robust and transparent. **Spain** has expressed concerns about comparability due to differences in study populations and designs, while **Germany's** position remains unclear.
- **PCOs and QoL: The Netherlands** considered these as essential components of their evaluation. **France** required robust data collection. Other countries, including **Spain and Germany**, seemed to ignore these measures when making their final decisions.
- **Societal Impact: France** was the only country to explicitly incorporate societal preferences and unmet needs into their evaluation.

Table 1. Summary of findings

Clinical Evidence	France	Belgium	Germany	Denmark	Spain	The Netherlands
Trial data	Comparative data from RCTs were preferred. Single-arm studies were accepted (for innovative products/ products addressing high unmet need)	Comparative data were preferred. Surrogate endpoints were accepted where thoroughly validated	Comparative data from RCTs were preferred. Single-arm studies were accepted in the absence of comparative studies	Comparative data from RCTs were preferred, although uncertainties due to lack of long-term data, small sample size etc., were seen as limitations	Comparative data were preferred, while variables like PFS and OS were criticized for being hard to interpret in non-comparator trials	Comparative data from RCTs were preferred. Single-arm studies were accepted in the absence of comparative studies
RWE	Given the uncertainties about data from clinical trials, registry data could be accepted	There was no indication of the relevance of RWE data in decision-making	Registry data could be accepted in the absence of RCT data	RWE data were accepted for validation of the target population, including country-specific data	There was no indication of the requirement for RWE data in decision-making	RWE data were accepted for validation of the target population
ITC	ITCs with robust methodologies (data availability & grouping, residual differences, and biases) were accepted	ITCs were sufficient to gain approval	There was no information on the use of ITC data	ITC data with robust methodologies were accepted	Some ITCs were provided but their importance in decision-making was not clear	ITCs were used in decision-making, but uncertainties on the quality of the evidence were criticized
PCO and QoL	Robust PCO estimates from comparative studies were preferred for decision-making, while the lack of QoL outcomes was criticized	There was no indication of the requirement for PRO data	There was no indication of the requirement for PRO data	PCO data were accepted, although the decision focused predominantly on survival outcomes	There was no indication of the requirement for PRO data in decision-making. Patients and clinicians were not engaged in decision-making	QoL was a crucial endpoint for decision-making
Societal values/ preferences	Unmet health need was relevant for the final decision	No references were made to societal values/unmet need				

Ranking based on relevance: Most Relevant — Least Relevant

Abbreviations: ITC, indirect treatment comparison; OS, overall survival; PCO, patient-centered outcomes; PFS, progression-free survival; QoL, quality of life; RCT, randomized controlled trial; RWE, real world evidence.

Discussion:

Study overview

The review analyzed HTA appraisals of eight EMA-authorized orphan oncology products from six European countries with active HTA participation to analyze how oncology therapies are assessed across diverse national systems. We evaluated HTA processes using five evidence domains: trial data, RWE, ITCs, PCOs, and societal values.

Key findings

- Trial data: There is an increased willingness to accept single-arm trials and validated surrogate endpoints, but RCTs continue to be the preferred evidence base.
- RWE: For now, the use of RWE is patchy and often confined to population validation.
- ITCs: ITCs are being increasingly used in submissions in the absence of head-to-head trials, but their acceptance hinges on methodological rigor and transparency.
- PCOs and QoL: Though increasingly central to economic models, QoL data are not consistently valued in clinical evaluations.
- Societal impact: Only France formally acknowledges societal preferences and unmet needs.

Implications and future directions

This cross-country comparison study reveals a **lack of harmonization** in clinical evidence expectations for ATMPs and OMPs. Building on these findings, it is important to consider their broader implications for research, clinical practice, and policy:

- **Flexibility vs. rigor in trial data**: The lack of trial data in rare diseases underscores the need for **adaptive trial designs, Bayesian approaches, and innovative evidence synthesis methods** to ensure that limited data can still meaningfully inform HTA decisions.
- **RWE's emerging role**: In the future, the establishment of the **European Health Data Space** may improve confidence in real-world data across Europe. This initiative can help elevate RWE from a supplementary tool to a primary source of evidence in healthcare decision-making.
- **ITCs require early planning: Early dialogue via Joint Scientific Consultations** is becoming increasingly important as ITCs gain traction. Alignment at this point will help ensure that methodological expectations are clearly understood from the outset and help avoid late-stage rejections.
- **PCOs remain underused**: Europe's HTA reforms, including the JCA, signal a deliberate effort to include **patient perspectives and lived experiences** in evidence evaluation. Their integration into decision-making will empower patients to define what constitutes therapeutic value and increase the relevance of clinical evaluations.
- **Societal values: Still missing in action**
  In case of rare diseases, assessments should capture not only the clinical outcomes but also the **wider societal value of timely access** to these innovative therapies. Future directions for the EU JCA should place stronger emphasis on equity and societal impact.

Conclusion:

As Europe moves toward a unified HTA process under the **JCA**, our findings underscore the need for more than just procedural alignment. The following are required:

- **Strategic evidence generation** that anticipates national nuances
- **Stronger, trusted RWE frameworks**
- **Broader assessments** that incorporate patient and societal perspectives

If the goal is to truly support innovative, high-need therapies such as ATMPs and OMPs, the **JCA must bridge, not just document, national differences.**

References

1. Eder, C. & Wild, C. (2019). Technology forecast: Advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption. *Journal of Market Access & Health Policy*, 7(1), 1600939. https://doi.org/10.1080/20016689.2019.1600939
2. European Medicines Agency. Spexotras. https://www.ema.europa.eu/en/medicines/human/EPAR/spexotras
3. European Medicines Agency: Finlee. https://www.ema.europa.eu/en/medicines/human/EPAR/finlee
4. European Medicines Agency: Talvey. https://www.ema.europa.eu/en/medicines/human/EPAR/talvey
5. European Medicines Agency: Carvykti. https://www.ema.europa.eu/en/medicines/human/EPAR/carvykti
6. European Medicines Agency: Kimmtrak. https://www.ema.europa.eu/en/medicines/human/EPAR/Kimmtrak
7. European Medicines Agency: Tepkinly. https://www.ema.europa.eu/en/medicines/human/EPAR/tepkinly
8. European Medicines Agency: Lunsumio. https://www.ema.europa.eu/en/medicines/human/EPAR/lunsumio
9. European Medicines Agency: Scemblix. https://www.ema.europa.eu/en/medicines/human/EPAR/scemblix

OPEN Health. The right combination to unlock possibilities.
At OPEN Health, we connect visionary minds, pioneering science, and advanced technology to drive real impact. By uniting people, science, and technology, we activate new opportunities for biopharma innovation. Our expertise across medical affairs and market access unlocks faster, smarter routes to market. We are committed to improving patient outcomes worldwide.

For information about OPEN Health's services and how we could support you, please **get in touch**.

OPEN HEALTH

www.openhealthgroup.com