ISPOR Europe 2025, Glasgow, Scotland HPR14

# Access and Evolving Evidence: A European HTA Analysis of Innovative Medicines Under Evidence Generation Agreements

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## Background and Objective

### What is PRIME?

The PRIME designation is a regulatory initiative launched by the EMA in 2016 to accelerate the development and approval of medicines that address unmet medical needs in the European Union.[1]

### Why it Matters for Manufacturers?

**Faster Review:** Accelerated assessment (150 vs. 210 days)

**Early EMA Support:** Scientific advice helps optimize clinical and regulatory strategy.

**Investor Appeal:** Signals high therapeutic potential, boosting funding opportunities.

**Regulatory Alignment:** Facilitates navigation of EU standards, potentially reducing costs.

### Challenge?

**Post-Approval Demands:**

National HTA bodies often require further evidence post-approval.

**The aim of this analysis was to describe the HTA outcomes and evidence requirements in the 3 largest European markets: France, Germany, and the UK.**

## Methods

This analysis focused on **EMA PRIME-designated medicines** authorized between **January 2023 and April 2025**, examining HTA reports from HAS (France), G-BA (Germany), and NICE (UK) to evaluate :

- Submitted evidence : Type of clinical data presented
- Key uncertainties : Gaps or concerns raised by HTA bodies
- Access conditions : Reimbursement decisions, restrictions, or managed entry agreements
- Post-launch data requirements : Obligations for additional evidence generation after market entry

This cross-country comparison highlights how PRIME designation interacts with national HTA expectations and post-authorization evidence demands.

## Results

A total of 8 medicines (9 indications) with PRIME designation were approved between January 1, 2023, and April 9, 2025, of which 7 held orphan drug designation and 6 received conditional marketing authorization, requiring post-approval evidence generation.

Completed HTA assessments were available from HAS for 7/9, from G-BA for 8/9, and from NICE for 6/9 of these medicines.

| Medicine (with PRIME designations, approved 2023-2025) | | Completed assessment | | |
|---|---|---|---|---|
| Medicine | Indication | HAS (France) | G-BA (Germany) | NICE (UK) |
| Sotatercept | PAH | - | ✓ | - |
| Danicopan | PNH | ✓ | ✓ | ✓ |
| Iptacopan | PNH | ✓ | ✓ | ✓ |
| Exagamglogene autotemcel | SCD | ✓ | ✓ | ✓ |
| | β thalassemia | ✓ | ✓ | ✓ |
| Fidanacogene elaparvovec[a] | Hemophilia B | - | - | - |
| Elranatamab | Multiple Myeloma | ✓ | ✓ | ✓ |
| Etranacogene dezaparvovec | Hemophilia B | ✓ | ✓ | ✓ |
| Talquetamab | Multiple Myeloma | ✓ | ✓ | - |

[a]no longer authorized by EMA

✓ positive recommendation

✓ positive recommendation conditional to evidence generation

- not yet assessed

### Medicines granted a positive recommendation under evidence generation agreement in France

| Medicine | Key critique of evidence submitted | | Type of evidence requested |
|---|---|---|---|
| Exagamglogene autotemcel[2,3] | β thalassemia:<br>• Lack of comparative data (No external control group, lack of direct comparison vs SoC) | • Limited long-term data<br>• Methodological concerns: Unclear clinical relevance of primary endpoint<br>• Small sample size and preliminary data (pivotal study interim analysis) | • Comparative data vs SoC using external controls and robust methodology (Data collection via official registries)<br>• Long-term efficacy and safety (official registries or new studies) |
| | Sickle cell disease:<br>• Lack of comparative data (lack of direct comparison vs SoC)<br>• Small sample size (less than 30) | • Limited long-term data<br>• Potential overestimation of efficacy<br>• Incomplete patient characterization<br>• Safety concerns (High rate of SEAs) | • Comparative data vs. SoC (Data collection via official registries)<br>• Detailed patient characteristics and treatment modalities, other relevant efficacy outcomes and long-term safety (ongoing or planned trials) |
| Elranatamab[4] | • Lack of comparative data (single-arm phase II study)<br>• Safety concerns (High rate of SAEs. Approx. 20% of patients experienced grade 5 Aes, | increased early deaths from infections)<br>• Limited long-term data (safety and durability of response) | • Results from the ongoing phase III study (Effectiveness, comparative data, safety, QoL)<br>• Continued local RWE collection on patient characteristics, treatment patterns, safety and QoL |
| Etranacogene dezaparvovec[5] | • Limited long-term data (only 2 y FU for 54 patients and 3 y data for 3 patients)<br>• Limited long-term data (durability of efficacy and safety) | • Variability in individual responses<br>• Unknowns about repeatability of treatment and cross-reactivity with other gene therapies | • Final 5 y FU results from ongoing trials<br>• Data from the European registry<br>• Local RW data collection, including patient characteristics, clinical outcomes, concomitant treatments, tolerance profile |
| Talquetamab[6] | • Lack of comparative data (non-comparative phase I/II study) | • Safety concerns (high frequency of AEs - e.g., neurotoxicity)<br>• Limited long-term data (FU duration median 18.8 m)<br>• Lack of evidence on impact on QoL or healthcare pathway | • Results from the final analysis of the ongoing phase I/II study.<br>• Results from phase III studies. |

### Medicines granted a positive recommendation under evidence generation agreement in Germany

Of note, ongoing data collection is taking place for Etranacogene dezaparvovec (non-quantifiable additional benefit) and the study design for exagamglogene autotemcel routine practice data collection is being finalized.

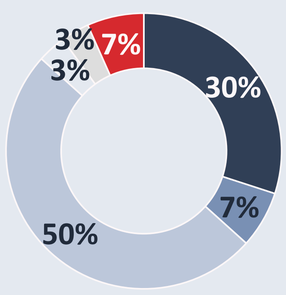
| Medicine | Key critique of evidence submitted | | Type of evidence requested | Type of evidence requested |
|---|---|---|---|---|
| Etranacogene dezaparvovec[7] | • Long-term risk/benefits | • Lack of comparative data | • RW comparative study: a registry or via dedicated data collection platform[a]<br>• Primary data source: German Hemophilia Register | • Observation period: at least 3 y |
| Exagamglogene autotemcel[8] | • Long-term risk/benefits | • Lack of comparative data | • RW comparative study: a registry or via dedicated data collection platform[a]<br>• Endpoint-specific inclusion of retrospective data (if necessary) | • Intention-to-treat principle for enrollment and start of observation<br>• Primary data source: GPOH registry SCD<br>• Observation period: at least 3 y |

[a] comparator study using a data platform to be set up specifically for the present routine practice data collection

### Medicines granted a positive recommendation under evidence generation agreement in the UK

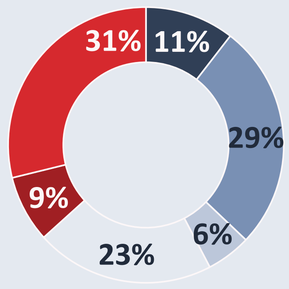
| Medicine | Key critique of evidence submitted | | Type of evidence requested |
|---|---|---|---|
| Exagamglogene autotemcel[9,10] | β thalassemia:<br>• Limited long-term data (relapse rate, rates of complications, | mortality, transfusion requirements)<br>• Limited comparative evidence | • Ongoing clinical trial: New malignancies, new or worsening hematologic disorders, all-cause mortality, SEAs, PROs,, etc.<br>• Local RWE collection: long-term safety and effectiveness |
| | Sickle cell disease<br>• Lack of comparative data<br>• Limited long-term data | • Sample size | • Ongoing clinical trial: New or worsening hematologic disorders, all-cause mortality, SEAs, PROs, reduction in inpatient hospitalizations, etc<br>• Local RWE collection: Demographic, prior treatment, safety outcomes, etc. |
| Elranatamab[11] | • Limited long-term data (number of people having IVIg and duration of IVIg treatment, immature data) | • Lack of comparative data (Lack of control arm)<br>• Limitations of indirect comparisons, and modelling assumptions | • Ongoing clinical trial: OS, PFS, TTD<br>• Local RWE collection: Number of patients starting treatment, baseline patient characteristics, prior treatments, treatment duration, dosing, OS |
| Etranacogene dezaparvovec[12] | • Limitations of indirect comparisons, and modelling assumptions | • Limited long-term data (only 24 m response data available, extrapolated to 60 y)<br>• Magnitude of improvement in bleeding uncertain | • Ongoing clinical trial: Annualized bleeding rates (according to different type and severity), SF-36, EQ-5D-5L QoL scores, safety outcomes etc; Local RWE collection: |

Key uncertainties prompting HTA bodies to request post-launch evidence generation:




- Lack of comparative data
- Small sample size
- Limited data on long-term outcomes *(e.g., biomarker levels used to infer clinical benefit)*
- Unclear clinical relevance of study endpoint(s)
- Incomplete patient characterization
- Lack of evidence on impact on QoL/healthcare pathway

Additional evidence requested by HTAs:




- Comparative data
- Long term efficacy/safety data
- Completion of baseline characteristics dataset
- Additional efficacy/safety data
- Quality of life data
- local RW data collection

## Conclusion

European HTA bodies frequently request additional comparative data and long-term follow-up evidence to address uncertainties identified at the time of submission. These requirements often include **completion of ongoing clinical trials** and **generation of RWE** through registries to validate preliminary results on key outcomes. **Beyond efficacy and safety, HTAs increasingly seek data on clinical durability of effect, survival, and patient-centered measures such as QoL and healthcare impact**, areas that are often underrepresented in initial submissions.

**Manufacturers launching innovative therapies should anticipate these evidence needs early in the development process. Proactive planning for post-launch data generation, including infrastructure for registries and RWE collection, is essential to support positive HTA recommendations, secure reimbursement, and ensure sustained patient access.**

Abbreviations: AE, adverse events; EMA, European Medicine Agency; FU, follow-up; GPOH, Society for Paediatric Oncology and Haematology; ITC, indirect treatment comparison; m, month; OS, overall survival; PAH, Pulmonary arterial hypertension; PFS, progression-free survival; PRIME, priority medicines; PRO, patient reported outcomes; QoL, quality of life; HTA, health technology assessment; PNH, paroxysmal nocturnal hemoglobinuria; RWE, real-world evidence; SEAE, serious adverse events; SCD, sickle cell disease; SoC, standard of care; TTD, time-to-treatment-discontinuation; y, year

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