ANSEA
YOUR ACCESS PARTNER

ANSEA INSIGHTS

Insights from the first three EU Joint Clinical Assessments

Implications for Comparative Evidence, Evidence Gaps, and the Future of EU HTA

THIS REPORT INCLUDES

- Comparative Analysis of the First Three EU JCA Reports
- HEOR & Market Access Insights from the Second and Third EU JCA Reports
- In-Depth Review of the First EU JCA Report

Healthcare Access | HEOR | Market Access | Health Policy

July 2026

ANSEA
YOUR ACCESS PARTNER

Table of Contents

SECTION 1

Comparative Analysis of the First Three EU JCA Reports

Understanding the emerging evidence landscape across the first three EU JCAs

July 2026

ANSEA
YOUR ACCESS PARTNER

Comparative evidence across the first three JCAs

The first three Joint Clinical Assessment reports under the EU HTA Regulation are now public:

	Tovorafenib	Tarlatamab	Lurbinectedin
Report date	June 9, 2026	July 8, 2026	July 8, 2026
Indication	Previously treated paediatric low-grade glioma	Previously treated extensive-stage small-cell lung cancer	Maintenance therapy in extensive-stage small-cell lung cancer
Sponsor	IPSEN Innovation for patient care	AMGEN®	Pharma Mar

We reviewed the reports collectively. The most important lesson is that the JCA process does not remove uncertainty but makes evidence gaps and their relevance across European markets more visible.

1. Tovorafenib: when the assessment scope is broader than the evidence base

The first JCA **defined three populations** and **eight PICOs**.

Comparative evidence reached the assessment for only one: **PICO 5**. No comparator data were submitted for PICOs 1–4, 6 and 8, while evidence for PICO 7 was excluded because the comparator study was insufficiently described. The sole included comparison relied on an **unanchored MAIC** derived from a **single-arm pivotal study**, with very small effective sample sizes and substantial residual uncertainty.

The report's contribution was therefore not to resolve relative effectiveness across the indication. It was to **document**, systematically and transparently, where **relative-effect evidence was unavailable**.

2. Tarlatamab: when one randomised trial must stretch across seven different PICOs

The tarlatamab assessment also had a **broad scope**, but the evidence pattern was materially different.

The **pivotal DeLLphi-304 study** was considered capable of informing all **seven PICOs**. It provided **direct evidence** against topotecan for PICOs 1, 4 and 6. The other four PICOs relied on **indirect comparisons** involving historical comparator studies, including network meta-analysis, Bucher comparisons and an unanchored MAIC.

This is a more populated evidence package than tovorafenib but "populated" does not mean equally robust.

The **strength of the conclusions varies by PICO**, **comparator** and **method**. Direct randomised evidence sits alongside indirect estimates requiring assumptions about study similarity, effect modifiers, consistency and data availability.

For HEOR teams, that distinction matters. A **relative-effect estimate** being present in a JCA does not automatically mean that it is equally defensible as an input into every national economic model.

3. Lurbinectedin: when the PICO is narrow and the evidence is direct, but uncertainty remains

The lurbinectedin assessment presents the **cleanest conventional design** of the three.

It addressed a **single PICO** using the **open-label IMforte randomised controlled trial**, comparing lurbinectedin plus atezolizumab with atezolizumab alone as maintenance treatment after induction therapy.

Risk of bias was considered low for overall survival and progression-free survival. However, it was considered high for objective response, complete response, duration of response, all patient-reported outcomes and all safety outcomes. Independent review of tumour outcomes also stopped after the first data cut, meaning several later analyses were **investigator assessed**.

So even the apparently straightforward JCA, a single PICO supported by a head-to-head RCT **does not produce a uniformly certain evidence package**.

ANSEA
YOUR ACCESS PARTNER

Overarching Lessons for future EU JCAs

There is no single "JCA evidence bar."

The framework can assess:

- An indication with mostly unpopulated PICOs.
- A broad multi-PICO scope combining direct and indirect evidence.
- A focused PICO supported by a randomised trial.

The standard is not that every dossier must contain the same evidence design. The Emerging standard is that the **availability, applicability and uncertainty of the comparative evidence will be made visible for every PICO**.

PICO coverage may become a performance measure.

Tovorafenib shows the consequence of **evidence generation** that addresses only a fraction of the consolidated scope.

Tarlatamab shows that **broad PICO coverage** is possible but may require multiple comparative methods whose validity must be defended separately.

Lurbinectedin shows the advantage of alignment between the **regulatory trial** and the **assessment question**, while also demonstrating that direct evidence does not remove risks related to open-label design, outcome measurement or missing outcomes.

JCAs do not remove uncertainty but make it transparent.

Across all three reports, **uncertainty arises from different sources**:

- Absence of comparative data.
- Reliance on unanchored comparisons.
- Limited overlap and reduced effective sample size.
- Cross-trial heterogeneity, risk of bias, and outcome maturity.
- Missing or incompletely reported outcomes.
- Limited subgroup evidence.

This is the real value of the process. The **JCA does not force uncertainty into a single benefit rating. It creates a common, structured account of what is known, what is not known and why.**

SECTION 2

HEOR & Market Access Insights from the Second and Third EU JCA Reports

Understanding how broader evidence packages and remaining uncertainties shape national HTA and reimbursement decisions.

July 2026

Contrasting comparative evidence challenges from the second and third JCAs

The publication on 8 July 2026 of two further EU Joint Clinical Assessment reports, covering **tarlatamab (Imdylltra®, Amgen)** and **lurbinectedin (Zepzelca®, PharmaMar)**, provides an early but important indication of how the **EU HTA Regulation** is being **implemented in practice**.

Although the assessments concern the same disease area, they illustrate very different evidence challenges.

Tarlatamab

For tarlatamab, the assessment scope included four patient populations and **seven PICOs**, reflecting differences in treatment-free or recurrence-free intervals and the comparators considered relevant across Member States. The evidence package therefore had to **combine direct randomised evidence** against topotecan with **indirect comparisons** for several other comparators.

This creates familiar but important HTA challenges:

- Whether the available studies are sufficiently comparable to support indirect treatment comparisons
- Whether all effect modifiers can be adequately adjusted for
- How reduced effective sample sizes and incomplete covariate information affect confidence in matching-adjusted analyses
- How decision-makers should interpret outcomes when multiplicity is not controlled
- How to address PICOs for which safety, subgroup or sufficiently reliable comparative-effectiveness evidence remains limited

The report itself notes important limitations across parts of the indirect evidence base, including difficulties assessing **network consistency**, **missing requested analyses** and results that require **cautious interpretation**.

Lurbinectedin

The lurbinectedin assessment presents a different picture. It addressed one population and **one PICO**: lurbinectedin plus atezolizumab compared with atezolizumab alone as maintenance treatment after first-line induction therapy. The evidence was based on the open-label IMforte randomised controlled trial.

Direct comparative evidence does not eliminate uncertainty:

The apparently simpler decision problem does not eliminate uncertainty. The assessment identified a high risk of bias for several outcomes, including patient-reported outcomes and safety outcomes, while some outcomes requested in the assessment scope such as PFS2 were not available.

ANSEA
YOUR ACCESS PARTNER

Early lessons for HEOR and market access

1. The breadth of the EU assessment scope may be as important as the pivotal trial itself.

A trial may provide **robust evidence** for one core comparison but still leave important Member State comparators or subpopulations dependent on **indirect or incomplete evidence**.

2. JCA does not remove uncertainty — it makes the sources of uncertainty more visible and more consistently documented.

Limitations relating to **indirectness**, **risk of bias**, **outcome maturity**, **missing data** and **subgroup evidence** will remain highly relevant when Member States proceed to national appraisal.

3. National HEOR remains essential, but its starting point is changing.

The JCA provides a shared assessment of **relative clinical effects**. It does not assess cost-effectiveness, budget impact, affordability or overall value. Those questions remain **national**, together with the need to account for local epidemiology, treatment pathways, resource use, costs and decision criteria.

The practical implication is that manufacturers will need an evidence strategy that works at two connected levels: A clinically robust and sufficiently broad evidence package for the EU JCA.

Country-specific economic and decision-analytic evidence that translates the JCA findings and its uncertainties into national reimbursement contexts.

For HEOR teams, the key task will not simply be to reuse the JCA results in economic models. It will be to understand which relative-effect estimates are sufficiently robust for modelling, which require scenario analysis, and which evidence gaps may materially affect national conclusions on value.

One of the **central implementation challenges** for EU HTA will be the translation of a common clinical assessment into heterogeneous national economic and reimbursement decisions.

SECTION 3

In-Depth Review of the First EU JCA Report

Examining what the first EU Joint Clinical Assessment reveals about comparative evidence, uncertainty, and future submissions.

July 2026

ANSEA
YOUR ACCESS PARTNER

Evidence gaps and uncertainty in the first EU JCA

On 9 June 2026, the European Commission published the first-ever Joint Clinical Assessment under the EU HTA Regulation: **tovorafenib (Ojemda®, Ipsen)** for previously-treated paediatric low-grade glioma, assessed by NCPE (Ireland) with IQWiG (Germany) as co-assessor.

We read the full summary report. Here's our HEOR/HTA read on what actually happened, beyond the "milestone" headlines.

01

The scope was ambitious. The evidence was not.

The assessment scope defined 3 patient populations and **8 PICOs**. Comparative data reached the report for exactly one — PICO 5 (BRAF V600E, >1 year), tovorafenib vs. dabrafenib + trametinib. PICOs 1–4, 6 and 8 had no comparator data submitted; PICO 7's data were excluded for insufficient information on the comparator study. That single populated PICO covers only a **minority of the claimed indication**.

02

One PICO, one unanchored MAIC, and a very small number.

The **pivotal FIREFLY-1** is a **single-arm**, non-comparative phase 2 study — so no direct comparison and no connected network were possible. The only available comparison was an **unanchored MAIC**, the weakest tier of comparative evidence. After matching, the effective sample size ranged from just 5.81 to 14.26 — a 34–52% reduction from the original — driving wide confidence intervals and flagging possible poor covariate overlap.

03

"Major uncertainties" is not a footnote here — it's the finding.

The assessors were unusually direct: **residual confounding** of unknown magnitude and direction, unadjusted prognostic/effect-modifying variables (histology, tumour location, prior chemotherapy), population differences that couldn't be corrected without IPD, and a manufacturer sensitivity analysis excluded outright for methodological errors. **Effect estimates**, should not necessarily be read as causal.

04

The safety signal that will travel.

The one comparison that reached nominal significance was **unfavourable: severe AEs (Grade ≥3)** at an odds ratio of 12.65 (2.30–69.58) for tovorafenib vs. the active comparator. Uncertain methodology, yes — but it's a finding **national payers** will not ignore.

ANSEA
YOUR ACCESS PARTNER

Key lessons from the first EU JCA

1. The JCA did its job.

JCA did not grade the drug — it transparently and rigorously documented how little **comparative evidence** exists to grade it. That is the process working as designed.

2. The clinical question ≠ the national perspective

The JCA is now the shared clinical foundation for 27 markets — but G-BA, HAS, NICE and others will each **re-interpret this same limited base** against their own comparators, endpoint standards, and (crucially) the economic evidence the JCA never touches.

3. The evidence bar is now visible — and it's high

For orphan and biomarker-defined indications built on **single-arm data**, this report is the clearest signal yet: robust PICO anticipation, early ITC planning, RWE strategy, and Joint Scientific Consultation are no longer "nice to have." They are essential components of a **high-quality JCA dossier**.

The first JCA didn't lower the bar for innovative therapies in difficult indications. It made the bar impossible to ignore. The manufacturers who internalise that now — at the evidence-generation stage, not at submission — will be the ones who navigate it.

With the evidence bar now visible,
early preparation makes all the difference

ANSEA
YOUR ACCESS PARTNER

ANSEA Insights are about drawing conclusions that offer perspective on key healthcare system shifts, clarifying what they mean for stakeholders, and translating them into actionable guidance.

Healthcare Perspective | **Strategic Relevance** | **Actionable Insights**

GET IN TOUCH

ANSEA ASIA OFFICE:
ANSEA Consultants Pte Ltd

151 Chin Swee Road,
#07-12 Singapore 169876

Email:
info@anseaconsulting.com

Telephone:
+65 69566164

ANSEA EUROPE OFFICE
ANSEA AG

Im Singeisenhof 9,
4125 Riehen, Switzerland

Email:
info@anseaconsulting.com

Telephone:
+41 61 5087332

FOLLOW ANSEA

Stay connected with ANSEA for the latest insights, best practices, and updates across healthcare access and affordability.