payers

Leonardo Symphony, every part is a masterpiece.

How HTA bodies navigate uncertainty, evidence gaps and diverging perspectives

From PICO to assessment report

From first wave to future practice: learning from early Joint Clinical Assessment procedures

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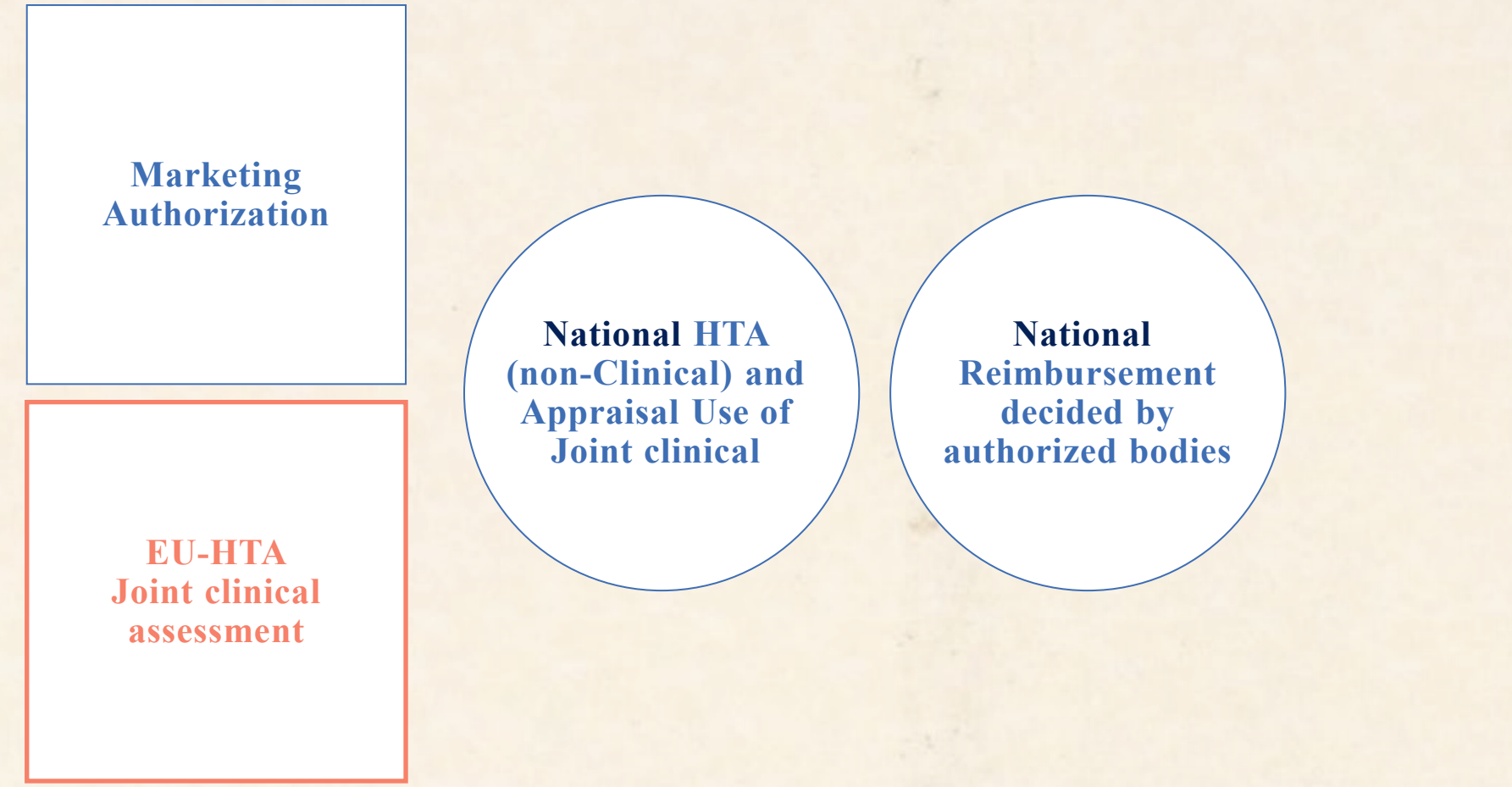
Evidence base: all JCA documents published up to July 2026

LEONARD SYMPHONY
combining what others keep apart.

European access system

(today)

- tomorrow -




Marketing
Authorization


HTA

Marketing Authorisation & HTA

Marketing Authorisation – binary decision + SmPC

Does drug X work? Do benefits outweigh risks?

- → Assessment of effect direction
- → Trial defines the question; SAP prospectively binding
- → acceptance of surrogate endpoints, PRO and safety supportive
- → Time-to-event: Hypothetical estimand, censoring at next therapy
- → Indirect comparisons rarely decision-relevant, rather for context
- → Weighed: unmet need, rarity, innovation, uncertainty

HTA – descriptive report, national appraisal

Is X better than current standard?

- → Assessment of effect magnitude
- → PICO defines it ex post; several PICOs per product
- → Single-arm data are not reported
- → Relative effects also for safety and PRO
- → Treatment-policy estimand explicitly requested
- → ITC as themethodological core
- → Unmet need, rarity, innovation: not weighed

STATUS

Where we stand: the first wave in numbers

3

JCA reports published

Tovorafenib 9 Jun
Tarlatamab + Lurbinectedin 8 Jul

2

discontinued — non-compliant dossier

Catequentinib, Tacquell
both 22 Jun 2026, Art. 10(5)

1

discontinued — MAA withdrawn

Sasanlimab, 13 Feb 2026
not a JCA failure

14

procedures ongoing

4 ATMPs · 1 accelerated
2 variations to existing MA

Onasemnogene abeparvovec (intrathecal): evaluated nationally prior to JCA publication

Of five completed procedures, two produced no assessment at all — and they failed on dossier compliance, not on methodology.

Source: HTA Secretariat lists of ongoing, completed and discontinued JCAs (extracted 8 July 2026)

How the HTACG actually works — one real timeline

Tovorafenib (JCA-MP-2024-06): 15 months from scope input to publication

1 · Scope
Mar – Jun 2025

- Member States submit PICO input
- Consolidated proposal to clinical experts and patients/carers
- Assessment scope issued to the developer

2 · Dossier
Sep – Dec 2025

- Dossier V0.1 submitted
- Two Commission requests under Art. 10(5)
- Dossier confirmed at V0.2

3 · Assessment
Dec 2025 – Apr 2026

- Assessor + co-assessor draft the report
- JCA Subgroup review
- Factual accuracy check by the developer
- Second expert consultation

4 · Adoption
Apr – Jun 2026

- HTACG endorsement 30 Apr
- Commission procedural review 18 May
- Publication 9 Jun 2026

Who decides The assessor pair drafts — the Member states, JCA Subgroup and the HTACG own the result.

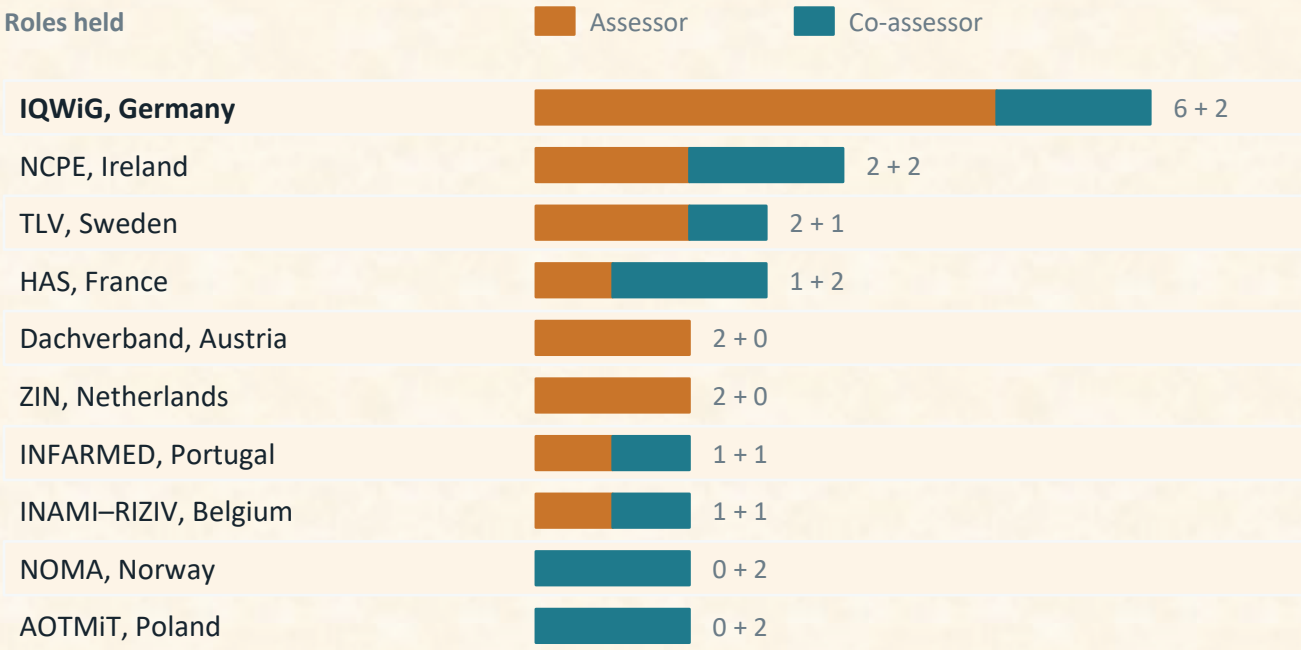
The bottleneck:

- Scope-to-dossier and
- the Commission request loop,
- assessment of requests from applicants on data considered by them to be commercially confidential
- not the assessment itself.

Source: JCA report Tovorafenib, Table 2 (procedural steps)

Who writes the report — and how concentrated is that?

Assessor pairings across all five completed procedures



Product	Assessor	Co-assessor	PICOs	Outcome
Tovorafenib	NCPE, Ireland	IQWiG, Germany	8	Published
Lurbinectedin	IQWiG, Germany	INFARMED, Portugal	1	Published
Tarlatamab	IQWiG, Germany	NCPHP, Hungary	7	Published
Catequentinib	TLV, Sweden	NOMA, Norway	≥ 4	Discontinued
Tacquell	HAS, France	AOTMiT, Poland	≥ 13	Discontinued

Plus 8 institutions appointed exactly once: DMC Denmark, G-BA Germany, NCPHP Hungary, SQHCA Slovenia, SBU Sweden, AEMPS Spain, AIHTA Austria, NIHO Slovakia — six of them only as co-assessor. 18 institutions from 15 countries have taken a role.

Six countries take an assessor seat for the first time in the ongoing wave — Austria, Portugal, Denmark, Belgium, the Netherlands, and Germany's G-BA alongside IQWiG. Four of those procedures are ATMPs and one is the first accelerated assessment. The convergence question becomes answerable only once these reports land.

Will JCA reports differ depending on who writes them?

What forces convergence

- One binding report template (Implementing Reg. 2024/1381, Annex)
- HTACG methodological guidelines the report must take into account
- Article 9: no value judgements, no conclusions on added benefit
- JCA Subgroup review before finalisation, then endorsement by all Member States
- Method sections diverge with evidence type — RCT-based reports carry outcome-level RoB tables, ITC-based reports do not

Where divergence is already visible

- The Irish-led report argues quantitatively — E-values, shifted null hypotheses, estimand framing
- Different thresholds for what still gets reported versus what is dropped from the report
- Different verbal registers for the same finding: 'highly uncertain' + narrative catalogue of specific uncertainties versus 'certainty is very low'

Reports converge on ***which*** uncertainties are identified, and diverge on how they are weighted and worded.
Because Article 9 forbids a conclusion, that wording ***is*** the signal national bodies will read.

Defining the PICO is a clinical negotiation, not a merge

Tarlatamab (JCA-MP-2024-17): 10 PICOs across 5 populations in the consolidated proposal → 7 PICOs across 4 populations in the final scope

What experts said about the proposed scope

Clinical expert	"EpiCO is very obsolete chemotherapy"
Clinical expert	"Comparator is not appropriate" — a platinum-eligible patient cannot sit in a topotecan arm
Clinical expert	The 3-month platinum-sensitivity cut-off does not match practice; 6 months does
Carer	"Are there enough patients to fill all these groups?"

Three lessons for scoping

- Expert input changes the scope- architecture materially — three PICOs disappeared, populations and comparators were re-specified.
- Population definitions fail on operational detail: performance status, treatment-free interval, prior lines.
- Nobody asks the feasibility question early enough: is there evidence that could ever answer this PICO?

Consequence: scope consolidation currently optimises for clinical completeness.

Source: JCA report Tarlatamab, Appendix A (expert and stakeholder input on the consolidated assessment scope proposal)

EVIDENCE GAPS

From scope to report: how much of the PICO set survives?

Tovorafenib — 3 populations, 8 research questions, one surviving comparison

8

PICOs in scope

3 populations, single-comparator and individualised-treatment arms

2

PICOs with comparator data

For 6 PICOs the developer identified no study covering the comparator

1

PICO in the final report

The second MAIC was excluded — too little information on the comparator study

The gap that nobody sees coming

Evidence is not only lost where a PICO has no comparator. It is lost silently, outcome by outcome, when definitions do not match: response assessed by RANO-LGG including the minor-response category cannot be compared with modified RANO-LGG excluding it. The assessors judged this expected to bias the comparison in the product's favour — and the alternative definition they requested was never supplied.

Same pattern in Tarlatamab: for most outcomes requested in the scope, no relative effect estimate could be reported at all

Two procedures never reached a report

Both stopped on 22 June 2026 after the second Commission request under Article 10(5)

Catequentinib (negative opinion 23. July)

JCA-MP-2024-03

Developer	Advenchen Laboratories, LLC (US)
Indications	Synovial sarcoma and leiomyosarcoma
Assessors	TLV, Sweden · NOMA, Norway
MAA validated	17 July 2025
Updated dossier V0.2	9 April 2026
List of missing items	8 May 2026

Tacquell (negative opinion 25. June)

JCA-MP-2025-02

Developer	Netherlands Cancer Institute (academic)
Indication	Melanoma — autologous TIL therapy, ATMP
Assessors	HAS, France · AOTMiT, Poland
MAA validated	27 March 2025
PICOs in scope	at least 13
List of missing items	13 February 2026

Note who these developers are.

A small US biotech and an academic cancer institute

What was actually missing — and what it was not

The Commission's published lists of missing information, grouped by requirement

1 Completeness of the evidence base

- Catequentinib, synovial sarcoma: no data or analyses on relative effectiveness or safety for any PICO
- **Tacquell: no information retrieval at all for five of the PICOs in scope**
- **No systematic search of HTA agency websites or patient registries**

2 Transparency of methods

- **No feasibility assessment for possible indirect comparisons, and no justification for omitting one**
- **Deliberate decision not to search non-randomised studies, left unexplained**
- **No list of excluded studies with reasons for exclusion**

3 Presentation of results

- Event proportions per arm instead of relative effect measures; no Kaplan-Meier curves
- **PICOs not reproduced in the format issued in the Commission's first request**
- **Unexplained omission of entire results sections**

4 Underlying documentation

- No programming code for the unanchored external comparison
- No source material per signalling question of the risk-of-bias tool
- A central claim about manufacturing non-comparability left undocumented

Not one item on either list is a methodological disagreement. Every one is completeness, transparency, documentation or template compliance. The Article 10(5) gate is binary — and roughly twelve months of assessor capacity were spent on each before it closed.

The JCA report is a technical document

Article 9 permits no value judgement and no conclusion. Three places where that constraint is already under pressure

The narrative is annexed

A carer's account of her daughter — diagnosed at nine months, five lines of therapy, quality of life weighed against growth suppression — is printed verbatim in the appendix of the Tovorafenib report.

Rarity and lived experience enter the file. The template offers them no place in the assessment.

The summary cannot exist

- Reviewing the Tarlatamab draft, a carer asks for one overall summary across the seven PICOs: where is the evidence strong, where uncertain, what are the trade-offs for shared decision-making.

That is precisely the document Article 9 forbids the assessors to write.

The accuracy check absorbs the dissent

- Developers use the factual accuracy check to argue interpretation and fairness — that the guidance cited against them post-dates their dossier, that two sections of the template contradict each other.

Most comments come back as outside the scope of the factual accuracy check.

The consequence. No forum in the procedure is designed to hear a disagreement about interpretation — only about facts. As orphan products fill the pipeline from 2028, that is where the pressure will build.

Source: JCA reports Tovorafenib and Tarlatamab, Appendix A; factual accuracy check annexes (Ipsen, Amgen)

What follows — the pipeline is getting harder

14 ongoing procedures as of July 2026

Already in the queue

- 4 ATMPs, including gene therapies and a CAR-T
- The first accelerated assessment (Lunsotogene parvec)
- The first JCAs on variations to an existing marketing authorisation
- Assessor roles spreading to AT, DK, SI, ES, BE, NL

The scale-up ahead

- 2028: all orphan medicinal products
- 2030: all medicinal products, plus medical device JCAs
- No practical experience yet with the update mechanism

Open questions

- Scope answerability — PICOs no evidence can address
- Single-arm and registry evidence in the ATMP wave
- Support for developers outside the industrial mainstream
- How national bodies actually use a report with no conclusion

Source: HTA Secretariat list of ongoing JCAs (extracted 8 July 2026)

Three things the first wave has taught us

01 The procedure works better than the dossiers do

- Timelines held and are shortening — 50 days from EC decision to publication, then 40.
- Two of five procedures still ended without any assessment, and both failed on completeness and transparency, not on method.
- The gap is not data, it is the reasoning about data — can a reader reconstruct why a study, an outcome or an indirect comparison is absent? Today, usually not.

02 A PICO without an answer is not a wasted PICO

- One PICO or thirteen matters less than whether comparator data and comparable outcome definitions exist.
- An unanswered PICO still informs: absence of comparator evidence is a finding, not a gap in the process
- Filter the scope by feasibility and the developer's evidence base is not the HTAR was built for

03 Divergence sits in national appraisal, not in the assessor team

- The reports do not diverge much by who drafts them. National appraisal will.
- Some systems — Germany among them — rarely rely on indirect comparisons anyway, because the residual uncertainty usually disqualifies them; a missing or weak ITC changes little.
- Other systems need a (quantified) relative effect to reach a reimbursement or pricing decision at all.
- The same report is therefore worth very different things depending on the national decision rule — and Article 9 places that translation step entirely outside the JCA..

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