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Access in all areas? A round-up of developments in market access and health technology assessment: first Joint Clinical Assessment report released

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The first Joint Clinical Assessment (JCA) report has been completed. In this update we examine what this inaugural report reveals in practice and draw out the implications for manufacturers.

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The arrival of the first endorsed Joint Clinical Assessment (JCA) report is a milestone for the EU HTA framework established under Regulation (EU) 2021/2282, which entered into application on 12 January 2025 with an initial scope covering new oncology active substances and advanced therapy medicinal products (ATMPs) routed through the European Medicines Agency's (EMA) centralized procedure [1–3]. Tovorafenib (Ojemda™) for relapsed or refractory pediatric low-grade glioma was endorsed by the Member State Coordination Group on Health Technology Assessment (HTACG) on 30 April 2026 [4]. Ireland's National Centre for Pharmacoeconomics acted as assessor and Germany's Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, (IQWiG) as co-assessor.

Tovorafenib is a type II RAF kinase inhibitor with orphan designation, indicated in relapsed or refractory pediatric low-grade glioma harboring a BRAF fusion, rearrangement or V600 mutation in patients who have received at least one prior systemic therapy. Its approval rests on FIREFLY-1, a non-comparative, open-label Phase II trial whose pivotal cohort enrolled 77 patients. The European marketing authorization is held by Ipsen, while the pivotal trial was sponsored by Day One Biopharmaceuticals.

The assessment scope subdivided the claimed indication into three populations and specified eight separate research questions in the PICO framework. Population 1 (the full claimed indication) generated PICOs 1 to 4; population 2 (BRAF V600E mutation in patients older than 1 year) generated PICOs 5 and 6; and population 3 (BRAF fusion, rearrangement, or V600 non-E mutation) generated PICOs 7 and 8. The comparators ranged from named single agents and combinations – dabrafenib plus trametinib, trametinib alone, carboplatin plus vincristine, vinblastine – to 'individualized treatment' baskets comprising multiple chemotherapy and targeted options whose selection depends on individual patient characteristics.

Eight PICOs is by the standards of the debate that has built up around the JCA, a relatively contained scope. Industry analyses have repeatedly warned that PICO counts could run to thirty or more depending on the indication [2], and an illustrative scoping by the Member State Coordination Group of a single immuno-oncology product for hepatocellular carcinoma produced thirteen PICOs [5]. The recurring concern has been that member states will request divergent comparators and that consolidation will be opaque and unpredictable. Against that backdrop, eight PICOs for a rare pediatric tumor looks relatively modest.

Of the eight PICOs, the health technology developer submitted comparative data for only two, PICO 5 and PICO 7. For PICO 5 (the BRAF V600E subpopulation), an unanchored matching-adjusted indirect comparison

(MAIC) of tovorafenib against dabrafenib plus trametinib was provided. For PICO 7, an unanchored MAIC against trametinib was submitted but was ultimately excluded from the assessment because the assessors judged that there was insufficient information about the comparator study to evaluate it. The remaining five questions – PICOs 1 to 4, 6 and 8 – could not be addressed at all, because no comparator data in the relevant relapsed/refractory, BRAF-altered pediatric population were available. The developer had attempted to construct external control arms from data acquired outside clinical studies, but a feasibility exercise concluded that no fit-for-purpose source existed; one US database initially looked promising but was deemed unsuitable owing to too few patients with BRAF alterations and inadequate follow-up in the relapsed/refractory setting.

The reasons PICO 7 fell away are instructive. Its comparator was trametinib, and the only evidence available for that arm came from a trial (TRAM-01) reported solely in conference abstracts rather than in a full publication. HTACG methods guidance is explicit that studies documented only by abstracts, posters or presentations should be excluded, because there is too little detail to verify how the results were produced; the developer argued that the rarity of the disease justified an exception, but the assessors declined. Compounding this, the abstracts reported only a single patient characteristic – age – so age was the only variable the indirect comparison could adjust for. On both counts the comparison was judged uninterpretable and set aside.

The overall consequence is striking and worth stating: the entire comparative assessment of a product approved across a broad pediatric indication ultimately rested on a single PICO.

The assessors identified a series of major uncertainties for the PICO 5 MAIC. Reliable estimation from an unanchored MAIC requires adjustment for all prognostic and effect-modifying variables, sufficient overlap between the populations, and consistent reporting across studies – assumptions the report judged were not met. FIREFLY-1 and the comparator publication (a small, single-arm Phase I/IIa pediatric study of dabrafenib plus trametinib in relapsed or refractory BRAF V600E-mutant tumors [6]) reported few baseline characteristics in common and several identified confounders, including histology, primary tumor location and prior chemotherapy, could not be adjusted for. The underlying numbers were very small: the relevant V600E subpopulation for tovorafenib amounted to a dozen patients, and after weighting the effective sample size for the principal analysis set fell to 5.81, a reduction of more than half, providing a heightened risk that a single influential observation could drive any results.

Within these limitations, it is worth discussing what the comparative assessment actually showed. Overall survival could not be estimated at all. The only outcome reaching nominal statistical significance was progression-free survival, and it favored the comparator. Objective response was inconclusive. There were no comparative data at all on health-related quality of life, disease symptoms or symptomatic disease control – arguably the outcomes that matter most to a child with a brain tumor and their family. On the descriptive safety data, tovorafenib showed numerically more serious and severe adverse events than the comparator. In short, the first JCA delivered a harmonized assessment whose substance amounts to insufficient evidence of added benefit, with what little (highly uncertain) signal existing tilting unfavorably.

What does this mean for Ojemda™ and, more broadly, for HTA? It matters that a JCA report issues no overall verdict. Unlike the German added-benefit ratings on which much of its method is modelled, the JCA presents the relative effects and the certainty of the evidence outcome by outcome and stops there, leaving each member state to draw its own conclusion for national pricing and reimbursement. The message member states receive here is dominated by uncertainty: no demonstrated advantage on any outcome, a progression-free survival signal that on its face runs against the product, and silence on quality of life and symptoms. Yet the limitations are so pervasive – small numbers, an unanchored comparison – that the report cannot conclude the drug is inferior. The practical risk for the manufacturer is that some payers read "no proven added benefit" as grounds for a low price, even though tovorafenib is the first targeted therapy approved in this setting and meets a genuine unmet need in children. That is the central tension this first report exposes: for a rare pediatric cancer approved on uncontrolled data, a relative-effectiveness assessment may be structurally unable to demonstrate the benefit that regulators and clinicians nonetheless recognize.

Several lessons follow for companies bringing oncology products and ATMPs through this framework. The first is that PICO proliferation is not, on its own, the binding constraint; the binding constraint is the availability of usable comparative evidence for each question. A scope of only eight PICOs still left seven unanswered here. Companies should map, as early as trial design, which PICOs their evidence can realistically support and which they cannot, and should be candid about the proportion of a likely scope that will go unaddressed.

The second is that single-arm assets are structurally disadvantaged under a relative-effectiveness framework and require a deliberate indirect comparison strategy built early and to a high standard. That means securing access to

comparator individual patient data where possible, pre-specifying the estimand, conducting rigorous prognostic and effect-modifier identification, and planning credible sensitivity analyses. The tovorafenib report shows that an under-powered MAIC, however unavoidable given the rarity of the disease, will be heavily discounted. Where external control arms are contemplated, the feasibility work should be done years ahead, not at the point of submission.

The third is to anticipate IQWiG-grade methodological scrutiny regardless of which member states assess a given product, and to resource the JCA dossier accordingly. Finally, because the JCA confers no benefit rating of its own, manufacturers must be ready to carry the value argument into each national process; a JCA dominated by uncertainty does not foreclose access, but it shifts the burden squarely back onto country-level dossiers and price negotiations.

The tovorafenib report functions as a stress test of the new framework and of the manufacturers' preparedness, and it sends mixed signals. Procedurally, the system can deliver a JCA. Substantively, it sets a high bar for comparative evidence – a bar that the very products in the current scope, rare-disease oncology agents and ATMPs often approved on uncontrolled data, are least equipped to clear. As further assessments conclude over the coming year, the questions to watch are whether the framework's clinical conclusions meaningfully inform national reimbursement timelines or simply add a harmonized layer of uncertainty on top of existing national processes, and whether the methods applied can accommodate the realities of rare and pediatric evidence generation without diluting their rigor. For manufacturers, the message from the first report is unambiguous: JCA readiness is a multi-year evidence-strategy problem to be solved at the point of trial design, not a documentation exercise to be completed after approval.

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