Review of Surrogate Endpoints' Acceptance Trends in German HTA and Implications for EU Joint Clinical Assessment

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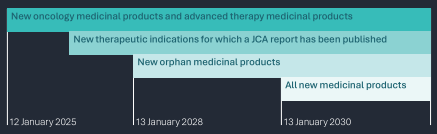
Elisa Capobianco[1], Inês Oliveira[1], Anna McCormick[1], Stephen Hall[1], Gerdi Strydom[1]

[1]Valid Insight (Part of the Bioscript Group), Macclesfield, Cheshire, UK

Introduction and objectives

The Joint Clinical Assessment (JCA) aims to harmonise clinical evidence evaluation across European Union (EU), Member States, and has started with a phased approach in early 2025, with evaluations of new oncology medicines and advanced therapy medicinal products (Fig 1).[1,2]

Fig 1. **Staggered approach toward all medicinal products seeking a centralised Marketing Authorisation[2]**



A Guidance on outcomes for the JCA published in June 2024, provided flexibility regarding how outcomes should be measured and analysed, including the use of surrogate endpoints (SEs) when mature clinical outcomes are unavailable.[3]

While SEs can expedite access to innovative therapies, their acceptance varies widely due to limited validation, which may affect perceived clinical benefit and reimbursement decisions. In Germany, the Federal Joint Committee (Gemeinsamer Bundesausschuss, G-BA) applies strict validation criteria, potentially influencing patient access in line with the JCA framework.

This study investigates how SEs have been assessed in Germany's early benefit assessments (EBAs) since the implementation of the (Arzneimittelmarkt-Neuordnungsgesetz, "Pharmaceuticals Market Reorganization Act") law in 2011. It aims to identify patterns in acceptance, understand decision rationales, and explore implications for pharmaceutical companies under the evolving EU JCA framework.

Methods

Guidelines and official positions on SEs from the European Commission, G-BA, and EUnetHTA (European Network for Health Technology Assessment), were analysed to compare surrogacy criteria.[1, 5, 8]

A targeted search of the G-BA resolutions' database was conducted to capture all G-BA EBAs that mentioned SEs. G-BA EBAs between January 2020 and September 2025 were further analysed to understand the surrogacy acceptance, therapy area, patient population, and resulting benefit assessment.[6]

Results

Assessments made by the G-BA since 2020

The G-BA has completed 1,139 EBAs for 507 medicinal products since the introduction of the AMNOG law in 2011. Since 2020, G-BA has completed 706 EBAs for 328 medicinal products. When considering the highest benefit rating per product, 1.7% offered a major additional benefit, 13.3% a considerable benefit, and 13.9% a minor benefit. Another 19.3% were rated as having a non-quantifiable benefit. Nearly half—49.4%—were judged to provide no additional benefit, while 0.1% were assessed as offering less benefit than the comparator therapy (Fig 2).[4]

Validation of surrogate endpoints by the G-BA

The G-BA requires high-certainty evidence from validation studies to accept SEs, with conclusions about patient-relevant outcomes based on the reliability of the data and the strength of correlation between endpoints. Surrogates must be statistically validated, and only those with strong correlation and robust study design may support proof or indication of benefit. [5]

G-BA assessments with surrogate endpoints

Since 2020, only 13 out of 109 G-BA EBAs that referred to SEs accepted an SE as patient-relevant, sufficiently validated, and incorporated the data into the clinical evaluation. The SEs that were accepted include: HbA1c change, oral glucocorticoid reduction, virological response, CD4 cell count, sustained virological response, and estimated glomerular filtration rate (eGFR) when used to define CKD (Chronic kidney disease) stage 4/5 or end-stage renal disease.[6]

In 37.6% of assessments, validation of the SEs was not available, and in 14.7% there was insufficient evidence to support the claim (see Fig. 3). No trend was identified between acceptance of SEs and the level of added benefit.[6]

Ongoing assessments by the EU JCA

Currently, there are 9 medicinal products undergoing a JCA, for which the EMA has validated their Marketing Authorisation application. The assessors and co-assessors have been appointed for these products and notably, IQWiG (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, "Institute for Quality and Efficiency in Health Care") from Germany will be the main assessor for 3 of these products and will serve as a co-assessor for one more (Fig 4).[7]

Validation of surrogate endpoints by the EU JCA

For the assessment of clinical outcomes, the HTA CG (Member State Coordination Group on HTA) Guidance on outcomes for JCA identifies three levels of evidence for surrogacy:[3]

Level 1: Strongest evidence from meta-analyses of randomised trials showing a clear correlation between treatment effects on surrogate and patient-centred outcomes, ideally with a correlation ≥ 0.85.

Level 2: Moderate evidence from interventional, epidemiological, or observational studies showing consistent associations.

Level 3: Weakest evidence based on biological plausibility from disease understanding or pathophysiological studies.

Although there is no universally agreed threshold for validating SEs, a correlation of ≥ 0.85 was considered strong. Assessors are encouraged to use meta-analytic methods and the surrogate threshold effect to support decision-making by estimating the minimum surrogate effect needed to decide whether improvements in the surrogate outcome are likely to lead to real benefits for patients.[3]

Fig 2. **Distribution of G-BA resolution per added benefit outcomes since 2020 (adapted)[5]**

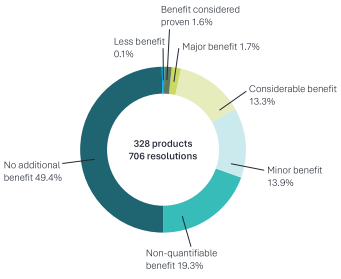


Fig 3. **Distribution of G-BA justifications for surrogate endpoint decisions across all assessed resolutions[6]**

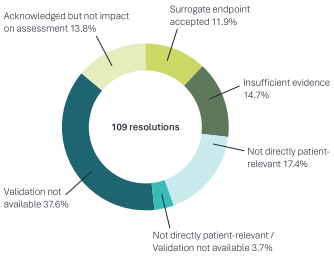


Fig 4. **Overview of active JCAs (as of 30 September 2025), highlighting IQWiG, Germany contributions**

International non-proprietary name	Indication - Summary	Assessor	Co-assessor
Autologous melanoma-derived tumor infiltrating lymphocytes, ex vivo-expanded	Treatment of melanoma		
Tovorafenib	Treatment of paediatric low-grade glioma (LGG)		
Sasanlimab	Treatment of bladder cancer		
Onasemnogene abeparvovec	Treatment of 5q spinal muscular atrophy (SMA)		
Lurbinectedin	Maintenance treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)		
Camizestrant	Treatment of adults with locally advanced or metastatic breast cancer		
Tarlatamab	Treatment of extensive-stage small cell lung cancer		
Catequentinib	Treatment of synovial sarcoma or leiomyosarcoma		
Senaparib	Maintenance treatment of advanced epithelial high-grade ovarian, fallopian tube or primary peritoneal cancer		

Discussion and conclusion

Despite their frequent use in clinical development, only 13 out of 109 EBAs that addressed SEs (11.9%) were accepted in resolutions by the G-BA over the past five years. This low acceptance rate is primarily due to limited validation, a lack of demonstrated patient relevance, and the fact that their acceptance does not consistently correlate with higher ratings of added benefit.

Certain SEs related to oncology, such as progression-free survival and pathological complete remission, have been emphasised in G-BA resolutions as points of contention regarding their relevance to patients, adding uncertainty, especially as the IQWiG will assess three of the current products undergoing JCA. This emphasises the importance of early strategic planning and alignment with HTA expectations to improve submission success across both national and EU frameworks.

While the acceptance of SEs remains a national decision, the JCA guidance outlines three levels of surrogacy evidence, with Germany's IQWiG standards generally corresponding to Level 1 or 2—requiring high reliability and a strong correlation with patient-relevant outcomes.

The limited acceptance of SEs by the G-BA poses a challenge for generation strategies for pharmaceutical companies. To improve outcomes, companies must prioritise robust validation, early engagement with HTA bodies, and clear linking of endpoints to patient-relevant benefits.

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