German HTA Outcomes for Rare Disease Drugs When Orphan Designation Does Not Legally Determine Added Benefit

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INTRODUCTION

BACKGROUND:

- For Germany's health technology assessment (HTA) the AMNOG legislation originally intended to grant automatic added benefit status to rare disease therapies affecting 500 to 1,000 individuals, recognizing the challenges of generating comparative evidence and frequent absence of therapeutic alternatives.
- However, this protection requires formal orphan drug (OD) designation but not all drugs targeting small populations receive OD designation or the G-BA customize the target population to smaller subpopulations, or the protection is lost when a specific revenue exceeds a threshold.

OBJECTIVES:

This study

- evaluated the proportion of drugs meeting OD criteria without OD designation or having lost OD protection,
- analyzed reasons why added benefit was not confirmed.

METHODS

A combined search of the AMNOG-Monitor database (June 1, 2025) and the G-BA website was conducted. Eligible subpopulations were those with still-valid G-BA decisions and without orphan drug protection.

Outcomes were classified as:

1. added benefit confirmed;
2. no added benefit — defined as

- accepted evidence without sufficient clinical relevance,
- rejected evidence,
- no data submitted.

Results were stratified by population size (≤1,000 vs >1,000 patients) and availability of therapeutic alternatives (best supportive care [BSC]/watch & wait (WW) vs active comparator). (BSC is a supportive treatment that alleviate symptoms and improve quality of life).

For cases where the G-BA concluded that "no data" were submitted (indicated with the symbol Ø in resolution documents), additional analyses captured:

- the number of population, intervention, comparator, and outcome (PICO) elements defined,
- the frequency with which companies requested an added benefit, and
- the frequency with which an added benefit was granted for any subpopulation within a dossier.

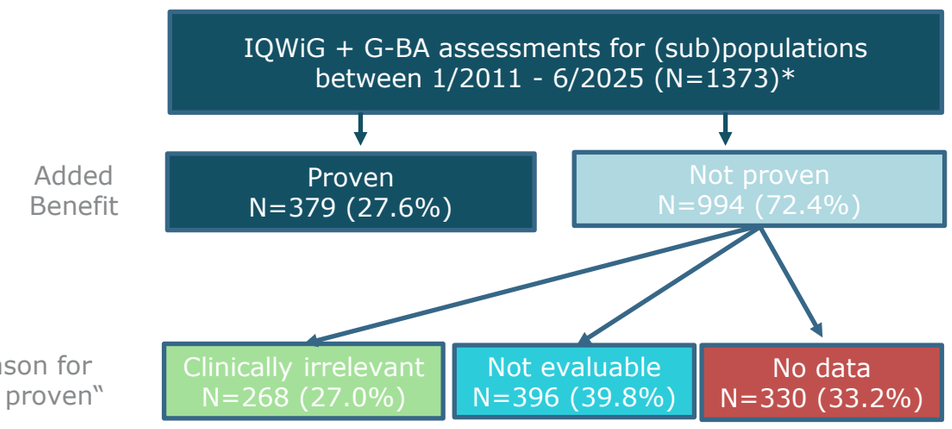
RESULTS

The search identified 1373 assessments of (sub)populations with assigned comparators and evaluation by IQWiG + G-BA. An added benefit was granted in 27.6% of cases. In the remaining 72.4%, the added benefit was not proven:

- evidence was accepted but judged clinically irrelevant in 27.0%,
- rejected in 39.8%, or
- not submitted in 33.2% (Figure 1).

Stratified analyses showed the following patterns (Table 1):

- The added benefit rate decreased to 21.7% when the German target population was <1,000 patients.
- The added benefit rate increased to 53.1% when the appropriate comparator was not an active therapy for the underlying disease.



* Without repealed decisions, antibiotics and orphan assessments by G-BA only

Figure 1. Frequency of added benefit and reasons for "not proven" in IQWiG- and G-BA–assessed subpopulations.

Table 1. Added benefit granted by the G-BA by subpopulation size and type of comparator therapy

	Added benefit (n/N (%)	
Overall	379/1373 (27.6%)	
Size of population <1K	112/516 **(21.7%)**	
Size of population >1k	267/857 (31.2%)	
Best Supportive Care	76/143 **(53.1%)**	
Active Comparator	303/1230 (24.6%)	
	<1k patients	>1k patients
Best Supportive Care	44/80 (**55.0%**)	32/63 (50.8%)
Active Comparator	69/571 (12.1%)	234/659 (35.5%)

Data are presented as number of respective assessments/number of total assessments (%). Orphan drugs, antibiotic and repealed decisions were excluded. 1k = 1 kilo = 1000.

Regarding "no data" conclusions by the G-BA (Table 2):

- The rate rose from 33.2% overall to 50.7% in subgroups without available alternatives.
- It further increased to 60.4% when the target population was <1,000 patients.

Table 2. Added benefit not proven where the G-BA concluded "no data" by subpopulation size and type of comparator therapy

	Added benefit not proven (n/N (%) (994/1373 (72,4%)) Proportion of "No data submitted"	
Overall	330/994 (33.2%)	
<1k	132/385 (34.3%)	
>1K	198/609 (32.5%)	
Best Supportive Care	34/67 **(50.7%)**	
Active Comparator	296/927 (31.9%)	
	<1k target population	>1K target population
Best Supportive Care	29/48 **(60.4%)**	5/19 (26.3%)
Active Comparator	103/337 (30.6%)	193/590 (32.7)

Data are presented as number of respective assessments/number of total assessments (%). Orphan drugs, antibiotic and repealed decisions were excluded. 1k = 1 kilo = 1000.

Of the 29 assessments with "no data" and BSC/WW as comparator (<1,000 patients) (Table 2), 19/29 (65.5%) were in oncology. In 24/29 (82.8%), the G-BA defined >1 PICO ("slicing") (Figure 2).

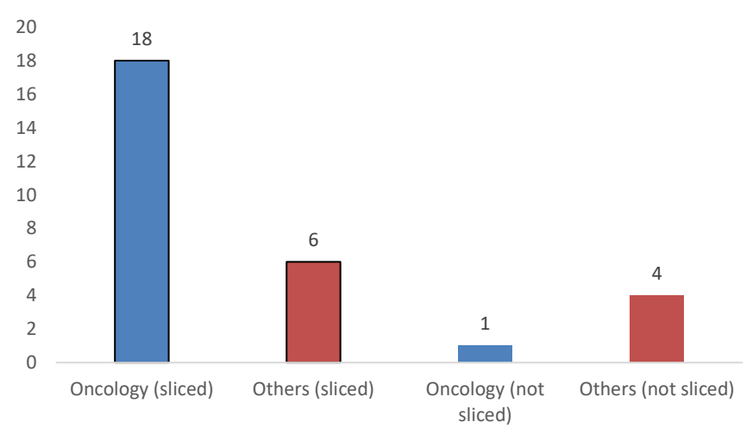


Figure 2. Procedures with BSC as comparator and "no data" (n=29, see Table 2); 24 involved indication "slicing", all populations <1000 patients

To assess consistency between company submissions and G-BA "no data" conclusions (n=29, Table 2), the frequency of company requests for added benefit was analyzed. Companies consistently requested added benefit for the BSC/WW population when only one PICO was defined (5/5 (100%)), but requests dropped substantially with multiple PICOs to 3/24 (12.5%). Overall, companies requested added benefit for 13/24 (54.2%) of PICOs where the company covered the BSC/WW population (Table 3).

Table 3. Added benefit requests in BSC subpopulations with "no data"

	1 PiCO	>1 PICO
Added Benefit requested for BSC/WW	5/5 (100%)	3/24 (12.5%)
Added Benefit requested for all PICOs*	0/5 (0%)	13/24 (54.2%)
Added Benefit not requested for BSC/WW	0/5 (0%)	8/24 (33.3%)

*Added benefit was requested for any or all PICOs where the BSC/WW population was included whether or not data were presented with BSC as comparator.
BSC/WW = Best Supportive Care/Watch & Wait

The G-BA determines the appropriate comparator(s) and defines subpopulations within the indication where necessary (PICOs). In cases with multiple PICOs, an added benefit can be granted for certain subpopulations even when data is insufficient for others, including the BSC population. Table 4 shows added benefit outcomes by dossier (1 vs >1 PICO). In 15/29 (51.3%), evidence against an active comparator was also not sufficient, resulting in no added benefit for all populations within the dossier.

Table 4. Added benefit granted by G-BA within dossiers with 1 vs >1 PICO (BSC/WW "no data" included)

	1 PiCO*	>1 PICO**
Added Benefit Dossier	0/5 (0%)	14/29 (48.3%)
Added Benefit not proven Dossier	5/5 (100%)	15/29 (51.3%)

* Size of population <1,000.
** Size of all populations 0-5100

DISCUSSION

Key Findings:

Small populations generally achieved lower added benefit recognition rates, while assessments with non-active comparators (e.g., best supportive care) achieved higher rates. However, small populations lacking active treatment alternatives experienced disproportionately high "no data" decisions from G-BA, undermining benefit recognition. When G-BA specified non-active comparators, "no data" decisions frequently coincided with multiple PICO-defined subgroups, indicating that fragmented evidence requirements created operational complexity.

Interpretation:

Companies focused on larger populations within multiple PICOs which appears rational given the licensing evidence and pricing implications — 48.3% of the dossiers obtained added benefit based on larger populations, enabling subsequent pricing negotiations. However, since 51.7% of dossiers received no added benefit overall, populations with non-active comparators could be crucial for reducing commercial non-viability risk, including market withdrawals. This pattern is supported by the low rate of companies specifically requesting added benefit for BSC/WW populations (12.5%).
While RCT evidence is typically required by the G-BA, the evidentiary threshold for BSC/WW populations can be lower, i.e. demonstrating a therapeutic response may suffice. Tomeczkowski et al. (2025) demonstrated that the G-BA has previously granted added benefit based on evidence showing disease progression discontinuation from natural history studies, rather than requiring RCTs.[1]

Limitations:

- No temporal trend or methodological change adjustments
- Heterogeneous negative decision rationales by G-BA ("evidence rejected" vs. "clinically irrelevant")

CONCLUSIONS

Smaller populations perform worse in the German HTA although these populations were intended to be protected under AMNOG especially when there is no alternative treatment available.
These populations met orphan drug criteria but either lost orphan protection or could not receive legal orphan drug benefit due to G-BA's subdivision of indications into multiple PICOs. EMA may also deny orphan designation for overly broad diseases (e.g., lung cancer), even when the marketing authorization is restricted to a subpopulation only (e.g., KRAS mutation).

Recommendations:

For G-BA
Reduce "no data" outcomes in small populations without active alternatives by systematically implementing flexible evidence pathways:

- Early scientific advice through the Federal Joint Committee
- Alternative evidence approaches where randomized trials are infeasible, including external controls, real-world evidence, and robust natural history comparisons

For Sponsors
Relying solely on larger subgroups is insufficient. Proactively address BSC subpopulations with credible evidence plans from study initiation:

- Predefined statistical approaches for external/real-world controls
- Feasibility-conscious recruitment strategies
- Documentation designed to meet G-BA scrutiny standards

Early G-BA dialogue and greater acceptance of external controls in BSC settings would enable timely evidence generation for small, high-need populations with limited treatment options.

REFERENCES

1.Tomeczkowski J, Heidbrede T, Eichinger B, Osowski U, Leverkus F, Schmitter S, Dintsios CM. Challenges and Criteria for Single-Arm Trials Leading to an Added Benefit in German Health Technology Assessments. Pharmacoeconomics. 2025 Jul 26. doi: 10.1007/s40273-025-01524-w. Epub ahead of print. PMID: 40715943. https://www.researchgate.net/publication/394028198_Challenges_and_Criteria_for_Single-Arm_Trials_Leading_to_an_Added_Benefit_in_German_Health_Technology_Assessments

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