June 2025

Factors impacting GKV rebates for orphan drugs in Germany

Part 1: Decision analysis using the CRA RADAR database

Background

The European Union (EU) introduced the European Orphan Medicinal Products Regulation (EC) No 141/2000 to encourage the development of treatments for rare diseases which impact a limited population. This regulation provided a framework for orphan drug (OD) designation in the EU, offering incentives such as fee reductions, prolonged market exclusivity and access to specialised assistance during the development process. Twenty-five years later, the data reflect that this regulation has succeeded. Over 200 drugs with orphan designation, intended to treat diseases affecting fewer than 5 in 10,000 people, have been approved by the European Medicines Authority (EMA) since then.

The flip side of developing drugs for very few patients is the expectation of high prices to achieve an appropriate return on investment for drug developers. National authorities responsible for assessment and public funding of medicines acknowledge this in the development of legislation. When Germany introduced AMNOG (Arzneimittelmarkt-Neuordnungsgesetz) in 2011, the two-step process of health technology assessment (HTA) was followed by reimbursement price negotiation, and some exceptions were made for ODs.

The benefit assessment by G-BA (Gemeinsame Bundesausschuss), which all drugs must undergo, acknowledges the benefit of ODs by granting a non-quantitative benefit by default. Only when the annual sales volume exceeds €30 million is a new AMNOG assessment performed on the same scientific grounds as for non-ODs. Reimbursement price negotiations between manufacturers and GKV (Gesetzliche Krankenversicherung, the German statutory health insurance system) are based on rebates on the manufacturer-set list price, without any exceptions for ODs. However, the default ‘non-quantifiable added benefit’ rating ensures a slightly different starting point for drugs expected not to exceed the budgetary threshold at launch.

After 14 years of the AMNOG process, sufficient data are available to analyse its impact on reimbursement prices via GKV rebates for drugs with orphan designation, as well as which factors have had the biggest impact on GKV rebates for ODs.

Introducing RADAR – the RAre Disease Assessment Review database

RADAR is a proprietary CRA database. For this analysis, only German data were used, but RADAR encapsulates data from many countries. The database includes publicly available information on EMA Marketing Authorisation (MA), indication, prevalence rates used by EMA and G-BA assessments, HTA outcomes, reimbursed list/net unit prices as published in Lauer Taxe (Germany's official price registry for medicines), calculated annual treatment cost based on dosing regimen derived from the Summary of Product Characteristics (SmPC), and negotiated rebates for all ODs that received EMA MA between July 1, 2013, and September 30, 2024. The data include the first EMA MA for an OD, its G-BA assessment and GKV-published reimbursement price for this first indication in Lauer Taxe. Potential indication expansions are not included in the database and not considered in the analysis. ODs that received mixed G-BA assessments for some sub-populations were included with the highest benefit rating in the analysis. The lock date for any data analysis was February 15, 2025.

In total, the database includes 164 drugs with orphan designation that received EMA MA within the observation period. For the analysis of impact factors on negotiated prices and GKV rebates, we had to exclude 49 drugs for the following reasons:

- 14 products were excluded due to missing G-BA assessments or non-applicability of the AMNOG process for different reasons (e.g., launched before 2019 for hospital-only use).
- 16 products were excluded due to missing list prices in Lauer Taxe.
- 19 products were excluded due to missing GKV rebates/negotiated reimbursed prices in Lauer Taxe. Many of these are in an ongoing AMNOG process which has not yet resulted in published G-BA ratings and/or published GKV negotiation results, or they were withdrawn by the manufacturer.

In total, 115 ODs are included in our analysis. The average time from EMA MA to the publication of a negotiated reimbursement price in Lauer Taxe was 537 days. While the number is impacted by the process timelines, it also explains why, for several products that received EMA approval after August 2023, no GKV-negotiated price was published by February 15, 2025, the date of data lockdown. As the included products cover a wide range of indications, we divided indications into oncology and non-oncology for the purpose of the analysis. Out of the 115 products analysed, 34 are indicated for various oncology purposes, while 81 are indicated for different non-oncology uses which cover more than a dozen different indication groups. Figure 1 provides an overview of the clinical evidence provided for these 115 OD products; Figure 2 shows the added clinical benefit ratings assigned by the G-BA.

Figure 1: Comparators of 115 orphan drugs submitted for G-BA benefit assessment, 2013–2024

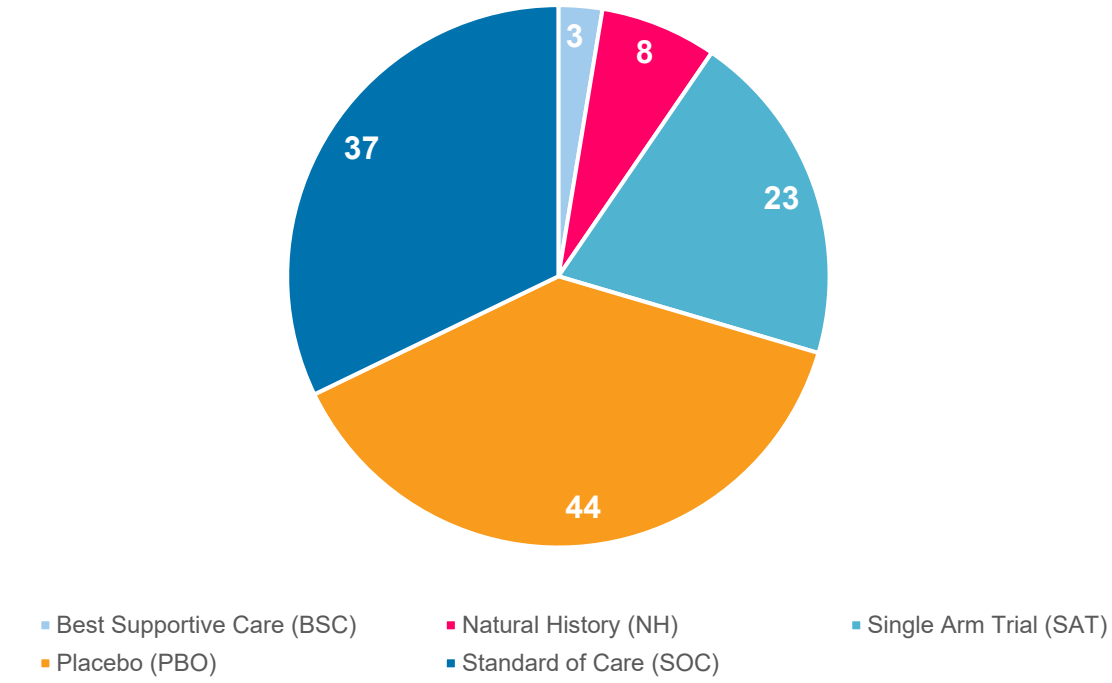
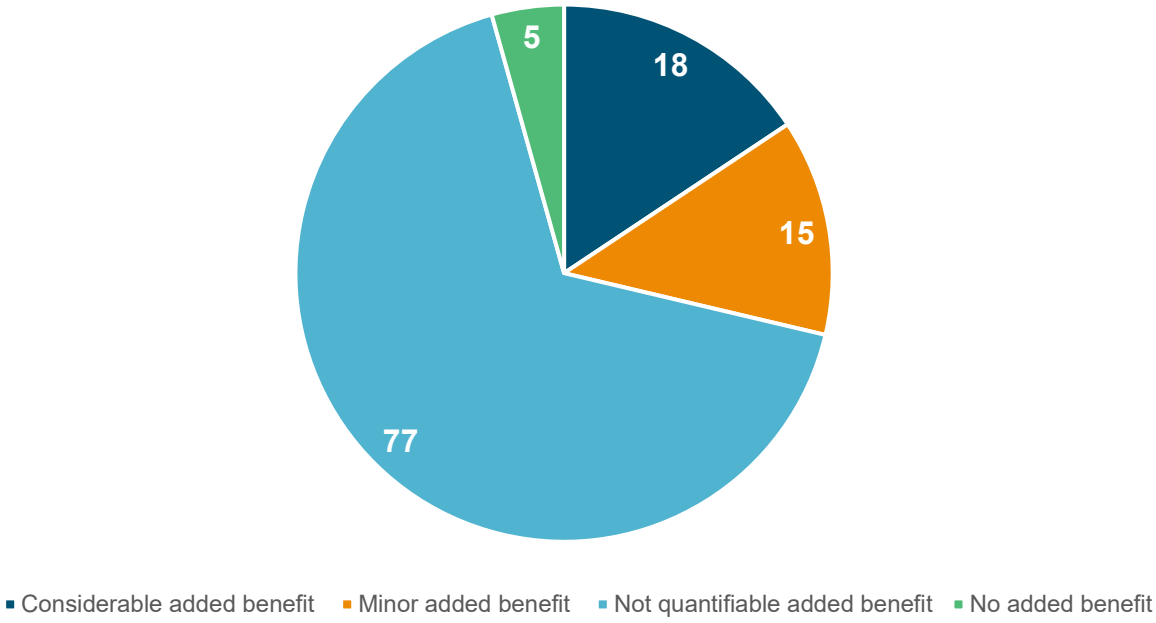


Figure 2: G-BA added benefit ratings for 115 ODs assessed between 2013 and 2024



Considering the specific introduction of automatic ‘not quantifiable added benefit’ ratings for ODs, it is noteworthy that the evidence provided for these ODs allowed G-BA in 33 cases to grant better than ‘default’ OD ratings. The five ‘no added benefit’ ratings suggest that the products exceeded the budget ceiling of initially €50 million/ later €30 million that allowed a deviation from the ‘default’ OD rating by G-BA.

Prevalence is a key element, as it is the base for an orphan designation. Looking at the 115 ODs, we find the average prevalence across all indications and products is 0.242 (standard deviation (SD) 0.427) per 10,000 – significantly lower than the required <5 per 10,000 for orphan designation.

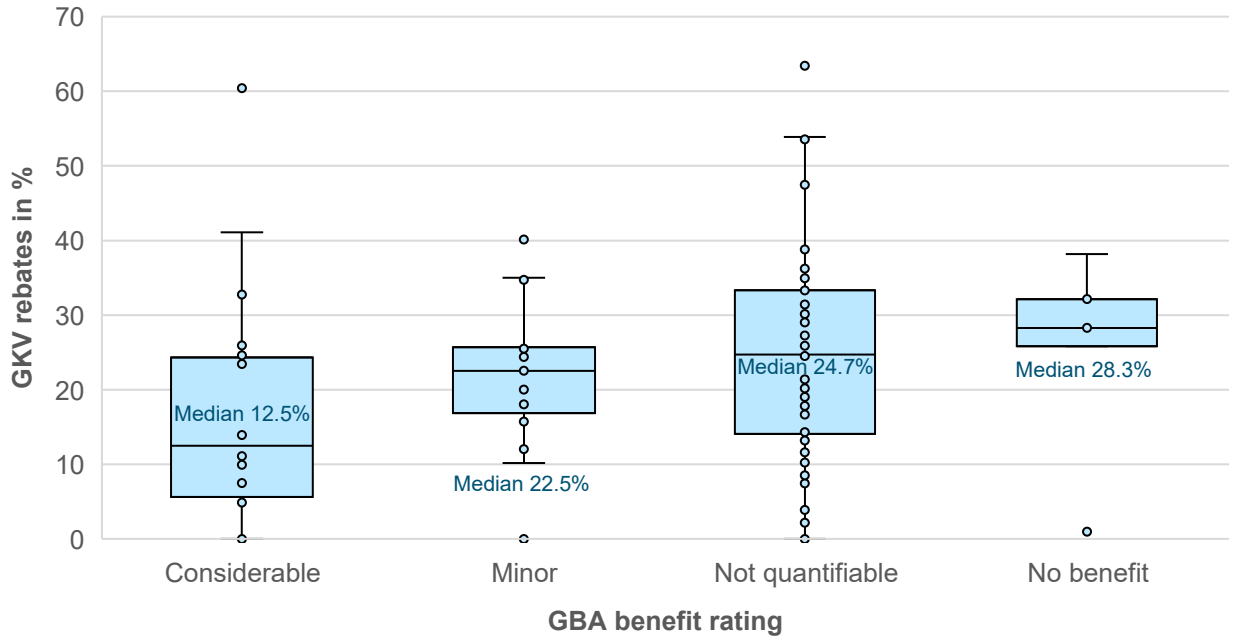
To compare rebates and prices of various products, we analysed the average annual treatment cost per product, considering both the manufacturer-set unit list price and the negotiated GKV rebate. This approach aligns with how GKV budget holders evaluate product prices, based on their impact on drug budgets. To calculate annual treatment cost, we used the manufacturer-set unit list prices from Lauer Taxe and applied SmPC dosing information. For weight-based dosing schemes, we used average weight measures for adults, children and infants. For all 115 products, the mean annual treatment cost based on the list prices at launch was €319,899 (SD 489,130). The mean and median negotiated GKV rebates were both 22.5% (SD 13.3; interquartile range (IQR) 20.1).

Using these data, we address several questions of significance for the pricing and market access of orphan drugs in Germany.

1) Are negotiated GKV rebates for OD impacted by G-BA benefit ratings?

The communicated objective of AMNOG is to negotiate justifiable reimbursement prices (as rebates on manufacturer-set list prices at launch), based on evidence for quantified and/or qualified added benefit over available alternatives. According to the objective, there should be a correlation between the G-BA rating and the GKV rebate. The question is whether this correlation applies to ODs as well, where at least a qualifiable benefit is presumed through their existence. The chart below indicates an affirmative answer to the question in the heading (see Figure 3).

Figure 3: Correlation of G-BA benefit ratings and GKV rebates for 115 ODs, 2013–2024



Although the low absolute numbers, particularly in the 'no benefit' group, have their limitations, the median analysis indicates that GKV negotiators adhere to their mandate. The G-BA benefit ratings appear to be reflected in the reimbursement price and rebate negotiations for the 115 ODs included in the research, especially for the highest and the lowest rating. Overall, the message of 'the better the rating, the lower the rebate,' seems to apply to ODs as well, as it aligns with the objectives of the AMNOG process.

2) Are negotiated GKV rebates for ODs impacted by clinical comparators in pivotal trials?

As G-BA benefit ratings are based on provided evidence, one might wonder whether there is a direct link between the clinical comparator in pivotal trials and GKV rebates for ODs. The whole concept of orphan drug designation suggests that there should not be such a link, as it is challenging to perform randomized clinical trials in small populations and comparators hardly seem to exist. For this reason, AMNOG introduced a 'non-quantifiable benefit' as the default benefit rating for OD. Table 1 below presents the distribution of G-BA benefit ratings and clinical comparators prior to analysing the potential correlation between trial comparators and negotiated rebates as presented in Figure 4.

Table 1: Clinical comparators across G-BA benefit ratings for 115 ODs, 2013–2024

Benefit vs. clinical comparator	NH	BSC	SOC	PBO	SAT
Considerable benefit (n=18)	2	1	7	8	
Minor benefit (n=15)			5	10	
Not quantifiable benefit (n=77)	6	1	24	25	21
No benefit (n=5)		1	1	1	2

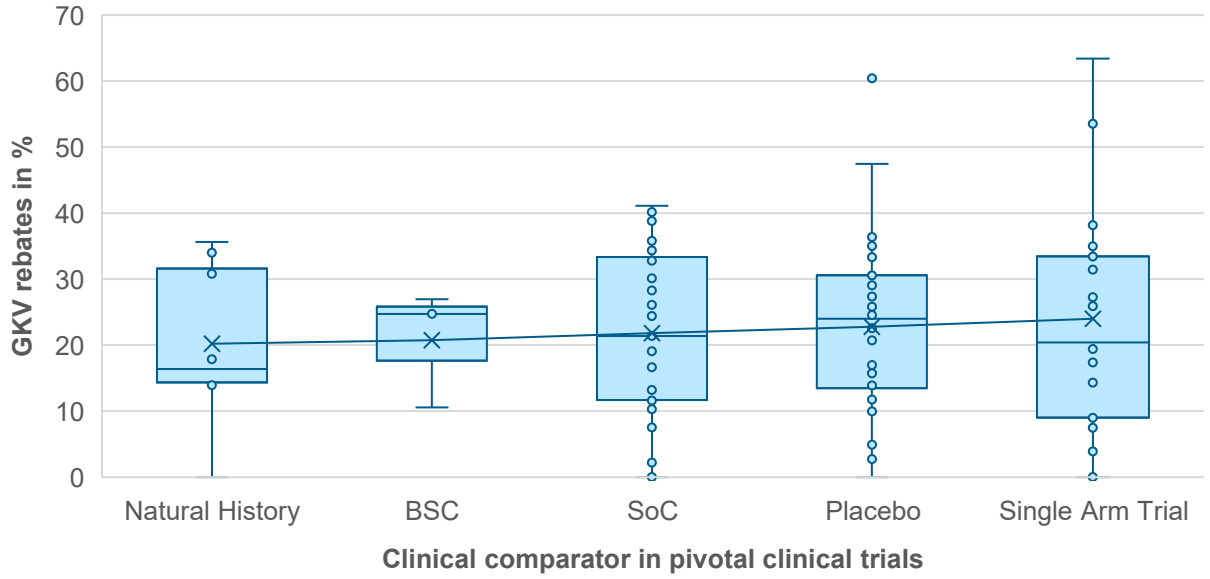
NH: natural history; BSC: best supportive care; SOC: standard of care; PBO: placebo; SAT: single-arm trial.

In Table 1, G-BA added benefit ratings seem to send one clear message: single-arm trials (SATs) lead to a 'non-quantifiable benefit' rating, and they risk receiving a 'no added benefit' rating later. This makes sense, as a single-arm trial cannot prove evidence of benefit; a comparator is missing. This scenario may pose a risk when products surpass the OD revenue threshold and are subjected to a standard AMNOG assessment without additional data from real-life, post-launch studies. Manufacturers might avoid that consequence when introducing results from observation studies for the full AMNOG assessment after exceeding the threshold.

With head-to-head trials, be it versus placebo (PBO) or standard of care (SOC), there seems to be a higher likelihood of achieving a 'minor' or 'considerable' benefit rating, as these allow quantification of benefit.

The ability to achieve 'considerable benefit' with best supportive care (BSC) or natural history (NH) as the comparator suggests that other factors play a significant role in the rating determination. These could include perceived unmet need in the indication or an acknowledged burden of disease that increases the perceived value of the first available treatment.

Figure 4: Correlation between clinical comparator and GKV rebate for 115 ODs, 2013–2024



In Figure 4, we try to understand whether there is a direct correlation between the clinical trial comparator and the GKV rebate for products with orphan designation. The answer is no.

The median (line within each box) and mean ('x' and line across parameters) analyses suggest that the clinical trial comparator has no discernible impact on the GKV rebate. Using NH as the comparator results in the lowest GKV rebates in both analyses (16.5% median/20% mean), suggesting other factors besides clinical evidence may impact price negotiations. Using SAT results in the highest mean GKV rebate (24%), potentially due to the inability to quantify value. The other endpoints seem to have less impact, as these are between 21% and 23% in the mean analysis (BSC has only three data points).

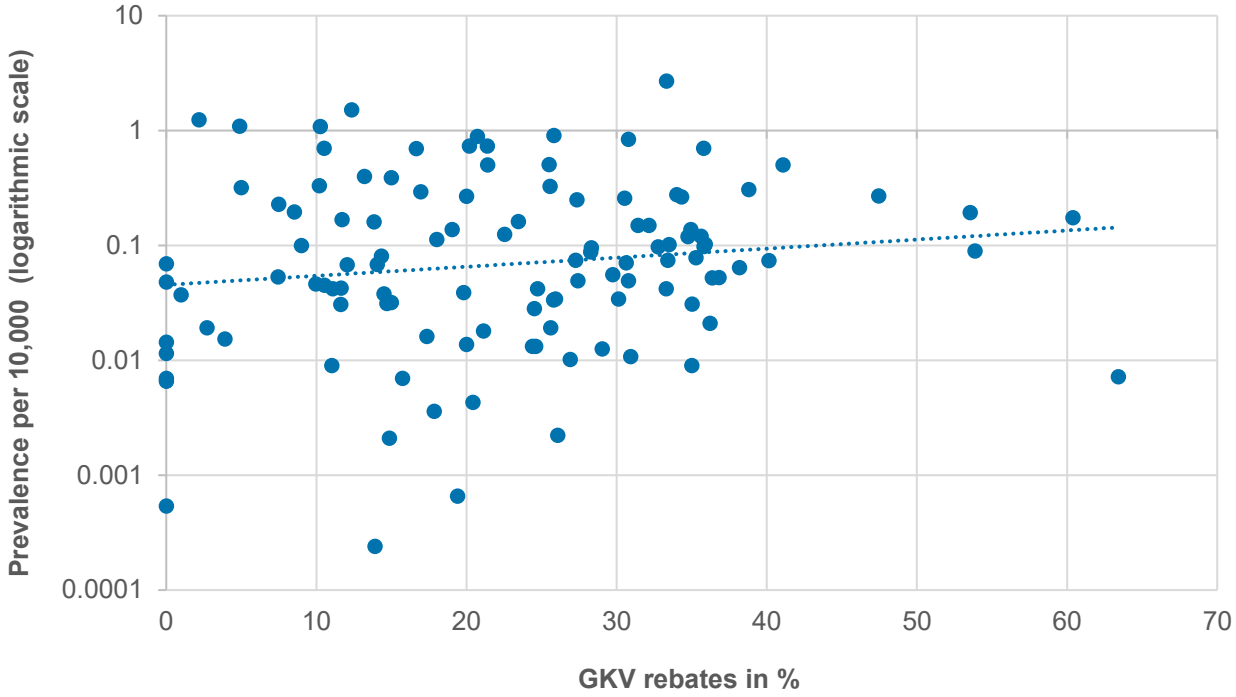
From the data above we might conclude that, as is often emphasised in discussions with G-BA and GKV representatives, negotiators do take the G-BA benefit rating in its entirety, rather than clinical evidence, as the basis for OD rebate negotiations.

3) Are negotiated GKV rebates for ODs impacted by disease prevalence?

'Price is only relevant insofar as it translates into annual costs that allow us to understand the impact on annual health care budgets; once we know how many patients shall be treated.'[1] This quote underscores an important point: prevalence should matter. Figure 5 reflects the situation for ODs.

1 Quote from anonymous regional KV department head for drug supplier (Leiter Arzneimittelversorgung).

Figure 5: Correlation of prevalence and GKV rebates of ODs launched 2013–2024



The trend line seems to suggest a correlation between prevalence and negotiated GKV rebates for products with orphan designation. For further analysis, all ODs in the database were divided into those above and below the median prevalence of 0.074 cases per 10,000 people, with mean prevalence of 0.0286 cases per 10,000 people (SD 0.02) in the lower half and mean prevalence of 0.458 cases per 10,000 people (SD 0.4) in the upper half (a statistically significant difference between the halves, with $p<.001$). The mean GKV rebate in the lower prevalence group was found to be 19.7% (SD 13.1), and the GKV rebate in the higher prevalence group was 25.5% (SD 12.9). The difference in GKV rebates is statistically significant ($p<.02$).

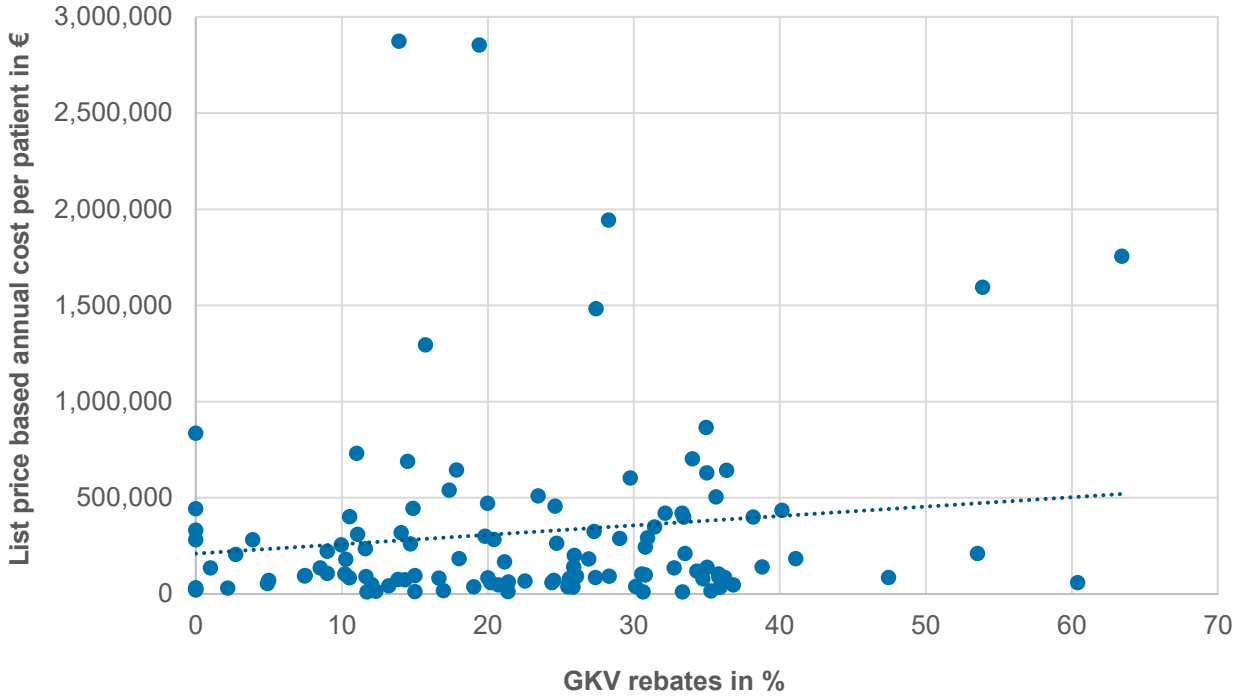
The results allow us to conclude that **yes**, prevalence does impact negotiated GKV rebates. GKV negotiators appear to consider patient numbers and overall budget impact in their negotiations with manufacturers, despite OD protection through default added benefit ratings by G-BA and small patient numbers.

4) Are negotiated rebates impacted by the list price freely set by the manufacturer?

The introduction of AMNOG did not impact the manufacturers' ability to set list prices at launch. So how does the freely set list price impact GKV rebate levels for ODs?

To compare the rebates and prices of our 115 ODs, we calculated annual treatment cost per product before AMNOG negotiation, based on the unit list price and SmPC dosing schemes. The negotiated GKV rebates were obtained from Lauer Taxe. Figure 6 below shows the situation for each product within our data sample.

Figure 6: Correlation of manufacturer-set list prices for OD and GKV rebates, 2013–2024



The trend line seems to indicate a correlation between list prices and GKV rebates: the higher the manufacturer-set list prices, the higher the negotiated rebates. However, statistical analysis does not allow us to answer the question of whether freely set list prices impact GKV rebates with a clear '**yes**', but rather with a '**maybe**'.

To understand what the impact means for different price levels, the 115 ODs were divided into three clusters of annual treatment costs: (1) products costing more than €500,000 annually; (2) products costing between €100,000 and €500,000 annually; and (3) products costing less than €100,000 annually, all based on manufacturer-set list prices at launch. Table 2 below shows the median GKV rebate levels for the three different price ranges.

Table 2: GKV rebates across different ranges of annual cost in the sample of 115 ODs

	GKV rebate median (IQR)
OD >€500,000 annual cost (n=19; median €731,194)	27.2% (19.3)
OD €100,000–€500,000 annual cost (n=48; median €255,980)	24.6% (22.5)
OD <€100,000 annual cost (n=48; median €59,850)	21.4% (17)

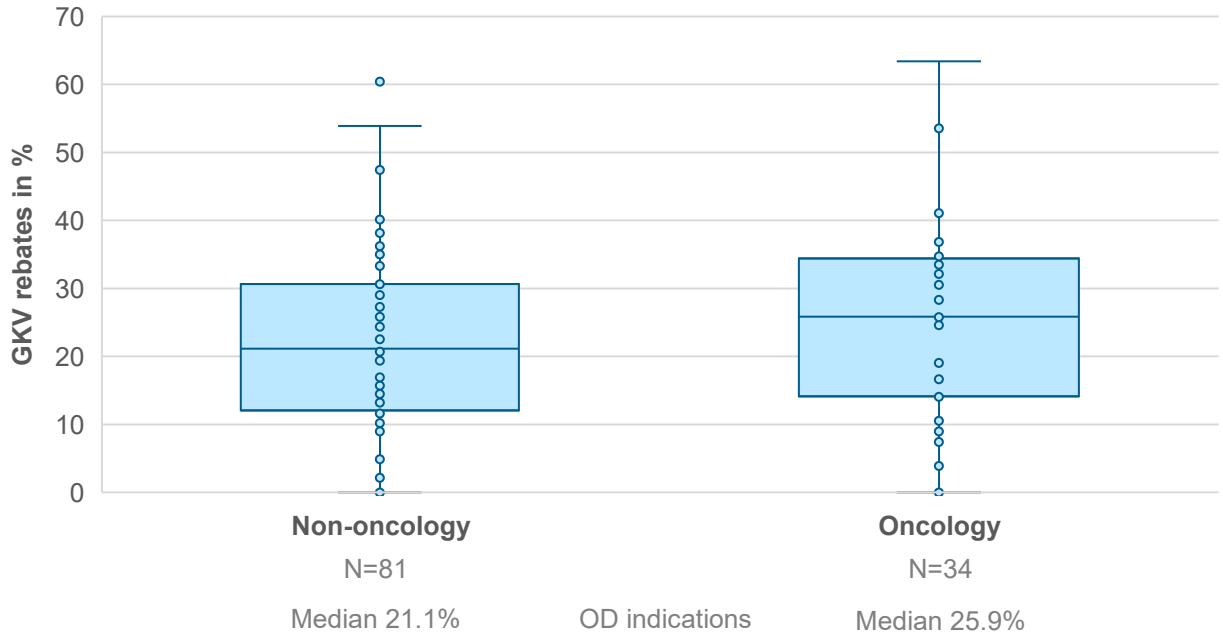
Both correlation and median analyses indicate some level of price sensitivity, suggesting GKV negotiators likely push for higher rebates for ODs with higher annual treatment costs. However, one might have anticipated a greater rebate disparity (and statistical significance) between the lower and upper thirds, considering the more than fivefold difference in annual treatment costs.

5) Are negotiated GKV rebates impacted by different OD indications?

To answer this question, we divided the indications into two groups: oncology (34 ODs) and non-oncology (81 ODs). The rationale for the grouping is that oncology is a well-established cluster of indications that seems to be relatively homogenous and is by far the largest group of indications. Although non-oncology ODs constitute the majority of the dataset, further division into smaller indication groups would reduce the robustness of the analysis.

First, we looked at the median GKV rebate negotiated for oncology and non-oncology ODs.

Figure 7: GKV rebate comparison for oncology and non-oncology ODs



The analysis seems to indicate that manufacturers of oncology ODs accepted higher GKV rebates (median 25.9%) compared to manufacturers of non-oncology ODs (median 21.1%). Even if the difference of negotiated rebates is not statistically significant, one might wonder why there is a disparity in the first place. In an attempt to answer this question, the analyses of the impacts of G-BA ratings, clinical evidence, prevalence and manufacturer-set list prices on GKV rebates were repeated for each of the indication groups.

First, we analysed G-BA ratings for each indication group. Table 3 reflects a similar trend for both oncology and non-oncology ODs. As such, the difference in rebates between oncology and non-oncology ODs does not appear to be driven by a difference in G-BA ratings.

Table 3: Impact of G-BA ratings on mean GKV rebates for oncology vs. non-oncology ODs

G-BA rating	Oncology ODs (34)	Non-oncology ODs (81)
Considerable added benefit (18)	18.3% (8)	15.4% (10)
Minor added benefit (15)	25.7% (3)	20.4% (12)
Non-quantifiable benefit (77)	25.9% (22)	22.5% (55)
No benefit (5)	32.1% (1)	30.8% (4)

Next, we looked at prevalence. While the analysis of the full cohort identified a significant impact of prevalence on GKV rebates, the indication group analysis revealed no significant difference in prevalence between the two. If anything, it suggests the opposite: the mean prevalence of oncology ODs seems to be lower (0.1561 in 10,000 people; SD 0.1969) compared to non-oncology ODs (0.2419 in 10,000 people; SD 0.4272).

The overall analysis of manufacturer-set price levels seems to indicate that the higher manufacturer-set list prices are, the higher the GKV rebates are. A hypothesis for higher oncology OD rebates may be that oncology drugs have higher manufacturer-set list prices. To validate this hypothesis, we split the earlier analysis of list price/annual cost impact on GKV rebate into the indication groups of oncology and non-oncology ODs. The results are shown in Table 4.

Table 4: Comparison of annual costs and GKV rebates for oncology vs. non-oncology ODs

	Oncology ODs (34)	Non-oncology ODs (81)
Mean annual cost at freely set list prices	€236,146 (SD 319,622)	€355,054 (SD 542,731)
Mean GKV rebate	24.6% (SD 14.6)	21.6% (SD 12.6)

Contrary to our hypothesis, the manufacturer-set list prices of oncology ODs seem to be lower compared to those of non-oncology ODs. GKV rebates for oncology ODs seem to be higher despite lower prices for oncology ODs.

There may, however, be a hint in the data that could explain the difference: low GKV rebates for drugs that use natural history (NH) as the comparator in clinical trials. All eight products with that clinical comparator have non-oncology indications. Their average GKV rebate is lower than that of other ODs.

Summary

Table 5 compiles the different factors, the underlying reasons and their relative impact on GKV rebates for drugs with orphan designations in Germany. To provide a comparative analysis, the mean=median GKV rebate of 22.5% across all 115 products was set as the benchmark. The identified mean GKV rebate linked to each impact factor is presented as a percentage of deviation from that overall benchmark (for those $\geq$10%).

Table 5: Ranking of key impact factors by % difference to mean GKV rebate across 115 ODs

G-BA rating: ‘considerable added benefit’	-44%
G-BA rating: 'no added benefit'	+25%
Manufacturer set list price >€500,000 annual cost	+20%
Oncology indication	+15%
Prevalence above median*	+13%
Prevalence below median*	-12%
Clinical comparator: ‘Natural History’	-10%
G-BA rating: 'not quantifiable added benefit'	+10%

**Statistically significant difference*

Table 5 suggests that strong G-BA benefit ratings may have the largest impact on achieved GKV rebates – in both directions. GKV negotiators seem to use the value identified by the G-BA as the basis for their negotiations, following the mandate and objective set out in the AMNOG process. As shown in this analysis, this is also true for ODs, where negotiators seem to recognise value in the very existence of the drug.

Another objective of the AMNOG process, the reduction of very high prices, appears to be achieved when considering that those drugs with the highest freely set list prices also seem to see the highest rebates, relative to those with lower prices and annual costs. The size of the difference in rebates relative to the differences in annual costs indicates a relatively low price sensitivity for ODs.

Despite low numbers of patients using drugs with orphan designation, prevalence seems to matter for the willingness of the statutory health insurance system (GKV) to pay for these drugs. This becomes clear when we look at the significant differences in mean GKV rebates between ODs with prevalence levels above and below the median.

Negotiations for orphan drugs with oncology indications may seem to result in higher average rebates compared to those for non-oncology ODs. This could be due to the wave of oncology products that made it to the market over the past 20 years. There seem to be sufficient products in the adjacencies to these orphan oncology indications that might be used as indirect price benchmarks during GKV negotiations.

Perceived unmet need seems to be relevant in GKV rebate negotiations, as indicated by the lower rebates achieved by those non-oncology ODs for which natural history (NH) is accepted as clinical evidence. The question is how long this will last, given the growing budget impact of non-oncology ODs and the many non-oncology orphan indications awaiting treatment.

Limitations to data in this report

This analysis is subject to several limitations. The sample size and available tools do not support rigorous scientific standards. The findings present indicators, not evidence. They also cannot identify or quantify all impacting factors, such as perceived unmet need, burden of disease, magnitude of treatment benefit (to the extent it does not translate into benefit ratings) or the 'human' element of negotiations. Also, some of the identified factors may impact each other and potentially exacerbate or offset other factors. Additionally, the numbers provided are static – they do not show developments over time. Further research in the RADAR database may explore dynamic development over time and further analyse the non-oncology OD cohort.

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