# Quantitative and qualitative analysis of differences in AMNOG outcomes between IQWiG and G-BA between 2011–2018

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## Introduction

Since the introduction of the Act on the Reform of the Market for Medicinal Products (AMNOG) in 2011, pharmaceutical companies (PC) must submit a dossier claiming an additional benefit (AB) of the new pharmaceutical over the appropriate comparator therapy (ACT) specified by the Federal Joint Committee (G-BA). The final decision on the AB is taken by the G-BA. In addition to the manufacturer's dossier, submitted data, and the recommendation by IQWiG (Institute for Quality and Efficiency in Health Care), the G-BA also considers the results of the commenting procedure.

In the majority of cases, the G-BA agrees with the assessments of IQWiG. However, discrepancies can exist regarding i) the extent of the AB, or ii) whether an AB is recognised or not.

Here, we sought to evaluate the incidence and nature of differences in the AMNOG assessment outcomes for non-orphan pharmaceuticals between IQWiG and the G-BA. We also identify the reasons and assess potential drivers of a discrepancies between the G-BA and IQWiG.

## Methodology

We collected and analysed the outcome of all 242 finalised G-BA non-orphan drug assessments (as of 1 January 2019) and identified those where the G-BA and IQWiG outcomes differed, i.e. cases in which the G-BA granted an AB in at least one population when IQWiG did not or vice versa. Here, a discrepancy was defined as a difference in G-BA and IQWiG assessments when granting an overall benefit (defined as the highest rating across sub-populations). We then analysed and categorised the reasons for the decision-making in both cases, and in particular what triggered the change in outcome.

## Discussion and conclusions

As of January 2019, 242 non-orphan assessments were conducted and finalised by the G-BA. Of those, 39 outcome assessments varied between IQWiG and the G-BA in terms of whether an overall benefit was granted or not. In 34 cases, the G-BA's opinion differed from IQWiG and an additional benefit rating was granted in at least one sub-population. In 5 cases, the G-BA did not confirm the positive IQWiG rating and ultimately did not grant additional benefit in any sub-population.

IQWiG often based the denial of additional benefit on reasons such as manufacturer-biased evidence, data inadequacy, discrepancies between label and trial, lack of evidence or choice of an inappropriate comparator. In 17 cases, the G-BA overruled the IQWiG decision based on input from the commenting procedure.

The G-BA overruled IQWiG for a variety of reasons. The German HTA system is usually seen as very rigid and rule-oriented. While IQWiG pays close attention to those rules, which for example require a double-blind comparative study or a perfectly executed indirect comparison, the G-BA has the ability to contextualise the presented evidence. The common denominator between all of the G-BAs reasons for overruling IQWiG (outside of new evidence being presented) was that the G-BA deviated from the scientific and theoretical standard procedures IQWIG used, instead accepting aberrations presented during the commenting procedure or the oral hearing.

The relevant number of cases in which the G-BA overruled IQWiG's decision has several implications for manufacturers. First, an unfavourable IQWiG decision does not represent the final decision. In 16 out of 100 cases, a negative assessment by IQWIG was overruled by the G-BA.

The reasons for this can depend on the therapeutic area, which in turn indicates what reasons the G-BA is willing to overrule. In oncology and infectology, for instance, a range of reasons for the GBA's overruling have been identified.

Last, manufacturers can actively influence the outcome of the benefit assessment through the commenting procedure. If IQWiG deemed the presented evidence unsuitable or insufficient, new evidence or analyses may be presented during the commenting procedure. Additionally, with support from relevant stakeholders, e.g. policy-advising key opinion leaders or medical societies/associations, the oral hearing can help provide context for critical aspects of the submitted dossier, for example the choice of endpoints or comparator therapies.

## Results

### Figure 1: Benefit assessment at a glance

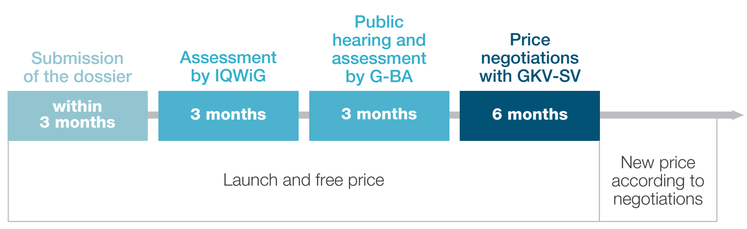



**Figure 1.** For the first year, the PC is free to set the price of the new drug. IQWiG evaluates the dossier within 3 months and issues a recommendation to the G-BA regarding the extent and probability of the AB. Three months after IQWiG's recommendation, the G-BA makes a final decision regarding the additional benefit. Subsequently, the Federal Association of Statutory Health Insurers (GKV-SV) and the PC must agree on a reimbursed price within 6 months. If no agreement is reached, the final decision is made by an arbitration board within 3 months.

### Figure 2: Agreement on the extent of benefit granted between IQWiG and G-BA

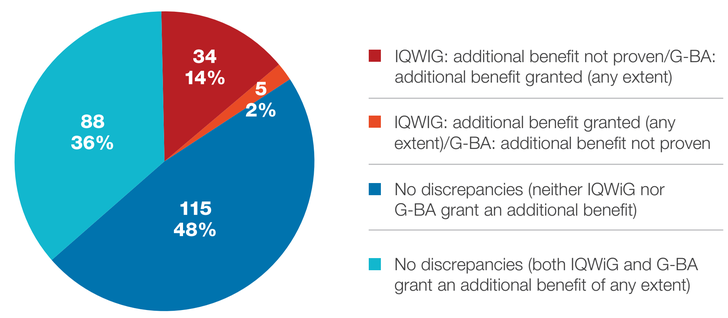
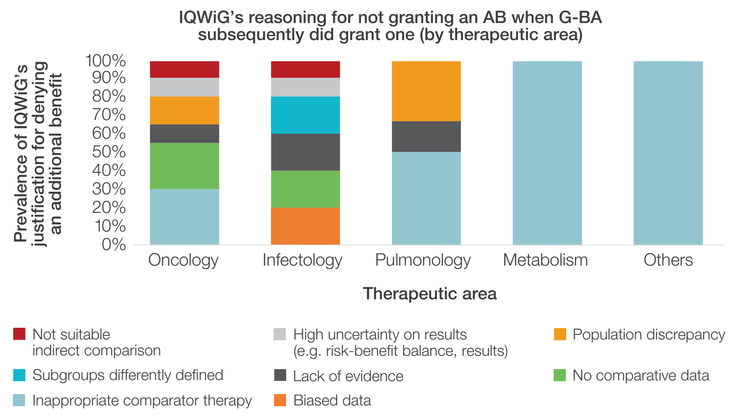



**Figure 2.** In 48% (115/242) of all non-orphan assessments until 1 January 2019 neither IQWiG nor the G-BA granted an additional benefit in any sub-population of the assessment. In 36% (88/242), both IQWiG and the G-BA granted an additional benefit of any probability/extent in at least one sub-population. In 16% (39/242) of the cases a discrepancy regarding the recognition of an AB was found. In 14% (34/242) of the cases IQWiG did not recognise an AB but the G-BA did. The G-BA did not recognise an additional benefit after IQWiG issued a recommendation of granting an additional benefit in only 5 cases (2%).

### Figure 3: Reasons for discrepancies in additional benefit




| IQWiG's reasons to not grant AB | G-BA's reasons to overruleIQWiG (exemplary) |
|---|---|
| **No comparative data (i.e. single arm trials** | There is a visible effect, even without comparator, which warrants an AB. G-BA emphasises that this is only done by way of exception and exclusively in severe diseases |
| **Unsuitable indirect comparison presented** | Relevant information (i.e. new analyses) is presented during the commenting procedure |
| **Population discrepancy** | An extrapolation from other sub-groups is conducted or the sub-groups are re-defined |
| **Inappropriate comparator therapy used** | During the commenting procedure, medical experts and specialist associations state that the comparator therapy is in fact the correct one in clinical practice |

**Figure 3.** In situations when the G-BA overruled IQWIG's decision by granting an AB when IQWIG did not grant one, IQWiG's most common reasoning for not granting an AB across all therapeutic areas was the use of an inappropriate comparator therapy. This was followed by lack of evidence in relevant endpoints or aspects, the lack of comparative data, population discrepancies (data presented by the PC did not match the indication description/sub-groups for which the benefit analysis was being conducted), biased data, high uncertainty of results (e.g. risk-benefit balance) and unsuitable indirect comparison. In 2 cases, the sub-groups to be assessed were defined differently by IQWiG and G-BA.

Depending on IQWiG's main criticism of a dossier, the G-BA had similar arguments against that criticism across assessments. Whenever the G-BA disagreed with IQWiG on whether the appropriate comparator therapy had been used, it was due to experts' opinions that came up during the commenting procedure (more on the impact of the commenting procedure in Figure 4). While IQWiG never accepts non-comparative data, the G-BA accepted single-arm trials when the advantage of the assessed drug over standard of care was obvious even without comparative data. However, this was only the case in serious indications (oncology and HCV).

### Figure 4: Influence of oral hearing statements in final resolution

| | |
|---|---|
| **Case** | Necitumumab; Advanced or metastatic NSCLC |
| **IQWiG** | Indication of a small added benefit due to positive effects in favor of Necitumumab for the outcome "overall survival" |
| **G-BA** | AB not proven |
| **Argumentation of G-BA** | • Taking into account the stage of the disease, the positive effect in overall survival (median: 11.7 for Necitumumab months vs 10 months for the ACT) was regarded as minor<br>• The G-BA considered that as the symptoms of advanced NSCLC are pronounced and distressing, a therapy with an effect on these would be meaningful for the patients. However, Necitumumab did not show advantages in terms of disease-specific symptoms<br>• In the overall assessment, the G-BA stated that the positive survival effect was not supported by further positive effects on patient-relevant outcomes |

**Oral hearing statements**

**German Society for Hematology and Medical Oncology (DGHO):** "The patient has to decide whether it is worth it. One has to tell the patient that he has a chance to live a little longer (the median survival time is significantly extended) but that together with that, he will have more side effects, and will have more medical follow-ups. Also, that the quality of life will be neither better nor worse and that the treatment has little impact on how the patient experiences and perceives the disease."

**Figure 4.** In 17 cases, statements during the commenting procedure/hearing process were explicitly mentioned in the final G-BA resolution as a major reason to deviate from IQWiG's assessment in either direction (see representative examples below). In several other cases, the commenting procedure was likely to be involved without being mentioned in the final assessment document (see example on the left).

**Lumacafor/Ivacaftor:** While LCI is not a validated surrogate endpoint, **in the oral hearing** it became clear that in the clinical practice, LCI is used in this population for recording early structural changes (disease progression)

**Emicizumab:** The deviation from the originally defined ACT was justified as it was **supported by the observations of the specialist associations** on the treatment situation of patients with hemophilia A and factor VIII inhibitors

**Ocrelizumab:** On the basis of the data submitted in the **commenting procedure and following the oral hearing**, it was found that the selected population by the pharmaceutical company did not correspond to the relevant sub-population that was undergoing the AB assessment

**Cabozantinib:** According to the opinion of medical societies in the **commenting procedure**, the role of MET expression as a biomarker is still uncertain and therefore no therapy decisions can be made based on it in clinical practice