ANALYSIS OF THE CHANGE OF THE ADDED BENEFIT AND RESPECTIVE REASONS IN RENEWED REGULAR BENEFIT ASSESSMENTS OF ORPHAN DRUGS DUE TO EXCEEDING THE SALES THRESHOLD IN GERMANY

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Objectives

Orphan drugs (ODs) have privileges in the early benefit assessment (EBA) and the subsequent price negotiation (PN) in Germany. The added benefit (AB) is acknowledged by law, no appropriate comparator therapy (ACT) is defined. If the sales of the OD exceeds a sales volume threshold (SVT) of 30m€ (50m€ until Nov 2022), the product is subjected to a regular EBA incl. comparison against an ACT. The reassessment under these regular conditions may result in the conclusion that an AB is not proven. As a consequence of the reassessment, the reimbursement will be renegotiated.

The objective of this study was to determine the change of the AB (cAB) and respective reasons after exceeding the SVT comparing to the EBA as OD.

Methods

The results of all completed EBAs due to exceeding the SVT regardless of the status of the PN by March 2023 were analyzed. The cAB and respective reasons were determined using qualitative text analysis (QTA). The QTA according to Kuckartz was modified. The main categories depicted the possible changes in the AB and were therefore formed inductively before the analysis of the material. The analysis of cAB was carried out at subpopulation level. The subcategories were developed inductively by reviewing the material. Each main category was considered on its own and the subcategories were identified and, if necessary, combined into further subcategories. All information was taken directly from the published G-BA documents using the IGES ARA database.

Results

A total of 39 subpopulations were analysed. In 5 subpopulations, there was an increase/quantification of the AB due to the submission of new evidence, whereas in 2 subpopulations the AB was no longer quantifiable. In 11 subpopulations the AB remained the same despite the submission of new evidence in 2 cases. In 9 cases the evidence already presented in the orphan EBA procedure continued to be sufficient to demonstrate an AB after exceeding the SVT. In 21 subpopulations the extent of the AB decreased. In case of a decrease of the AB, a RCT of the assessed drug was often available in the orphan procedure. However, that comparison was not adequate for deriving an AB in the exceeding procedure due to a comparison that was not against the ACT (6), an inappropriate study design (1) or the combination of both (3). Although the AB decreased, new evidence was also presented in 9 populations, whereas only in 2 populations did the data show no AB (see Table 1).

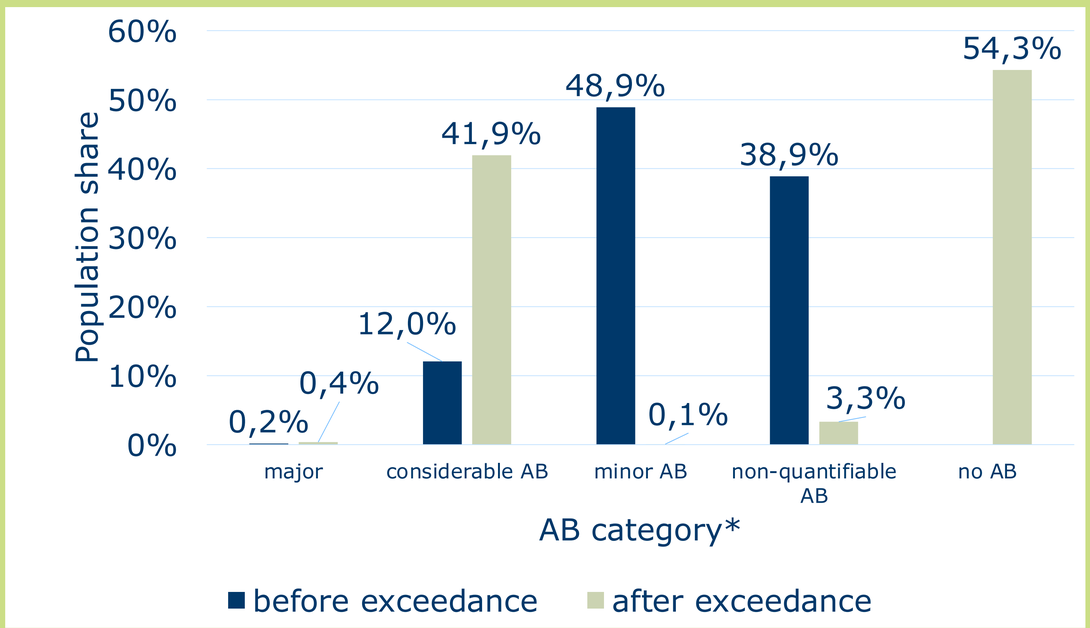
Table 1: Frequency and reasons for the change in the additional benefit

Change in AB (frequency)	Reason (frequency*)
Increase (4)	Submission of another data cut (3) Submission of new studies (1)
Quantification (1)	Submission of new studies (1)
No longer quantifiable (2)	Other reasons (2)
Decrease (21)	No evidence in orphan procedure (2) Evidence from orphan procedure no longer appropriate in the exceedance procedure: • No direct comparison (2) • Direct comparison, but ▪ Not against the ACT (6) ▪ Study design (duration of study, administration of study medication) not appropriate (1) ▪ Not against the ACT and study design not appropriate (3) • Population split (4) Additional submission of new/other evidence: • Not suitable for the benefit assessment (7) • No additional benefit (2) Formal incompleteness (3)
No change (11)	No change in evidence: • Evidence transfer or historical comparison + single arm study were also accepted in the exceedance procedure (2) • RCT was already available in the orphan procedure and ACT was appropriate (partially incomplete, but was accepted) (7) Additional submission of another data cut/new studies (6) Other reasons (2)

*The frequency of the reasons may not add up to the sum of the change in AB since several reasons may apply.

Figure 1 shows the population share by AB before and after exceeding the SVT. In the orphan procedure, the most frequent assessments (by population share) were a minor (48,9%) and a non-quantifiable AB (38,9%) while after exceeding, the most frequent assessments were no AB (54,3%) and a considerable AB (41,9%).

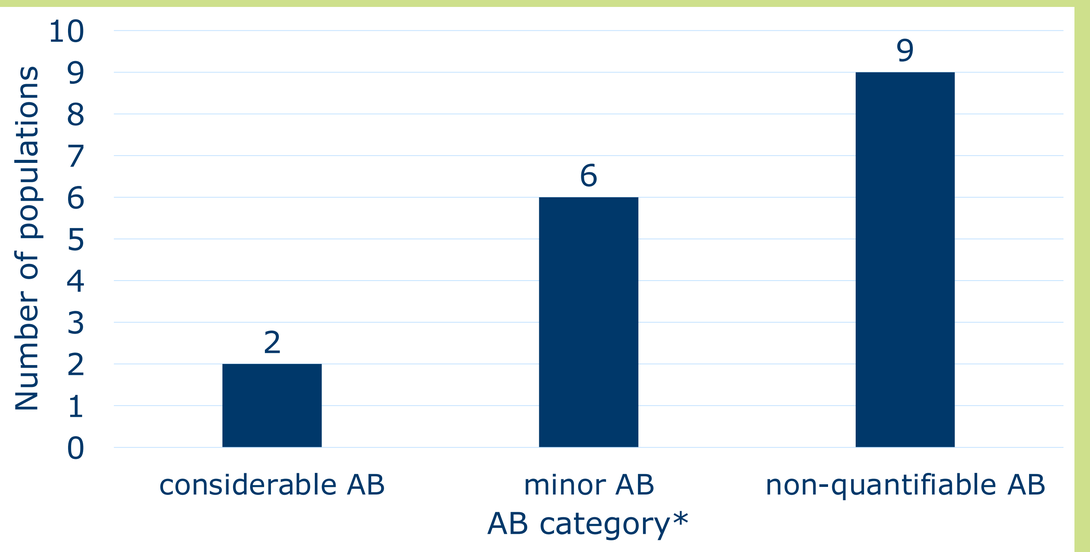
Figure 1: Population share by AB before and after exceeding the SVT



*Because no subpopulation was assessed as having a major AB or a lesser benefit, these two categories are not presented.

In detail, an analysis of the procedures with an unproven AB in the exceedance procedure showed that not only procedures with a non-quantifiable AB in the orphan procedure were assessed with no proven AB in the exceedance procedure (see Figure 2). Two procedures (tezacaftor/ivacaftor and lanadelumab) with a considerable AB in the orphan procedure were assessed with an unproven AB in the exceedance procedure.

Figure 2: Evaluation of populations with an unproven AB in the exceedance procedure by AB category in the orphan procedure.



*Because no subpopulation was assessed as having a major AB the category is not presented.

Conclusions

The analysis showed that there are several obstacles that arise when an OD is being faced with a regular EBA. The most common obstacle was the lack of AMNOG-eligible trials for a regular EBA. In most cases the available RCTs were often not suitable because the ACT was not adequately implemented. Pharmaceutical companies should consider a possible exceeding of the SVT and the resulting requirements when planning pivotal studies.

References

Gemeinsamer Bundesauschuss: Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL), https://www.g-ba.de/informationen/nutzenbewertung/ (depending on respective EBA)

IGES ARA - AMNOG Resolution Analyzer (https://ara-info.iges.com/Home)