# Application-related data collection during early benefit assessments in Germany – an analysis of current procedures

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## Objectives

In Germany, the Act for Greater Safety in Drug Supply empowered the Federal Joint Committee (G-BA) in 2019 to require manufacturers to conduct application-related data collection (AbD) as part of the benefit assessment, mainly in case of initially missing evidence [1,2]. As the number of new approvals of advanced therapeutic medicinal products (ATMPs) and orphan drugs increases, evidence gaps appear for the initial assessment, which are to be closed by data from AbD, while providing access for patients [1]. We aimed to analyze which AbDs were commissioned so far, in which process steps the procedures are and which challenges appeared.

## Methods

We conducted a retrospective quantitative content analysis. Benefit assessments of IQWiG/G-BA and other data on AbD (e.g. statistical analysis plans (SAPs), submitted study protocols (SPs)) from the G-BA homepage were used. The extraction took place until 31 March 2024.

The data for the systematic presentation of the process steps for AbDs was extracted from the overview ("profile" and "deadlines") of the individual AbD procedures on the G-BA homepage.

For the detailed presentation of the AbD procedures of Onasemnogen-Abeparvovec and Brexucabtagen-Autoleucel, the data was extracted from the documents "resolution" and "justification" of the corresponding process steps.

For the overview of the identified deficiencies of the submitted study documents, data were extracted from the section "Summary and conclusion" of the document "IQWiG addendum" of the process step "First review of study protocol and statistical analysis plan". For Onasemnogen Abeparvovec, since the document did not contain a conclusion, all of the company's measures that were described by IQWiG as "inappropriate" were extracted. The categorization of the IQWiG's deficiencies was adopted in all cases. The extracted data were aggregated. Only AbD procedures for which an AbD was required were included. The procedure for the active substance Fedratinib was excluded, as the procedure for requesting an AbD was discontinued. After excluding the procedure for the active substance Fedratinib, 5 AbD procedures remained.

## Conclusions

Conducting AbDs is time-consuming and complex due to the individual requirements for data collection. The establishment of the process of conducting AbDs is still in its early stages. However, the generation of data close to care has the potential to improve the evidence for quantifying the additional benefit of a drug and to close possible evidence gaps. Both IQWiG and the vfa consider the legal requirement to conduct an AbD to be appropriate [4,5]. The legal requirement that AbDs may only be conducted as non-randomized studies must be viewed critically.

The vfa is in favour of conducting the AbDs as non-randomized studies, as randomization would result in considerable additional effort. Furthermore, these are not feasible in small populations and would not represent the populations of patients with relevance for everyday life, according to the vfa [6]. IQWiG calls for randomized controlled trials (RCTs) to be maintained as a quality standard [7] and at the same time to facilitate the feasibility of conducting RCTs in the form of registry-based randomized controlled trials (RRCTs) or pragmatic randomized trials. Compared to RCTs, RRCTs are less costly, more reliable in terms of results, easy to plan and interpret from a methodological point of view and can be conducted in small study populations [8]. Examples include the TASTE study and the RECOVERY trial [9].

The resulting increased methodological requirements for data collection, especially the identification, adjustment and collection of confounders, leads to a lower reliability of the effects found. IQWiG identified the most deficiencies in the study documents submitted by the company in the category of confounders. As a result, the probability of closing the identified evidence gaps decreases. This does not correspond to the required usefulness of AbDs. Consequently, the effects of using a non-randomized comparative study design are contrary to the aim of conducting an AbD.

Thus, the question is not so much whether AbDs are useful, but how the process can be optimized.

According to Beate Wieseler, head of IQWiG's Drug Assessment Department [10], platform studies could be carried out prior to approval in order to accelerate evidence-based patient care. It would also make sense to conduct AbDs of several drugs of the same drug class in the form of an adaptive platform study under a master protocol (see Figure 3). This would accelerate data collection and generate high-quality data. The comparison with a common control group would reduce the number of patients required for the study. As soon as an additional benefit can be quantified for an active substance, this would become the new appropriate comparator therapy (zVT) [10].

Similar to the debate about the randomization of studies, it must be evaluated whether it makes more sense to try to close evidence gaps with data from expensive AbDs or to change the approval process in such a way that the emergence of evidence gaps can be avoided.

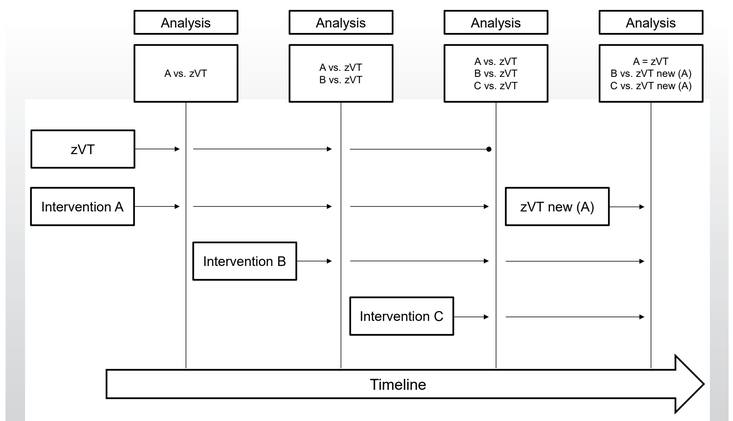


Fig. 3: Structure of an adaptive platform study for the AbD of several active ingredients of a drug class (according to IQWiG Rapid Report A21-37)

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## Results

The procedure for requesting an AbD and evaluations is divided into:

1. the procedure for requesting an AbD and evaluations according to § 35a paragraph 3b sentence 1 SGB V and
2. the procedure for review in accordance with § 35a para. 3b sentence 10 SGB V with regard to the obligation to conduct an AbD and evaluation of data obtained in accordance with §§ 60 ff. [3].

The first procedure comprises (a) the assessment of the necessity, (b) the decision initiating the procedure, (c) the preparation of a concept for the requirements of an AbD and of evaluations with the participation of expert authorities, (d) the evaluation of the participation of the expert authorities and (e) the decision of the plenary on the requirement of an AbD and of evaluations from the pharmaceutical company [3].

The second procedure is divided into (a) the review of the SP and SAP prior to the implementation of the AbD and, if necessary, the determination of the time for the start of the AbD, (b) the review of the submission of information on the progress of the data collection (status report) and (c) the reviews of interim analyses [3] (see Figure 1).

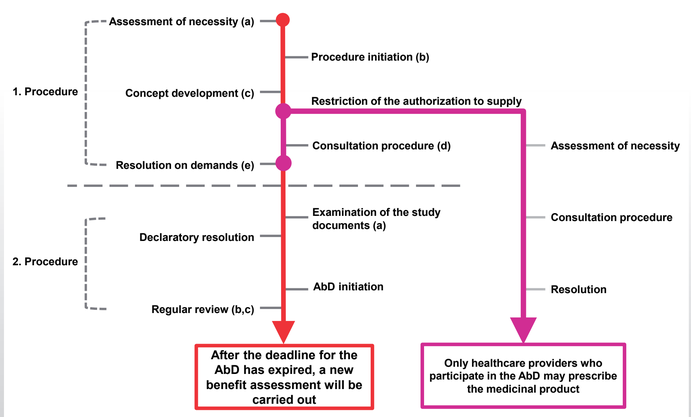


Fig. 1: Procedure of an AbD for medicinal products (according to G-BA)

### General overview

To date, 13 procedures have been initiated to request an AbD. The procedure was discontinued in 2 cases. In total, 6 AbDs were requested up to the data cut-off. Of these, 1 (fedratinib) was discontinued due to non-submission of study documents. In 2 cases, an AbD is currently running. The respective therapies can be divided into 3 therapeutic areas: neurodegenerative diseases, oncological diseases and diseases of the blood and blood-forming organs. On average, 300 days passed from the start of the procedure to the request for an AbD. During the first review of the SPs and SAPs prepared by the company, a total of 61 deficiencies were identified. Most of them were found in the categories Population Intervention Comparator Outcome (PICO), identification and collection of confounders and their adjustment, and quality and completeness of data collection (see Table 1).

| Orphan Drug | Brand name | Pharmaceutical manufacturer | Therapeutic indication | Start of the AbD procedure | G-BA Status |
|---|---|---|---|---|---|
| **Onasemnogen-Abeparvovec** | Zolgensma | Novartis Gene Therapies EU Limited | Spinal muscular atrophy | 16.07.2020 | AbD ongoing |
| **Risdiplam** | Evrysdi | Roche Pharma AG | Spinal muscular atrophy | 07.10.2021 | AbD required |
| **Brexucabtagen-Autoleucel** | Tecartus | Gilead Sciences GmbH | Relapsed or refractory mantle cell lymphoma | 07.10.2021 | AbD ongoing |
| **Fedratinib** | Inrebic | Bristol Myers Squibb | Myelofibrosis | 21.10.2021 | AbD won´t be conducted |
| **Valoctocogen Roxaparvovec** | Roctavian | BioMarin International Ltd. | Hemophilia A | 03.02.2022 | AbD required |
| **Etranacogen Dezaparvovec** | Hemgenix | CSL Behring GmbH | Hemophilia B | 04.08.2022 | AbD required |
| **Brexucabtagen-Autoleucel** | Tecartus | Gilead Sciences GmbH | B cell precursors acute lymphocytic leukemia | 03.11.2022 | Procedure discontinued |
| **Exagamglogen Autotemcel** | n.a. | CRISPR Therapeutics; Vertex Pharmaceuticals | Sickle cell disease | 01.06.2023 | Procedure initiated |
| **Exagamglogen Autotemcel** | n.a. | Vertex Pharmaceuticals | Beta thalassemia | 06.07.2023 | Procedure discontinued |
| **Fidanacogen Elaparvovec** | n.a. | Pfizer Pharma GmbH | Hemophilia B | 05.10.2023 | Procedure initiated |
| **Talquetamab** | Talvey | Janssen Cilag | Relapsed and refractory multiple myeloma, at least 3 previous therapies | 19.10.2023 | Procedure initiated |
| **Odronextamab** | Tbd | Regeneron GmbH | Relapsed or refractory follicular lymphoma | 01.02.2024 | Procedure initiated |
| **Odronextamab** | Tbd | Regeneron GmbH | Relapsed or refractory diffuse large B-cell lymphoma | 01.02.2024 | Procedure initiated |

Table 1: Overview of AbD procedures

| Abbreviation | Meaning |
|---|---|
| ATMP | Advanced therapeutic medicinal product |
| AbD | Application-related data collection |
| G-BA | Federal joint committee |
| IQWiG | Institute for Quality and Efficiency in Health Care |
| PICO | Population intervention comparator outcome |
| RCT | Randomized controlled trial |
| RRCT | Registry-based randomized controlled trial |
| SAP | Statistical analysis plan |
| SP | Study protocol |
| vfa | Association of research-based pharmaceutical companies |
| zVT | Appropriate comparator therapy |

### Deficiencies of SPs & SAPs

A total of 61 necessary adjustments to the SPs and SAPs were identified, which were divided into 13 categories. Most of the deficiencies, with 9 and 8 respectively, can be assigned to the categories "PICO", "Identification and collection of confounders, adjustment" and "Quality and completeness of data collection". In total 7 necessary adjustments were identified in each of the categories "Comments on the planned evaluations of the endpoints" and "Study population of the registry study", and 6 in the category "Data source" (see Table 2).

| | Amount of deficiencies | Amount of deficiencies [%] |
|---|---|---|
| **A priori determination of all definitions, operationalizations and analyses** | 2 | 3,3 |
| **PICO** | 9 | 14,8 |
| **Data source** | 6 | 9,8 |
| **Index date, assignment to treatment groups and observation period** | 3 | 4,9 |
| **Study population of the registry study** | 7 | 11,5 |
| **Identification and collection of confounders, adjustment** | 9 | 14,8 |
| **Comments on the planned evaluations of the outcomes** | 7 | 11,5 |
| **Examining potential effect modifiers and subgroup analyses** | 1 | 1,6 |
| **Quality and completeness of data collection** | 8 | 13,1 |
| **Further adjustments to the AbD** | 4 | 6,6 |
| **Interpretation of the results** | 1 | 1,6 |
| **Schedule** | 1 | 1,6 |
| **Miscellaneous** | 3 | 4,9 |
| **Total** | 61 | 100,0 |

Table 2: Overview of the deficiencies in the submitted study documents at the first review time

The categories were expanded to include subcategories for specification purposes. The subcategories "Endpoints" and "Consideration of important confounders in the analysis" were the most frequently identified deficiencies, with 6 each. A total of 5 and 4 deficiencies were identified in the subcategories "Case number planning", "Handling of missing data" and "General comments" respectively. Almost all SPs and SAPs were criticized for not describing the handling of missing data in sufficient detail. 3 deficiencies were described in each of the subcategories "Identification and collection of important confounders", "Measures to ensure the quality and completeness of data collection" and "Population" (see Table 3).

| | Amount of deficiencies | Amount of deficiencies [%] |
|---|---|---|
| **A priori determination of all definitions, operationalizations and analyses** | 2 | 3,3 |
| **PICO** | 9 | 14,8 |
| **Population** | 3 | 4,9 |
| **Intervention and Comparator** | 0 | 0,0 |
| **Outcome** | 6 | 9,8 |
| **Data source** | 6 | 9,8 |
| **Index date, assignment to treatment groups and observation period** | 3 | 4,9 |
| **Study population of the registry study** | 7 | 11,5 |
| **Sample size planning** | 5 | 8,2 |
| **Recruiting of the study population** | 1 | 1,6 |
| **Evaluation population** | 1 | 1,6 |
| **Identification and collection of confounders, adjustment** | 9 | 14,8 |
| **Identification and collection of important confounders** | 3 | 4,9 |
| **Consideration of important confounders in the analysis** | 6 | 9,8 |
| **Comments on the planned evaluations of the outcomes** | 7 | 11,5 |
| **General remarks** | 4 | 6,6 |
| **Evaluation of the outcome: overall mortality** | 0 | 0,0 |
| **Evaluation of Patient related outcomes** | 1 | 1,6 |
| **Evaluation of the outcome: adverse events** | 2 | 3,3 |
| **Examining potential effect modifiers and subgroup analyses** | 1 | 1,6 |
| **Quality and completeness of data collection** | 8 | 13,1 |
| **Measures to ensure the quality and completeness of data collection** | 3 | 4,9 |
| **Dealing with missing data** | 5 | 8,2 |
| **Further adjustments to the AbD** | 4 | 6,6 |
| **Interpretation of the results** | 1 | 1,6 |
| **Schedule** | 1 | 1,6 |
| **Miscellaneous** | 3 | 4,9 |
| **Total** | 61 | 100,0 |

Table 3: Detailed overview of the deficiencies in the submitted study documents at the first review time

### Duration of AbD procedures

At the time of the data cut, the procedure for Onasemnogen-Abeparvovec was the oldest and for Etranacogen Dezaparvovec the most recent. The shortest duration of the procedure, from the start of consultations to the request for an AbD, was 203 days (Onasemnogen-Abeparvovec) and the longest duration was 378 days (Fedratinib). The average duration of the procedure was 300 days. AbD is already ongoing for Onasemnogen-Abeparvovec and Brexucabtagen-Autoleucel. Between the request for an AbD and the start of the AbD, 362 days passed for Onasemnogen-Abeparvovec and 396 days for Brexucabtagen-Autoleucel. In total, the time between the start of the consultation procedure on the request for an AbD and the start of the AbD was 565 days for Onasemnogen-Abeparvovec and 683 days for Brexucabtagen-Autoleucel (see Figure 2).

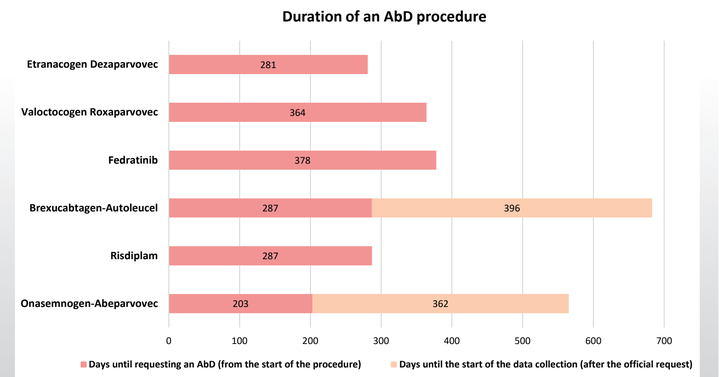


Fig. 2: Overview of the duration of initiated AbD procedures

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