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Uncertainty in AMNOG Benefit Assessments: Reflection of G-BA's Underlying Motivation to Cause AbD

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Background

- In 2020, Chapter 5 of the Rules of Procedure for new medicinal products in Germany was revised to include details about an application-accompanying data collection (Anwendungs-begleitende Datenerhebung [AbD])[1].
- The aim of this procedure is to close evidence gaps objected during the authorization procedure by the European Medicines Agency (EMA), which is also required by the Federal Joint Committee (G-BA) for the added benefit assessment.
- An AbD can only be applied to drugs with[2]:
  - conditional approval
  - approval under exceptional circumstances
  - an orphan designation
- When an AbD is imposed, the pharmaceutical company (pU) is obliged to collect care-related data of patients by the inclusion of registries to gather additional information about benefits and harms associated with the new drug.
- After expiry of the AbD, the medicinal product must undergo a new benefit assessment procedure in which the G-BA will take the additionally generated data into account.

Objectives

- The aim of this study was to provide a detailed description of the chronologic order and duration of the individual steps of the AbD process based on current procedures as well as to evaluate similarities and potential parameters that lead to an AbD.

Methods

- A systematic search of present AbD assessments published on the G-BA website was performed[3].
- All procedures initiated since the start in 2020 have been evaluated for the indication, kind of authorization, assessed benefit, among others.
- In particular, the justifications of the claim resolution were analyzed to identify the underlying reasons for an AbD assignment by the G-BA.

Conclusions

- The AbD procedure is a continuously evolving process with dynamic timelines.
- It can be initiated at any point during the admission process, even without a completed benefit assessment.
- The major similarity amongst all substances with an AbD is the innovative therapeutic character, which can lead to uncertainties in the evidence generation.
- In all AbD procedures the missing comparative evidence with a therapeutic alternative was stated by the G-BA as a justification for an AbD.
- Other reasons were a too short study duration or missing patient subpopulations.
- The G-BA identified uncertainties in the indirect and historical comparisons as well as in the pivotal studies that were submitted by the pharmaceutical companies for the added benefit assessment.
- Since not all innovative therapeutics or substances where the pivotal study lacks a direct comparison have an AbD imposed, no distinct predictive factors for a mandatory AbD could be identified.

Advice box

In case of uncertainties of evidence, pharmaceutical companies should anticipate to actively consider collecting evidence early on in their clinical development program through registries to comply with G-BA's information needs.*

*The information provided on this poster does not constitute legal advice.

References

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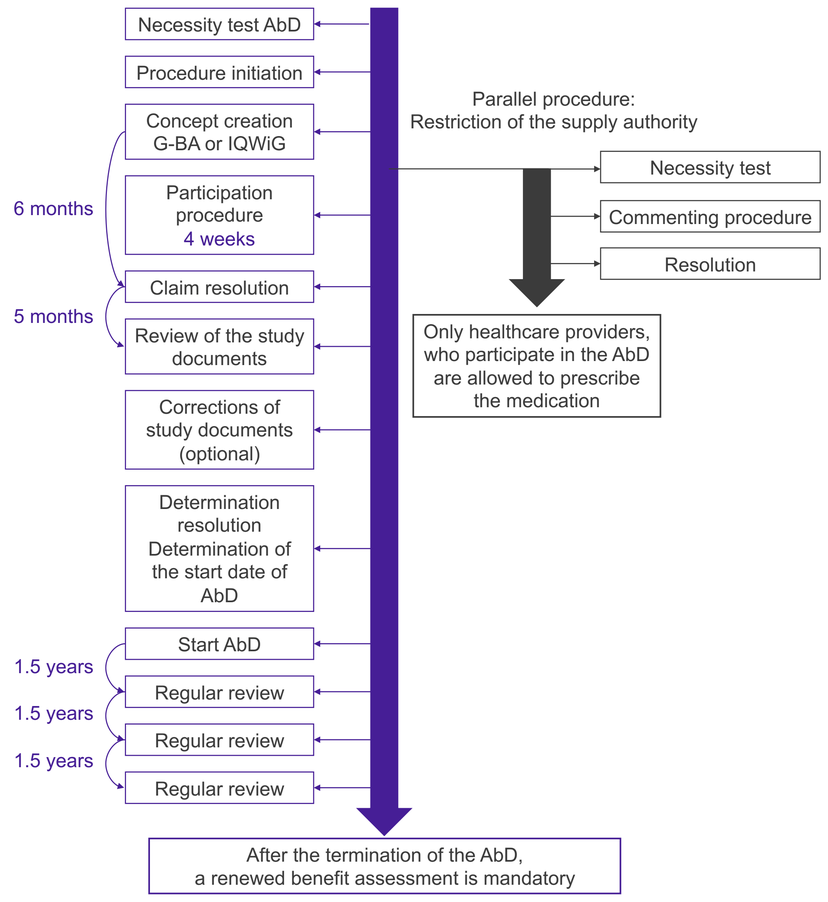
3. Gemeinsamer Bundesausschuss (G-BA). *Anwendungsbegleitende Datenerhebungen und Beschränkungen der Versorgungsbefugnis.* Accessed September 4, 2023. https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/.

Results

Figure 1. Flow diagram of the AbD process[3]



Key: AbD – application-accompanying data collection; G-BA – Federal Joint Committee; IQWiG – Institute for Quality and Efficiency in Health Care.

- Firstly, the G-BA examines whether there is a need for an AbD to improve the evidence base for a subsequent benefit assessment (**Figure 1**).
- If an AbD is required, the G-BA or the Institute for Quality and Efficiency in Health Care (IQWiG) develops a content-related concept, in which expert committees are also involved in a four-week procedure.
- The plenum then decides in a claim resolution on the requirements for an AbD.
- Based on this, the pU is commissioned to develop a statistical analysis plan and clinical study protocol within 5 months, the suitability of which is then reviewed by the G-BA.
- After deficiencies have been remedied by the pU, the study documents are finalized and the start date of the AbD is specified in the declaratory decision.
- During the AbD, the pU is obliged to submit status reports and interim analyses at regular intervals.
- In a parallel procedure, the G-BA conducts whether there is a necessity to restrict the supply only to providers participating in the AbD.
- Subsequently a draft resolution commenting procedure is executed by organizations and experts.
- A restriction of supply availability is decided by the plenum at the same time as the claim resolution for an AbD.
- After completion of the AbD, the product must undergo a renewed benefit assessment.

Table 1. Overview of products with an AbD assignment (status September 2023)[3]

Active substance (Trade name)	Indication	Approval status	Assessed benefit	Start of procedure	AbD-Status	Primary register	Therapy costs[a]
Onasemnogen-Abeparvovec (Zolgensma®)	Spinal muscular atrophy	OD	no	16.07.2020	Ongoing data collection	SMArtCARE	2.314.550,00 €
Risdiplam (Evrysdi®)	Spinal muscular atrophy	OD	non-quantifiable	07.10.2021	Request for AbD	SMArtCARE	94.166,44 € - 313.888,14 €
Brexucabtagen Autoleucel (Tecartus®)	Mantle cell lymphoma	OD	non-quantifiable	07.10.2021	Ongoing data collection	EMCL	360.000,00 €
Fedratinib (Inrebic®)	Myelofibrosis	OD	non-quantifiable	21.10.2021	AbD is not performed	GSG-MPN	65.005,77 €
Valoctocogen Roxaparvovec (Roctavian®)	Haemophilia A	OD	non-quantifiable	03.02.2022	Request for AbD	DHR	2.143.958,40 €
Tabelecleucel (Ebvallo™)	EBV-positive post-transplant lymphomas	OD	n.a.[b]	05.05.2022	No procedure initiated	n.a.	n.a.[b]
Etranacogen Dezaparvovec (Hemgenix®)	Haemophilia B	OD	n.a.[b]	04.08.2022	Request for AbD	DHR	n.a.[b]
Brexucabtagen Autoleucel (Tecartus®)	B-cell precursor acute lymphocytic leukemia	OD	non-quantifiable	03.11.2022	Procedure discontinued	n.a.	282.000,00 €
Exagamglogene Autotemcel (n.a.)	Sickle cell disease	OD	n.a.[b]	01.06.2023	Procedure initiated	n.a.	n.a.[b]
Exagamglogene Autotemcel (n.a.)	Beta thalassemia	OD	n.a.[b]	06.07.2023	Procedure initiated	n.a.	n.a.[b]

Key: AbD – application-accompanying data collection; DHR – German Haemophilia Register; EBV – Epstein-Barr virus; EMCL – European Mantle Cell Lymphoma; GSG-MPN – German Study Group for Myeloproliferative Neoplasms; n.a. – not available; OD – orphan drug.
[a] Annual therapy cost per patient. [b] Early benefit assessment is not completed yet.

- Since inception, 9 AbD procedures have been initiated (status September 2023) of which two currently commenced AbD. All of them can be categorized as OD (**Table 1**).
- In two cases, the procedure was discontinued at different stages during the process.
- Since the necessity review for Tabelecleucel (Ebvallo™) revealed a too-small patient population, an AbD was no longer considered.

Figure 2. Reasons of the assignment of an AbD by the G-BA[3]

Key: AbD – application-accompanying data collection; G-BA – Federal Joint Committee.

- A major reason for the G-BA requesting an AbD, was the lack of a head-to-head trial for all 9 procedures (**Figure 2**).
- In 5 cases the G-BA considered the study duration to be too short to reliably assess the efficacy and safety profile of the substances.
- For two substances, the G-BA required additional subpopulations that were not covered in the pivotal study.
- In one procedure, uncertainties were identified regarding the indirect and historical comparisons used.
- In another procedure, uncertainties and limitations (eg, the early termination of the study and the comparator used did not reflect the German healthcare context) were identified by the G-BA in the pivotal study, due to which the G-BA could not ensure a reliable additional benefit assessment.

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