A critical review six years after the GSAV

The procedure for the collection of data accompanying the application for the early benefit assessment

On 16 August 2019, the Act for More Safety in the Supply of Medicinal Products (GSAV) came into force. Amendments were made to Section 35a SGB V, which enable the Federal Joint Committee (G-BA) to require the submission of application-related data collection (AbD) for the purpose of a (renewed) benefit assessment for medicinal products for the treatment of a rare condition (orphan drug), medicinal products with a conditional marketing authorisation (CMA) and medicinal products with a marketing authorisation under exceptional circumstances (MAEC). The focus here is on observational studies, case-control studies and registry studies. Randomised controlled trials (RCTs) are excluded. For the first time, a new assessment situation was introduced as part of the established AMNOG procedure, which regularly provides for the inclusion of data of an evidence level below the gold standard RCT.

>> The GSAV also introduced a provision in Section 130b para. 3 SGB V, which interacts with the provision in Section 35a para. 3b SGB V. If, after conducting an AbD, the additional benefit of an orphan drug is still not quantifiable on the basis of the data obtained, the National Association of Statutory Health Insurance Funds (GKV-SV) must agree a discount on the reimbursement amount negotiated as part of the initial assessment. In the case of a sole CMA or MAEC, new price negotiations also take place. The legislator formulated the following objectives that it wanted to achieve with this amendment to the law: (1) Medicinal products that have been granted marketing authorisation on the basis of weak evidence, in particular orphan drugs, should (continue to) be made available to patients in statutory health insurance without delay and, at the same time, a better database should be created for the (renewed) assessment of the additional benefit (2).

The aim is to create an incentive to carry out AbDs and at the same time to prevent the reimbursement amount from remaining permanently high even though there is insufficient evidence of added benefit [1]. The AbD should therefore be seen both as an instrument for creating a better evidence base and as an instrument for price regulation.

Since orphan drugs in particular are intended for use in small target populations, the G-BA can restrict the authorisation to prescribe such a medicinal product at the expense of the statutory health insurance to those healthcare providers who participate in the required AbD. This is intended to ensure that the most complete and valid data possible is collected from the care of insured persons and that fragmentary data collection is avoided [2]. Approximately 6 years after the GSAV came into force and 5 years after the first initiation of the procedure to require an AbD for the gene therapy Onasemnogene-Abeparvovec (Zolgensma®) for the treatment of spinal muscular atrophy, the present analysis is intended to provide a critical review of the AbD procedure. In this context, considerations on the future handling of orphan drugs in the context of benefit assessments are also discussed based on AMNOG decisions in the comparable period.

Interim assessment of the AbD procedure

IQWiG's rapid report on the generation of healthcare-related data for the purpose of benefit assessment was published on 24 January 2020. The decision to amend the G-BA's rules of procedure (VerfO) was taken together with the decision to initiate the first procedure for the gene therapy Zolgensma® in plenary session on 16 July 2020. Since March 2020, the G-BA has been reviewing ongoing authorisation procedures with regard to the suitability of the medicinal products in question for AbD, taking into account the legal requirements. For the initial screening, the G-BA usually uses available information from the authorisation procedures at the European Medicines Agency (EMA) and from study registers. In general, in an authorisation procedure without data from an RCT, it is assumed that there is a lack of meaningful evidence for a benefit assessment [3]. In the period from March 2020 to March 2025, a total of 69 medicinal products with orphan designation and/or possible CMA/ MAEC were identified on the basis of 262 monitored active substances, whose authorisation procedure was based on single-arm clinical trials, so that it was generally assumed that an AbD was required [Fig. 1]. A sole CMA or MAEC was issued relatively rarely by the EMA [4]. These 69 medicinal products formed the pool of possible AbD candidates to be discussed by the G-BA. The selection is a case-by-case decision and, according to Section 54 para. 2 VerfO, is made taking into account the feasibility and appropriateness of data collection. For this purpose, a search for available registers in the area of application (AWG) can be carried out.

It should be noted that when developing a new registry for an AbD, a period of 18 to 36 months must be expected before data collection can begin [5]. An attempt is also made to assess whether an AWG with a particularly small number of patients is present. This is based on a limit of 100 patients proposed by IQWiG, above which an adjusted indirect comparison is methodologically feasible [6, 7]. A comparator therapy is also determined, which forms the basis for the discussions on possible comparators. Drug candidates in AWGs without an available alternative therapy are usually not pursued further. It is unrealistic to assume that patients with a serious or life- threatening disease will forgo treatment

with an authorised promising new drug. The prospective collection of comparative data against the natural course of the disease would also be ethically questionable.

If a candidate is considered potentially suitable, a decision is taken to initiate the procedure and IQWiG is commissioned to draw up a concept for the AbD. A further decision on the binding requirement of the AbD will be taken after an expert exchange with registry operators, affected pharmaceutical companies (MAHs), medical experts and representatives of the Federal Institute for Drugs and Medical Devices (BfArM) or the Paul Ehrlich Institute (PEI). To date, 20 AbD procedures have been initiated on the basis of 69 candidates. Of these, an AbD has been requested for 9 active substances. Following a decision to request an AbD, 2 AbD procedures were discontinued because the MAHs did not fulfil their obligation to prepare a study protocol (SP) and a statistical analysis plan (SAP). On one occasion, the loss of the legal basis with the marketing authorisation led to the procedure being discontinued. [Fig. 1, Tab. 1, Tab. 2].

RCTs were running in parallel in earlier treatment lines for 8 medicinal products for which a procedure was initiated. Of these, 7 medicinal products with a CMA were placed on the market [Tab. 3]. Ultimately, by 20 March 2025, around 6 years after the GSAV came into force, only 5 AbDs had been started and collected data from the practical use of the respective medicinal products in Germany. The duration of an AbD procedure from the entry into force of the decision on the claim to the new decision on the benefit assessment has so far been around 6.5 years (81 months) and comprises the preparation of the SAP/SP by the company, its review by IQWiG, the adaptation of the registry, the recruitment and data collection phase and the subsequent benefit assessment [8, Tab. 1]. An extension of the procedure is possible if, for example, more time is required to recruit the necessary number of patients. Due to the legal requirements, an AbD can be requested as early as possible with effect from the time of market availability in Germany.

Benefit assessments of orphan drugs in a comparable period

In the AMNOG database accessible on the G-BA website, a total of 217 benefit assessments for orphan drugs were identified that were initiated between 2020 and 2024. The procedures considered were those for which the G-BA carried out the dossier assessment as part of the statutory additional benefit fiction and for which a decision was available for the first time by 20 March 2025. This provides a good representation of the evidence base at the beginning of availability in Germany and also included orphan drugs in particular, for which the implementation of an AbD could be discussed. A total of 93 assessment procedures were included in the present analysis. Of these, 72 procedures were carried out at the time of first marketing in Germany and 21 procedures after authorisation of a new AWG.

There were 31 procedures for oncologicals and 62 procedures in non-oncological AWGs. According to the published decision documents, 33 procedures had a particularly small population size of less than 100 patients [Fig. 2]. The lower range of the specified number of patients was considered in order to be able to reliably record AWGs with very small population sizes, taking uncertainties into account. In the case of AWGs with several subpopulations formed by the G-BA, the patient numbers were added together as part of the analysis.

In total, data from RCTs were available for 60 of 93 procedures. RCTs were conducted more frequently in non-oncological AWGs than in oncological AWGs (71% vs. 52%). However, the added benefit could only be quantified in 26 of 60 cases on the basis of an available RCT. In a further 11 procedures with RCTs, an advantage could be derived by the G-BA at least at outcome level, but in 3 procedures only disadvantages could be derived [Fig. 3]. Overall, the added benefit could not be quantified in 66 of 93 cases. No data usable for the benefit assessment were available for 33 procedures. In 52 of 93 procedures, the added benefit was determined solely on the basis of the legal added benefit fiction. In only one procedure could the added benefit be quantified without an RCT [9].

Only 15 of the 93 orphan drugs assessed

Übersicht über aktive AbD-Verfahren und Verfahrensdauer laufender AbD

Wirkstoff u. Handelsname Zulassungsstatus	Indikationsgebiet Wirkstoffklasse	Beschlussdatum	Erneute Nutzenbewertung
Onasemnogen – Zolgensma® Orphan Drug und CMA	Spinale Muskelatrophie ATMP: Gentherapie	Forderung: 04.02.2021 Start: 01.02.2022	01.07.2027 Verfahrensdauer: 83 Mon.
Risdiplam – Evrysdi® Ehemals Orphan Drug	Spinale Muskelatrophie Niedermolekularer Wirkstoff	Forderung: 21.07.2022 Start: 30.10.2024	01.04.2028 Verfahrensdauer: 74 Mon.
Brexucabtagen – Tecartus® Orphan Drug und CMA	MCL ab Drittlinie ATMP: CAR-T-Zellen	Forderung: 21.07.2022 Start: 21.08.2023	21.07.2028 Verfahrensdauer: 78 Mon.
Valoctocogen – Roctavian® Orphan Drug und CMA	Schwere Hämophilie A ATMP: Gentherapie	Forderung: 02.02.2023 Start: 30.08.2024	02.11.2029 Verfahrensdauer: 87 Mon.
Etranacogen – Hemgenix® Orphan Drug und CMA	Schwere Hämophilie B ATMP: Gentherapie	Forderung: 12.05.2023 Start: 30.08.2024	02.11.2029 Verfahrensdauer: 84 Mon.
Fidanacogen – Beqvez® CMA	Schwere Hämophilie B ATMP: Gentherapie	Forderung: 18.04.2024 Nicht in Verkehr	offen
Exagamglogen – Casgevy® Orphan Drug und CMA	Schwere Sichelzellkrankheit ATMP: Gentherapie	Forderung: 21.12.2023 Start: offen	offen
Odronextamab – Ordspono® Orphan Drug und CMA	DLBCL ab Drittlinie Bispezifischer Antikörper	Einleitung: 01.02.2024	offen
Epcoritamab – Tepkinly® CMA (ehemals Orphan Drug)	DLBCL ab Drittlinie Bispezifischer Antikörper	Einleitung: 16.01.2025	offen
Glofitamab – Columvi® Orphan Drug und CMA	DLBCL ab Drittlinie Bispezifischer Antikörper	Einleitung: 16.01.2025	offen
Loncastuximab – Zynlonta® CMA	DLBCL ab Drittlinie Antikörper-Wirkstoff-Konjugat	Einleitung: 16.01.2025	offen
Belumosudil – Rezurock® Nicht zugelassen	Chronische GvHD Niedermolekularer Wirkstoff	Einleitung: 20.02.2025	offen

Tab. 1: Overview of active AbD procedures (as of 18 April 2025). Abbreviations: ATMP = advanced therapy medicinal product, MCL = mantle cell lymphoma, DLBCL = diffuse large B-cell lymphoma, GvHD = graft-versus-host disease. Source: Decisions of the G-BA from https://www.g-ba.de/anwendungsbegleitendedatenerhebung-verfahren/

fulfilled two central AbD criteria: (1) no RCT was available as a basis for assessment and (2) the AWG included more than 100 patients [Fig. 2]. In this group, an AbD procedure was initiated for 6 active substances.

Problem description of the AbD procedure

1. long duration of the procedure

It has become apparent that the duration of an AbD procedure is significantly longer than the time limits previously imposed under the AMNOG procedure. Particularly in dynamic therapeutic areas, it is to be feared that the relevance of the data collected to healthcare is no longer given or at least severely limited at the time of the benefit assessment. The EMA often takes an adaptive approach to authorisation procedures in oncological indications. An active substance is initially authorised on the basis of initial clinical data for a limited patient population with a high medical need with a CMA. The phase III RCT in an earlier line of therapy is already recruiting and the active substance is expected to be authorised and used in this new treatment situation in the medium term [10, 11]. This raises the question of the future relevance of data from an AbD that exclusively addresses the initially adaptively authorised indication. It is critical if the AbD, taking into account previously estimated procedural deadlines, can only be completed when higher-quality evidence in this earlier line of therapy is already foreseeable [Tab. 1, Tab. 3].

There is also the risk that the comparators defined in the context of the claims resolution no longer correspond to the state of medical knowledge at the time of the subsequent benefit assessment. In principle, it is possible to adapt the comparator selection by means of an amendment resolution, but the deletion of active substances that account for a relevant proportion of the patients already recruited is particularly problematic. Two procedurally relevant regulations in the AM-NutzenV contradict each other. On the one hand, according to Section 7 (2a), the data collected and analysed from an AbD must be used by the G-BA for the benefit assessment; on the other hand, according to Section 6 (2), the appropriate comparator therapy (ACT) must correspond to the generally recognised state of medical knowledge at the time of the decision.

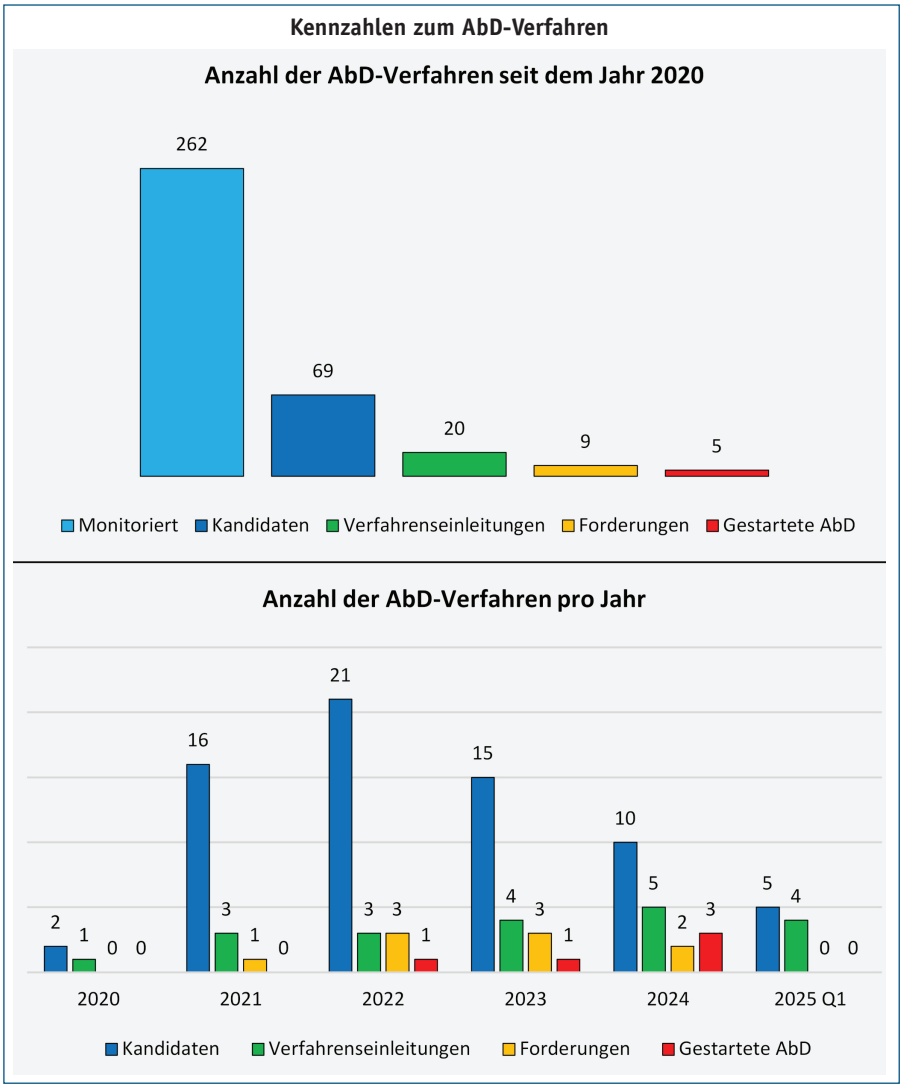


Fig. 1: Number of AbD procedures since 2020 and per year (source: own illustration)..

2. Very large effect differences necessary

For methodologically adequately conducted comparative studies without randomisation, IQWiG requires that conclusions on the benefit or harm of an intervention are only possible if the 95% confidence interval for an observed effect for outcomes in the serious/serious complications category exceeds a threshold value of 2-5 for the relative risk [12]. Although this is below the threshold of a dramatic effect, the AbD is foreseeably only sufficiently sensitive to detect very large effect differences for patient-relevant outcomes, assuming a shifted null hypothesis. The more effective the treatment alternatives available as comparators are, the less likely this is to be the case. Although perhaps technically/administratively feasible, the expected gain in knowledge of an AbD with the comparison of two or more drugs of a drug class (parallel developments) is particularly doubtful. An obvious dilemma arises here, as the AbD is supposed to lead to lower reimbursement amounts, especially for drugs without sufficient evidence of additional benefit. A classic case number estimation, as carried out in the context of a clinical trial to confirm a superiority hypothesis, has its limits with the AbD. There are also doubts as to how a treatment effect should be assigned to the benefit categories specified in Section 5 (7) AM-NutzenV with the necessary gradations..

3. Even established registries can only be used after adaptation

For the implementation of an AbD, it is advantageous to be able to use an existing registry that already collects patient-relevant

outcomes and covers a significant proportion of the respective target population. So far, however, even established disease-specific registries have only been suitable as a data source for an AbD subject to adjustments still to be made. During the concept development process, IQWiG repeatedly criticised the fact that patient-reported outcomes and adverse events were not collected to a sufficient extent, that the basic data did not include relevant confounders for indirect comparisons and that the measures to ensure the completeness and accuracy of the collected data (source data verification) were insufficient. Due to the limited scope of the defined oncological basic data set, the clinical cancer registries were previously not suitable as a data source for an AbD [13, 14]. The possibility of using historical data from clinical registries for adjusted indirect comparisons in the context of an AbD or benefit assessment has so far been fundamentally denied due to the aforementioned shortcomings. Problems can arise if, due to the lack of a suitable registry, the AbD is not initially requested despite insufficient evidence. For reasons of equal treatment, it may then be necessary to carry out an AbD at a later date if a registry is available and the AbD is discussed for an active substance in the same AWG [15]. This is in contrast to the proportionality of conducting a data collection for an active substance that may have been established in practice several years after placing on the market.

Übersicht über eingestellte AbD-Verfahren und die Gründe der Einstellung

Wirkstoff u. Handelsname Zulassungsstatus	Indikationsgebiet Wirkstoffklasse	Beschlussdatum	Gründe Einstellung
Fedratinib – Inrebic® Orphan Drug	Symptomatische Myelofibrose Niedermolekularer Wirkstoff	Einleitung: 21.10.2021 Forderung: 03.11.2022 Einstellung: 01.06.2023	Opt-out durch den pU. Nach der Forderung einer AbD wurden Studienprotokoll und SAP nicht vorgelegt.
Brexucabtagen – Tecartus® Orphan Drug und CMA	ALL ab Zweitlinie ATMP: CAR-T-Zellen	Einleitung: 03.11.2022 Einstellung: 20.07.2023	Stark eingeschränkte Rekrutierbarkeit in der klinischen Praxis. Geringere Effektunterschiede erwartbar.
Exagamglogen – Casgevy® Orphan Drug und CMA	Beta-Thalassämie ATMP: Gentherapie	Einleitung: 06.07.2023 Einstellung: 01.02.2024	Eingeschränktes AWG zugelassen. Fallzahl für eine adäquate Confounder-Kontrolle nicht rekrutierbar.
Marstacimab – Hympavzi® Reguläre Zulassung	Schwere Hämophilie A oder B Monoklonaler Antikörper	Einleitung: 04.04.2024 Einstellung: 05.12.2024	Keine Zulassung als Orphan Drug und keine CMA. Fehlende Rechtsgrundlage für die Forderung einer AbD.
Epcoritamab – Tepkinly® CMA	FL ab Drittlinie Bispezifischer Antikörper	Einleitung: 04.04.2024 Einstellung: 06.03.2025	Registerbetreiber gaben an, dass in drei Jahren nur 80–90 Patienten der Zielpopulation rekrutiert werden könnten.
Odronextamab – Ordspono® Orphan Drug und CMA	FL ab Drittlinie Bispezifischer Antikörper	Einleitung: 01.02.2024 Einstellung: 06.03.2025	Registerbetreiber gaben an, dass in drei Jahren nur 80–90 Patienten der Zielpopulation rekrutiert werden könnten.
Iptacopan – Fabhalta® Orphan Drug	Paroxysmale Hämoglobinurie Niedermolekularer Wirkstoff	Einleitung: 01.08.2024 Einstellung: 20.03.2025	Aufgrund der Struktur und der Vertragsgestaltung ist das im AWG etablierte IPIG-Register für die AbD ungeeignet.
Talquetamab – Talvey® Orphan Drug und CMA	MM ab Viertlinie Bispezifischer Antikörper	Einleitung: 19.10.2023 Forderung: 18.07.2024 Einstellung: 17.04.2025	Opt-out durch den pU. Nach der Forderung einer AbD wurden Studienprotokoll und SAP nicht vorgelegt.

Tab. 2: Overview of discontinued AbD procedures (as of 18 April 2025). Abbreviations: ALL = acute lymphoblastic leukaemia, FL = follicular lymphoma, MM = multiple myeloma. Source: Decisions of the G-BA from https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/

4. High administrative effort

AbDs are associated with a high administrative burden. This is mainly due to the high data volume and data quality requirements. Although the legislator has stipulated that the data collection should accompany the application and that there are no restrictions for the prescribing physicians with regard to drug supply (no randomisation or study specifications), the AbD must nevertheless be carried out for the purpose of the benefit assessment [1]. In particular, the implementation of the collection of patient- reported outcomes is associated with a high personnel and logistical effort. The narrow time tolerance window for data collection for the respective patient must also be taken into account [16, 17]. In addition, the requirements for source data verification pose challenges for registry operators and service providers [17]. Since the data generated at the company's expense must be taken into account in the new benefit assessment according to Section 7 para. 2a of the German Ordinance on the Assessment of Pharmaceutical Benefits (AM-NutzenV), extensive examination and consultation of the respective AbD projects by the G-BA is required in advance. Important resources are tied up at IQWiG by the development of concepts and the approval of study protocols and statistical analysis plans.

5. Negative effects of the restriction of care

The prescribing behaviour of healthcare providers is likely to be influenced if an AbD with supply restriction has been requested for an active substance for which there is at least one current alternative recommended by guidelines, but for which prescribing is not restricted. In view of the additional effort associated with an AbD, it is possible that this alternative therapy will be used in everyday practice. A shift in patient flows then takes place and makes it more difficult to generate data on the target active substance. If possible, a joint AbD should be carried out for several new medicinal products in the same AWG. Data collection on the basis of a master protocol in the same registry or in the same platform study with a joint control group can reduce the administrative effort and costs for the participating MAHs [18]. However, if an AbD with supply restriction is to be conducted for several active substances in the same

AWG, the company that refuses the AbD and forces a new reimbursement amount negotiation with the SHI-SV would have a competitive advantage over competitors who endeavour to generate further evidence.

pUs reduzieren [18]. Wenn für mehrere Wirkstoffe im gleichen AWG eine AbD mit Versorgungsbeschränkung durchgeführt werden soll, hätte allerdings der pU, welcher sich der AbD verweigert und eine erneute Erstattungsbetragsverhandlung mit dem GKV-SV forciert, einen Wettbewerbsvorteil gegenüber Mitbewerbern, die sich bemühen, weitere Evidenz zu generieren.

6. Overestimation of the available number of patients

IQWiG usually estimates the available number of patients in the AbD concept on the basis of publicly available information, in particular taking into account decisions already made in the benefit assessment. Without adequate data on the expected effectiveness, however, estimating the number of cases is associated with a high degree of uncertainty.

The reason for 3 procedure discontinuations in the indication areas follicular lymphoma and acute lymphoblastic leukaemia was a lower number of patients that could be recruited in practice, which, according to the assessment of the experts and registry operators, was significantly below the hypothetically existing number of patients used by IQWiG [19, 20]. Confounder adjustment procedures can also lead to fewer patients being included in the analyses due to trimming. This means that a higher number of cases is required to prove an effect than initially calculated [17, 21]. A complete survey of all available patients as a basis for calculation is generally considered unrealistic.

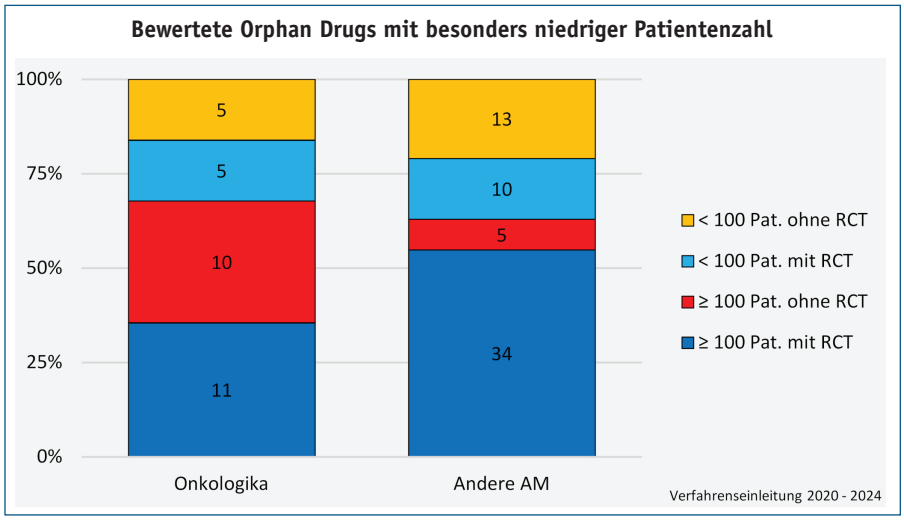


Fig. 2: Orphan drugs assessed with a particularly low number of patients (source: own illustration).

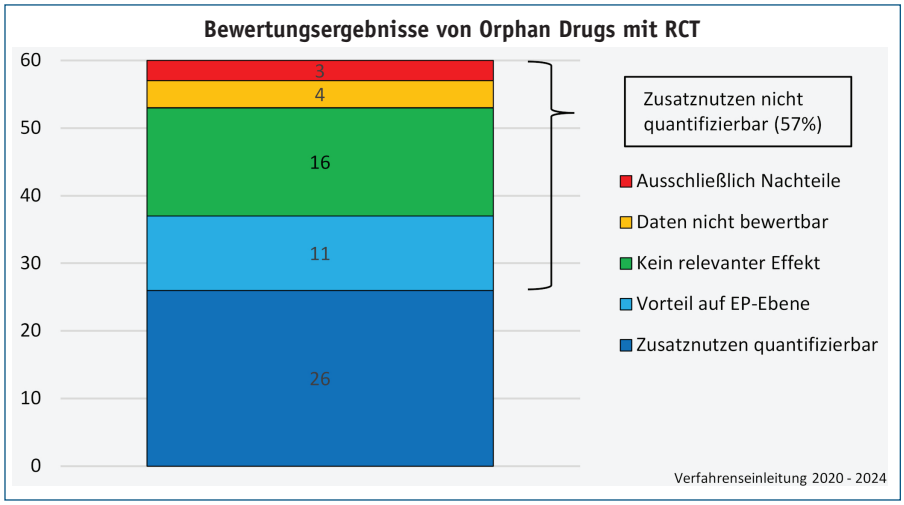


Fig. 3: Assessment results of orphan drugs with RCT (source: own illustration).

Conclusions

The AbD procedure falls short of expectations. The legislator originally assumed that around 9 to 10 AbDs per year would be required by the G-BA [1]. After 5 years of procedural practice, it has become clear that the feasibility and appropriateness of an AbD can be questioned in advance in many cases. Even at the beginning, the procedure was only seen as an emergency solution in individual cases [22]. The number of eligible candidates is reduced, as the majority of data from RCTs are available as evidence for a benefit assessment for orphan drugs. This is particularly true for non-oncological indications. In addition, a relevant number of orphan drugs are authorised on the basis of single-arm studies in AWGs with particularly small numbers of patients, in which an AbD cannot be implemented for methodological reasons [Fig. 2].

Quality deficiencies within the submitted RCTs, such as a comparator that does not correspond to the current standard of care or a comparative study duration that is too short for a chronic disease, are reasons why the added benefit cannot be quantified. Frequently, however, there are also no advantages in patient-relevant outcomes accepted by the G-BA [Fig. 4]. Laboratory parameters without reference to symptoms are not yet accepted by the G-BA. However, no comprehensive methodological and content-related review of the identified studies can be carried out in advance as part of the candidate selection process. This is the responsibility of the subsequent benefit assessment. Closing existing evidence gaps with an AbD only after authorisation is associated with high hurdles. In many cases, it is no longer possible to generate the necessary comparative evidence to quantify the added benefit of an orphan drug once it is available on the market, especially within a practicable timeframe and with reasonable effort. In the case of a CMA, high-quality RCT evidence can often be expected in an earlier line of therapy. Overall, the AbD is a complex procedure that involves considerable effort and resources, both for the G-BA, the registry operators and the authorised healthcare providers as well as IQWiG. Due to the small number of suitable candidates, the potential for cost reduc-

AbD-Verfahren mit laufenden RCTs in früherer Linie und Auflagen der EMA zur Erfüllung der CMA		
Wirkstoff u. Handelsname Fristen aus der CMA	**Indikationsgebiet Beschlussdatum**	**Laufende RCTs in früheren Linien**
Loncastuximab - Zynlonta® CMA: Ergebnisse der Studie LOTIS 5 bis Q4/2025	DLBCL ab Drittlinie Einleitung: 16.01.2025	Loncastuximab mit Rituximab versus Chemoimmuntherapie bei Patienten mit rezidiviertem oder refraktärem DLBCL (LOTIS-5) – Primärer Endpunkt: 30.06.2025 / Einleitung bis erstes Studienziel: **etwa 5 Monate**
Odronextamab - Ordspono® CMA: Ergebnisse der Studie OLYMPIA-4 bis Q4/2028	DLBCL ab Drittlinie Einleitung: 01.02.2024	Odronextamab mit Chemotherapie versus Rituximab mit Chemotherapie bei nicht vorbehandelten Patienten mit DLBCL (OLYMPIA-3) – Primärer Endpunkt: 18.09.2028 / Einleitung bis erstes Studienziel: **etwa 56 Monate** Odronextamab versus Chemotherapie/ASZT bei Patienten mit rezidiviertem oder refraktärem aggressivem B-Zell-NHL (OLYMPIA-4) – Primärer Endpunkt: 14.05.2027 / Einleitung bis erstes Studienziel: **etwa 39 Monate**
Epcoritamab - Tepkinly® CMA: Ergebnisse der Studie EPCORE DLBCL-1 bis Q4/2024	DLBCL ab Drittlinie Einleitung: 16.01.2025	Epcoritamab mit R-CHOP versus R-CHOP bei nicht vorbehandelten Patienten mit DLBCL (EPCORE DLBCL-2) – Primärer Endpunkt: xx.06.2027 / Einleitung bis erstes Studienziel: **etwa 29 Monate** Epcoritamab versus Chemotherapie bei Patienten mit rezidiviertem oder refraktärem DLBCL (EPCORE DLBCL-1) – Primärer Endpunkt: xx.12.2025 / Einleitung bis erstes Studienziel: **etwa 11 Monate**
Glofitamab - Columvi® CMA: Ergebnisse der Studie GO41944 bis Q3/2024	DLBCL ab Drittlinie Einleitung: 16.01.2025	Glofitamab mit GemOx versus Rituximab mit GemOx bei Patienten mit rezidiviertem oder refraktärem DLBCL (GO41944) – Primärer Endpunkt: 15.02.2026 / Einleitung bis erstes Studienziel: **etwa 13 Monate**
Epcoritamab - Tepkinly® CMA: Ergebnisse der Studie EPCORE FL-1 bis Q4/2030	FL ab Drittlinie Einleitung: 04.04.2024	Epcoritamab mit Rituximab und Lenalidomid versus Chemoimmuntherapie bei nicht vorbehandelten Patienten mit FL (EPCORE FL-2) – Primärer Endpunkt: xx.11.2037 / Einleitung bis erstes Studienziel: **etwa 163 Monate** Epcoritamab mit Rituximab und Lenalidomid (R2) versus R2 bei Patienten mit rezidiviertem oder refraktärem FL (EPCORE FL-1) – Primärer Endpunkt: xx.10.2030 / Einleitung bis erstes Studienziel: **etwa 78 Monate**
Odronextamab - Ordspono® CMA: Ergebnisse der Studie OLYMPIA-5 bis Q3/2031	FL ab Drittlinie Einleitung: 01.02.2024	Odronextamab Monotherapie versus Rituximab mit Chemotherapie bei nicht vorbehandelten Patienten mit FL (OLYMPIA-1) – Primärer Endpunkt: 04.04.2029 / Einleitung bis erstes Studienziel: **etwa 62 Monate** Odronextamab mit Lenalidomid versus Rituximab mit Lenalidomid bei Patienten mit rezidiviertem/refraktärem FL/MZL (OLYMPIA-5) – Primärer Endpunkt: 23.01.2029 / Einleitung bis erstes Studienziel: **etwa 60 Monate**
Talquetamab - Talvey® CMA: Ergebnisse der Studie MonumenTAL-3 bis Q2/2027	MM ab Viertlinie Einleitung: 19.10.2023	Talquetamab mit DaraPom versus DaraPomDex bei Patienten mit rezidiviertem oder refraktärem MM (MonumenTAL-3) – Primärer Endpunkt: 06.02.2026 / Einleitung bis erstes Studienziel: **etwa 28 Monate**
Belumosudil - Rezurock® *Nicht zugelassen*	Chronische GvHD Einleitung: 20.02.2025	Belumosudil mit Kortikosteroiden versus Kortikosteroide in Patienten ab 12 J. mit neu diagnostizierter chronischer GvHD (ROCKnrol-1) – Primärer Endpunkt: 29.09.2028 / Einleitung bis erstes Studienziel: **etwa 43 Monate**

Tab. 3: AbD procedures with ongoing RCTs in earlier lines (as of 22 April 2025). Abbreviations: DLBCL = diffuse large B-cell lymphoma, ASZT = autologous stem cell transplantation, NHL = non-Hodgkin's lymphoma, FL = follicular lymphoma, MM = multiple myeloma, MZL = marginal zone lymphoma, J. = years, GvHD = graft-versus-host disease. Source: Decisions of the G-BA from https://www.g-ba.de/anwendungsbegleitende-datenerhebung-verfahren/ and information from https://clinicaltrials.gov/

tions through downstream AbDs is considered marginal compared to the overall AMNOG procedure. In view of the rapid innovation cycles in the pharmaceutical industry and the long duration of the procedure, it is also often questionable whether findings relevant to healthcare can be generated. Due to the deadlines set by the G-BA, experience with the results of the ongoing AbDs will not be available until 2027, but the procedure is already proving to be unsuitable for solving the problem of the often poor evidence base for orphan drugs and effectively regulating the high therapy costs.

Outlook and proposals

RCTs will remain the gold standard for authorisation and benefit assessment in the future [23]. Numerous assessment procedures over the past 5 years have shown that RCTs can also be successfully conducted in patient groups with rare diseases. Advantages of RCTs in rare diseases can be that the number of patients required can be lower than for an AbD, as no confounder adjustment is necessary. In addition, an RCT is the more suitable instrument if low to moderate effect sizes are expected. The primary objective should therefore be to conduct RCTs and improve the quality of planned RCTs so that they can be used not only for the authorisation process, but also for the benefit assessment or the EU HTA procedure. Only in this way can the maximum benefit and knowledge gain be obtained from a study programme. The possibility for early consultations at the G-BA with the involvement of the BfArM or PEI anchored in Section 35a (7) SGB V should always be utilised and the recommendations taken into account. If RCTs are not feasible, it is advisable to prospectively collect comparative data on the natural course of the disease or on the previous standard of care in parallel with the authorisation study in order to be able to present these for the benefit assessment. Established registries should be specifically adapted and utilised for this purpose. For the EMA, statistical models and tests in which data from single-arm studies are compared with external controls are not sufficient to prove efficacy, as neither modelling procedures nor matching approaches could sufficiently reduce the bias. External data from registries could therefore only be used as support [23, 24]. The authorisation procedure therefore does not yet provide sufficient incentives to collect suitable data for adjusted indirect comparisons in advance in the exceptional situations in which single-arm study data are accepted for the benefit-risk assessment.

Orphan drugs are already included in the first implementation stage of the EU HTA procedure if they are oncologicals or ATMPs. A joint European clinical assessment will be carried out for all other orphan drugs from 13 January 2028 [25]. The EU HTA procedure is basically designed as a comparative assessment. As part of the scoping process, a complete PICO with a comparator is also drawn up for an orphan drug to determine the scope of the assessment [26].

It therefore makes sense to discuss the future handling of orphan drugs in the

downstream national AMNOG procedure again. In order to standardise the procedure, it would only be logical to carry out the benefit assessment of all medicinal products with new active substances transparently, regardless of their orphan drug status vis-à-vis a zVT. As clarified by the amendment to the AMNutzenV of 27 July 2023, best supportive care, watchful waiting or off-label use can also be considered for a comparative assessment.

The available evidence will probably not be sufficient to derive an added benefit in a relevant number of assessment procedures. Corresponding incentives for orphan drugs in therapeutic areas with a high medical need or if it is not possible to carry out adjusted indirect comparisons due to the particularly low number of patients could instead be set at the level of agreements on reimbursement amounts in Section 130b of the German Social Code Book V (SGB V). In the case of a regular benefit assessment of orphan drugs versus a zVT, the duplication of work in the context of the reassessment after exceeding the turnover thresholds of 30 million euros would be unnecessary and the legal basis for the AbD would be removed. If the added benefit cannot be demonstrated, Section 35a para. 5 SGB V already allows the company to generate additional evidence on a voluntary basis and apply for a benefit assessment based on new scientific findings.

The AbD procedure should be discontinued in the future, as the objectives formulated by the legislator cannot be realised in practice. No systemically relevant savings can be achieved with AbDs, nor can they improve the poor evidence situation at the time of authorisation of orphan drugs in a timely and comprehensive manner. The methodological findings and experience gained from dealing with AbDs should be used for future study planning and authorisation procedures as well as to improve the quality of the registry landscape in Germany..

Summary

In 2019, the Act for More Safety in the Supply of Medicinal Products (GSAV) introduced application-related data collection (AbD) as a new instrument for the benefit assessment of medicinal products with limited evidence - in particular orphan drugs. The aim was to create a better basis for a new benefit assessment through downstream data collection in healthcare practice. Despite initially high expectations, only 5 AbD procedures have actually been implemented since 2020. The procedures have proven to be costly, lengthy, administratively complex and often methodologically inadequate. Problems include the low availability of suitable patients, the lack of suitable registries, high data quality requirements and the low significance of non-randomised studies. The expected improvement in evidence and cost control is unrealistic. Instead, high- quality randomised studies are also recommended for rare diseases. The AbD procedure should therefore be phased out as it is neither efficient nor effective. It is proposed that in future a regular benefit assessment should also be carried out for orphan drugs by the Federal Joint Committee (G-BA) compared to an appropriate comparative therapy (ACT). Incentives for orphan drugs could be set at the level of agreements on reimbursement amounts in Section 130b SGB V. If randomised controlled trials (RCTs) are not feasible, it is advisable to prospectively collect comparative data on the natural course of the disease or the previous standard of care in parallel with the authorisation study in order to be able to present this data for the benefit assessment. Established registries should be specifically adapted and utilised for this purpose. Previous experience with AbDs can contribute to the improvement of study designs and registry quality. <<

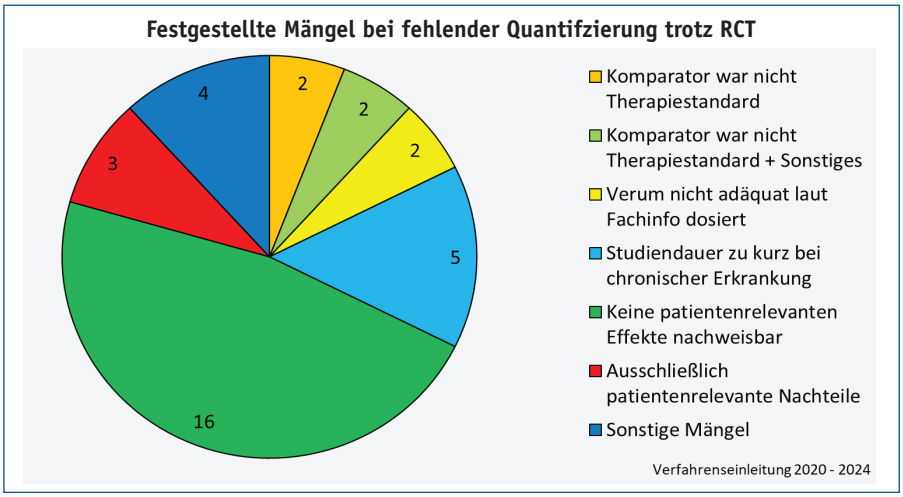


Fig. 4: Identified deficiencies in the absence of quantification despite RCT (source: own illustration)

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Author's declaration

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