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Evidence on orphan drugs[1]

Working Paper

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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

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The responsibility for the contents of the report lies solely with IQWiG.

IQWiG employees

- Philip Kranz
- Gertrud Egger
- Thomas Kaiser
- Fabian Lotz
- Can Ünal
- Siw Waffenschmidt

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AIS	Arztinformationssystem (physician information system)
AMNOG	Arzneimittelmarktneuordnungsgesetz (Act on the Reform of the Market for Medicinal Products)
COMP	Committee for Orphan Medicinal Products of the European Medicines Agency
EMA	European Medicines Agency
EU	European Union
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GSAV	Gesetz für mehr Sicherheit in der Arzneimittelversorgung (Law for More Safety in the Supply of Medicines)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
N	number of orphan drugs
n	number of research questions
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

Executive summary

The topic of evidence on orphan drugs was investigated within the scope of the general commission.

Background

Orphan drugs have a special position in the German Act on the Reform of the Market for Medicinal Products (AMNOG). Orphan drugs do not undergo the regular benefit assessment procedure after market access, since, according to § 35a of the German Social Code Book (SGB) V (1) Sentence 11, their added benefit is already considered proven with the approval at the European level. The Federal Joint Committee (G-BA) assesses the evidence submitted by the pharmaceutical company; no standard care (called "appropriate comparator therapy") is specified for these procedures (in the following, they are referred to as "limited assessments"). If, on the basis of this evidence, no quantification by the G-BA of the added benefit of the orphan drug into the categories "minor", "considerable" or "major" is possible, the drug is granted a "non-quantifiable" added benefit. A regular benefit assessment of an orphan drug versus the appropriate comparator therapy is only conducted if an annual revenue threshold of 50 million euro is exceeded, if the pharmaceutical company relinquishes the orphan drug status or if the disease no longer meets the prevalence criteria of a rare disease. In the regular benefit assessment, "no added benefit" or even "lesser benefit" of an orphan drug versus the appropriate comparator therapy can also be determined.

Research question

The aims of the present investigation are

- the systematic comparison of the (fictitious) added benefit in limited assessments and the inferred added benefit of an orphan drug versus the appropriate comparator therapy in regular benefit assessments of orphan drugs, and
- the description of the available evidence in regular benefit assessments versus previous limited assessments

Methods

Information retrieval

For the present project, all assessments of an orphan drug were used for which a regular benefit assessment according to § 35a SGB V was available. This could include, on the one hand, the first regular benefit assessment of the respective orphan drug after market access and, on the other, any subsequent assessments in the case of one or more extensions of the therapeutic indication, provided that the orphan drug status still existed at the European level at the time of this extension. The respective decisions of the G-BA were decisive for the determination of the assessment result.

To ensure a systematic presentation, the database of the G-BA on benefit assessments according to § 35a SGB V with the integrated filter on orphan drugs was used. All decisions on orphan drugs with their associated procedures were considered according to the above criteria.

Information synthesis

For the primary analysis, assessments were used where both a result according to § 35a SGB V (1), Sentence 11 (limited assessment) and that of a regular benefit assessment were available. The added benefit inferred in each case in a limited assessment was compared with that inferred in the subsequent regular benefit assessment. In addition, the underlying evidence base was described for these assessments.

For the secondary analysis, those assessments were considered where only a regular benefit assessment was available and it was examined how often no added benefit was determined for the orphan drug. This resulted in the proportion of potentially discrepant assessments to fictitious limited assessments that were not conducted because the revenue threshold had previously been exceeded. For these assessments, the underlying evidence base in each case was also described.

The assessment results on the added benefit were considered according to the distinction in the respective G-BA decision (i.e. within a decision, if necessary, at the level of several research questions).

Results

Information retrieval results

Information retrieval identified N = 20 orphan drugs for which at least one regular benefit assessment had been conducted. These orphan drugs were assessed in a total of n = 79 research questions. For 41 questions, both a limited assessment and a regular benefit assessment had been conducted (relevant for the primary analysis). One question was excluded from the primary analysis because it was the subject of the limited assessment, but not of the subsequent regular benefit assessment. For 37 questions, only a regular benefit assessment was available (relevant for the secondary analysis).

Results of the primary analysis

The primary analysis considered assessments where both the result of a limited assessment and that of a regular benefit assessment were available (41 research questions).

Results of the limited assessments and the regular benefit assessments

In the limited assessments of the 41 research questions on orphan drugs, an added benefit with the extent "non-quantifiable" was most commonly inferred (51%; n = 21). The extent of added benefit was minor in 32% (n = 13) of the questions, considerable in 15% (n = 6), and major in 2% (n = 1). In contrast, in the regular benefit assessments of these research questions on orphan drugs, no added benefit ("not proven") was most commonly inferred (54%; n = 22). The extent

of added benefit was non-quantifiable in 15% (n = 6) of the questions, minor in 7% (n = 3), considerable in 22% (n = 9), and major in 2% (n = 1).

Agreement between the results of the limited assessments and regular benefit assessments

Overall, 27% (n = 11) of all research questions relevant for the primary analysis showed an identical extent of added benefit between the limited and the regular benefit assessments. In 73% (n = 30) of cases, the extent of added benefit deviated between the two types of assessments. Among these, a greater extent of added benefit for the orphan drug was inferred in 14% (n = 6) of the research questions in the regular benefit assessment; in 5% (n = 2) the extent of added benefit was lower, and in 54% (n = 22) no added benefit was shown for the orphan drug.

Separated by drugs, an added benefit was inferred for only 25% of the 20 orphan drugs (N = 5; ivacaftor, ruxolitinib, nintedanib, olaparib, and carfilzomib) in all research questions of the regular benefit assessment. In most cases, however, the extent of added benefit deviated between the two types of assessments. For the remaining 75% (N = 15) of orphan drugs, in each case no added benefit was shown in the regular benefit assessment for at least 1 research question. For 45% (N = 9) of the orphan drugs, an added benefit was not determined in any research question.

Evidence base of the results of the limited assessments and regular benefit assessments

For the limited assessments, randomized controlled trials (RCTs) were available as an evidence base for 68% (n = 28) of the research questions. Non-randomized studies (non-RCTs) were available for 27% (n = 11) of the questions, and no (usable) data were submitted for 5% (n = 2) of the questions. Adjusted indirect comparisons or evidence transfers were not available in any assessment. The quantification of the added benefit by the G-BA into the categories “minor”, “considerable” or “major” was exclusively based on RCTs. In the case of non-RCTs or no (usable) data, a non-quantifiable added benefit was always inferred.

The evidence base of the regular benefit assessments of orphan drugs showed that for 39% (n = 16) of the research questions, direct comparative evidence from RCTs was available on orphan drugs versus the appropriate comparator therapy. For 5% (n = 2) of the questions, an adjusted indirect comparison was used. For 2% (n = 1) of the questions, usable data from non-RCTs were available. An evidence transfer was performed for 5% (n = 2) of the questions. No (usable) data were available for 49% (n = 20) of the questions. In the regular benefit assessment, the quantification of the added benefit into the categories “minor”, “considerable” or “major” was also exclusively based on RCTs.

For 66% (n = 27) of the 41 research questions, no new data were available for the regular benefit assessment versus the limited assessment. In these cases, mostly no added benefit was inferred (70% [n = 19] of the 27 questions). Data from newly conducted studies were available for 10% (n = 4) of the questions. New data from studies already known were available for 17% (n = 7) of the questions. If new studies or new data from known studies were available, an added benefit

was always inferred in the regular benefit assessment. New usable adjusted indirect comparisons were available for 7% (n = 3) of the questions; an added benefit was not inferred for any of them.

Results of the secondary analysis

For the secondary analysis, assessments of orphan drugs were considered where only a regular benefit assessment was available. This was, for example, the case for a newly approved therapeutic indication of an orphan drug if its revenue had already exceeded the threshold of 50 million euro before approval of the new therapeutic indication.

Results of the regular benefit assessments

In the regular benefit assessments of the 37 research questions, the conclusion "no added benefit" was most commonly inferred (54%; n = 20). The extent of added benefit was non-quantifiable in 22% (n = 8) of the questions, minor in 5% (n = 2), considerable in 11% (n = 4), and major in 8% (n = 3).

The results are consistent with those of the regular benefit assessments from the primary analysis.

Evidence base of the results of the regular benefit assessments

For 32% (n = 12) of the research questions, direct comparative evidence from RCTs was available for the orphan drug versus the appropriate comparator therapy. For 3% (n = 1) of the questions, usable data from an adjusted indirect comparison were available. Evidence transfers were used for 19% (n = 7) of the questions. No (usable) data were available for 46% (n = 17) of the questions. Non-RCTs were not considered. The quantification of added benefit into the categories "minor", "considerable" or "major" was based on RCTs in 89% (n = 8) of the 9 questions.

The results are largely consistent with those of the regular benefit assessments from the primary analysis.

Summary of the primary and secondary analysis

In a further analysis, the results of the primary and secondary analysis on regular benefit assessments were summarized (78 questions in total). This analysis enables a summary of the evidence on orphan drugs versus standard care (= appropriate comparator therapy) in the case of a regular benefit assessment.

Summary of the results of the regular benefit assessments

The frequencies of the extent of added benefit inferred are comparable to those of the primary and secondary analyses. No added benefit ("not proven") was most commonly inferred in the research questions (54%; n = 42). The extent of added benefit was non-quantifiable in 18% of the questions (n = 14), considerable in 17% (n = 13), minor in 6% (n = 5), and major in 5% (n = 4). A "lesser benefit" was not inferred in any question.

At the drug level, an added benefit was only inferred for 15% (N = 3) of the 20 drugs (ruxolitinib, nintedanib and olaparib) in all the research questions assessed during the period under review. For the remaining 85% (N = 17), no added benefit was inferred in at least 1 question. In the limited assessment, at least an added benefit with the extent "non-quantifiable" was granted or would have been granted for all of these questions and thus all 20 drugs.

Summary of the evidence base of the regular benefit assessments

The evidence base shows that for 47% (n = 37) of the 78 research questions, most commonly no usable data were available for the regular benefit assessment of the orphan drugs considered here. The fact that no usable data were available was also the most common reason for the conclusion "added benefit not proven" (88% [n = 37] of the 42 questions with this assessment).

For 36% (n = 28) of the 78 research questions, data from RCTs were available for the assessment. The quantification of the added benefit into the categories "minor", "considerable" or "major" was almost exclusively based on RCTs, with the exception of 1 question.

Conclusion

The present report shows that specifying a fictitious added benefit at market access of orphan drugs is misleading in more than half of the cases, as no proof of added benefit is shown in subsequent regular benefit assessments. This not only leads to misleading communication about the added benefit of new orphan drugs, but also discriminates against existing treatment options for rare diseases by letting them appear to be inferior through the fictitious added benefit granted to orphan drugs. Furthermore, this general fictitious added benefit prevents a distinction between orphan drugs with and without real progress for patient care. The misleading communication on added benefit is maintained for years and in some cases not corrected if the revenue threshold of 50 million euro per year is not exceeded or the pharmaceutical company voluntarily relinquishes the orphan drug status. Overall, a main goal of AMNOG, namely, "separating the wheat from the chaff", is prevented for orphan drugs through the privilege of a fictitious added benefit.

The evidence base shows that RCTs are also possible for orphan drugs. However, many of these RCTs have so far not focused on questions relevant to health care (comparison of orphan drugs with existing treatment options in respect of patient-relevant outcomes), but in particular address the criteria for approval. Efforts must therefore be undertaken to ensure that in future, patient-relevant and health care-related questions are increasingly considered in the planning and conduct of studies. In particular, routine data collection according to the German Law for More Safety in the Supply of Medicines (GSAV) should be expanded to include the possibility of conducting pragmatic (registry-based) RCTs. This could also promote the development of the registry landscape in Germany, with the aim of clarifying open health care questions as promptly and reliably as possible in the future.

1 Background

Drugs for rare diseases (orphan drugs) in the European Union

In the European Union (EU), diseases with a prevalence of ≤ 5 per 10 000 inhabitants are considered rare diseases. Adequate therapies for these rare diseases often do not exist. In order to create incentives for the pharmaceutical industry to invest in the development of orphan drugs despite market risks, the regulation on orphan medicinal products was adopted in 1999 [1]. A decisive incentive laid down in this regulation was market exclusivity, which guarantees manufacturers of orphan drugs that no similar drugs for the same therapeutic indication will be approved for the next 10 years. The period of market exclusivity may however be reduced to 5 years if the disease no longer meets the prevalence criteria of a rare disease. Furthermore, market exclusivity may be withdrawn if another pharmaceutical company (hereinafter referred to as "company") has developed a similar drug in the same therapeutic indication and has been able to establish clinical superiority of this drug.

Orphan drugs in AMNOG procedures

Orphan drugs have a special position in AMNOG [2]. Orphan drugs do not undergo the regular benefit assessment procedure after market access, since, according to § 35a SGB V (1) Sentence 11, their added benefit is already considered proven with the approval at the European level. The G-BA assesses the evidence submitted by the company; no ACT is specified for these procedures (in the following, they are referred to as "limited assessments"). If, on the basis of this evidence, no quantification by the G-BA of the added benefit of the orphan drug into the categories "minor", "considerable" or "major" is possible, the drug is granted a "non-quantifiable" added benefit. A regular benefit assessment of an orphan drug versus the ACT is only conducted if an annual revenue threshold of 50 million euro is exceeded, if the company relinquishes the orphan drug status or if the disease no longer meets the prevalence criteria of a rare disease. In the regular benefit assessment, "no added benefit" or even "lesser benefit" versus the ACT can also be determined. In case of newly approved therapeutic indications, these then also undergo a regular assessment versus the ACT.

Approved orphan drugs

Currently (as of November 2021), 127 orphan drugs are approved in the EU. A further 68 drugs no longer have orphan drug status because it has expired after 10 years in accordance with the regulation or has been relinquished by the company [3].

Current developments

On 11 August 2020, the European Commission published its evaluation of the legislation on rare diseases and conditions in children [4]. This evaluation found that the regulation on orphan medicinal products [1] has promoted the development and availability of medicines as planned. However, it was emphasized that the regulation has not sufficiently succeeded in promoting development in the areas of highest unmet need of drugs. Incentives to encourage the development of orphan drugs are therefore still relevant. In addition, inefficiencies and

undesirable consequences of the regulation were identified, which ought to be addressed in the Pharmaceutical Strategy for Europe [5].

There are also regular discussions on orphan drugs at national level in Germany, in the G-BA as well as in the Federal Ministry of Health; and IQWiG contributes to the public discourse by means of comments, among other things [6]. Against the background of the current developments at the EU level, it must be assumed that the issue of orphan drugs will become more topical again after the Bundestag election in September 2021 and that there may be relevant changes to the benefit assessment procedures for orphan drugs.

Necessity and potential benefits of the project

IQWiG takes a critical view of the special position of orphan drugs in AMNOG procedures and in principle argues for a regular benefit assessment of orphan drugs directly at market access.[6,7]. This is mainly due to the fact that the added benefit of orphan drugs, which, according to §35a SGB V (1), Sentence 11, is already proven by the approval, often cannot be established in a regular benefit assessment based on the evidence submitted by the company. In such cases, a non-quantifiable added benefit that is nevertheless established not only suggests the impression of a therapeutic improvement by the new drug. In addition, it is implicitly associated with the notion that any treatment options already available have a lesser benefit than the new drug. This is reinforced by the recent integration of the results of the benefit assessments into the German physician information system (AIS) according to §35a SGB V (3a).

A systematic investigation of the potential discrepancy of the inferred added benefit between limited assessments and regular benefit assessments of orphan drugs can provide a solid data basis for making criticism of the added benefit of orphan drugs already proven by the approval more objective. Furthermore, a systematic presentation of the evidence submitted in limited assessments and subsequent regular benefit assessments provides an overview of the type and quality of the studies submitted by the companies.

As described above, adjustments to the orphan drug regulations are currently being discussed at the European level, but also in the Federal Ministry of Health (most recently in 2018) and G-BA. With this project, IQWiG actively participates in the discourse and enables the various stakeholders to gain a perspective from an independent scientific point of view. The project also serves to inform and raise awareness among the general public about the often insufficient evidence available on orphan drugs at market entry, which does not justify an added benefit based solely on the approval granted.

In addition, the project provides the basis for a further analysis of the previous orphan drug dossiers (e.g. on patient numbers and/or costs) in an independent separate project by the Department of Health Care and Health Economics.

2 Research question

The aims of the present investigation are

- the systematic comparison of the (fictitious) added benefit in limited assessments and the inferred added benefit of an orphan drug versus the ACT in regular benefit assessments of orphan drugs, and
- the description of the available evidence in regular benefit assessments versus previous limited assessments.

3 Course of the project

3.1 Timeline of the project

The topic of evidence on orphan drugs was investigated within the scope of the general commission. The project started on 29 April 2021.

A working paper was prepared on the basis of the project outline. This report was sent to the G-BA and published on the IQWiG website 4 weeks later.

4 Methods

4.1 Information retrieval

For the present project, all assessments of an orphan drug were used for which a regular benefit assessment according to §35a SGB V was available. This could include, on the one hand, the first regular benefit assessment of the respective orphan drug after market access and, on the other, any subsequent assessments in the case of one or more extensions of the therapeutic indication, provided that the orphan drug status still existed at the European level at the time of this extension. The respective decisions of the G-BA were decisive for the determination of the assessment result.

To ensure a systematic presentation, the database of the G-BA on benefit assessments according to § 35a SGB V with the integrated filter on orphan drugs was used [8]. All decisions on orphan drugs with their associated procedures were considered according to the above criteria.

4.2 Information synthesis

For the primary analysis, assessments were used where both an assessment result according to §35a SGB V (1), Sentence 11 (limited assessment) and that of a regular benefit assessment were available. The added benefit inferred in each case in a limited assessment was compared descriptively with that inferred in the subsequent regular benefit assessment. In addition, the underlying evidence base was described for these assessments.

For the secondary analysis, those assessments were considered where only a regular benefit assessment was available and it was examined how often no added benefit was determined for the orphan drug. This resulted in the proportion of potentially discrepant assessments to fictitious limited assessments that were not conducted because the revenue threshold had previously been exceeded. For these assessments, the underlying evidence base in each case was also described.

The assessment results on the added benefit were considered according to the distinction in the respective G-BA decision (i.e. within a decision, if necessary, at the level of several research questions).

5 Results

5.1 Information retrieval results

Information retrieval identified N = 20 orphan drugs for which at least one regular benefit assessment had been conducted. These orphan drugs were assessed in a total of n = 79 research questions. For 41 questions, both a limited assessment and a regular benefit assessment had been conducted (relevant for the primary analysis). One question was excluded from the primary analysis because it was the subject of the limited assessment, but not of the subsequent regular benefit assessment. For 37 questions, only a regular benefit assessment was available (relevant for the secondary analysis). An overview of the relevant orphan drugs, the period of the orphan drug status at EU level, the research questions assessed and whether a limited assessment was previously conducted by the G-BA is presented in Table 6 in Appendix A. Figure 1 shows the information retrieval results.

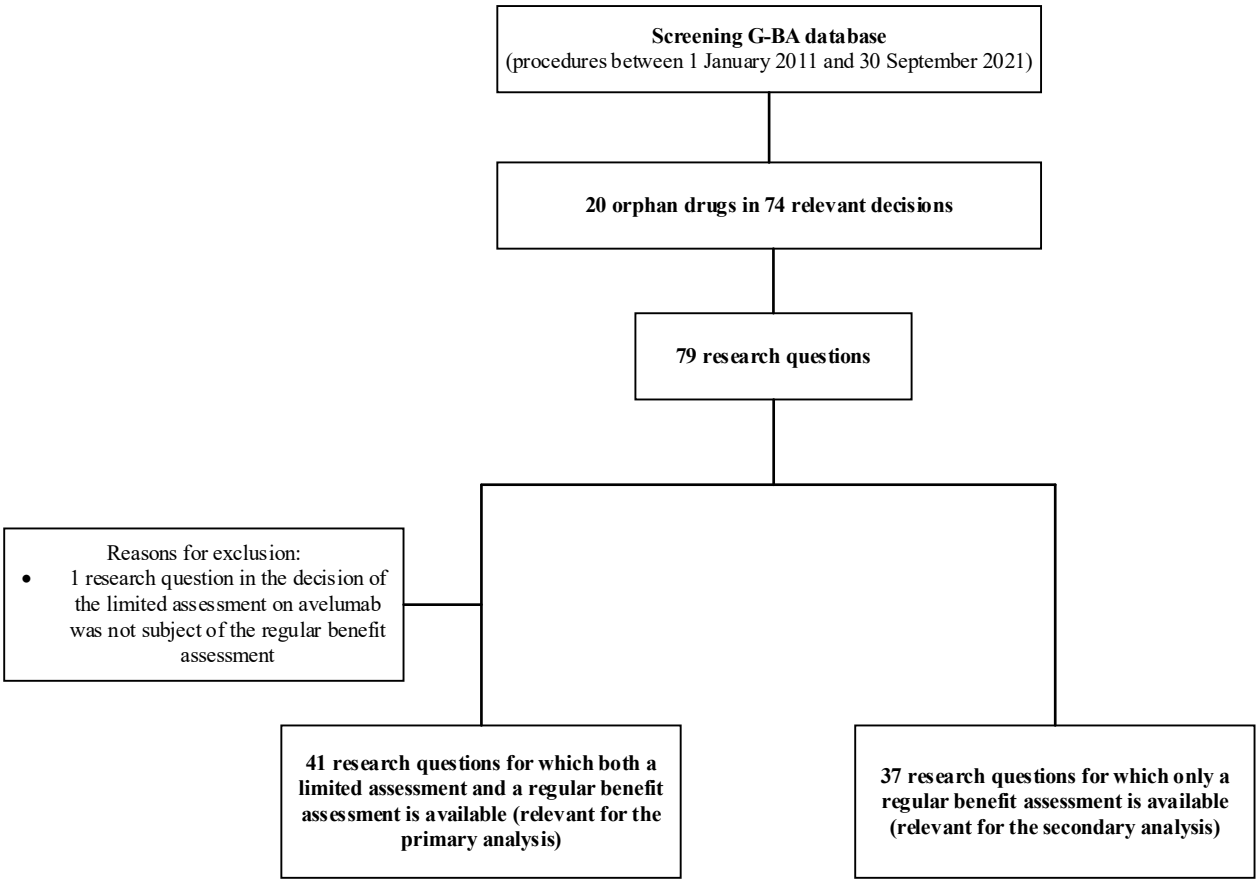

Figure 1: Information retrieval results

5.2 Primary analysis

For the primary analysis, assessments were used where both an assessment result of a limited assessment and that of a regular benefit assessment were available.

5.2.1 Results of the limited assessments and the regular benefit assessments

For the primary analysis, 41 research questions were identified where both a limited assessment and a regular benefit assessment were available (see Section 5.1). The relevant orphan drugs, the research questions assessed, the evidence base and the extent of added benefit in the limited assessments as well as in the regular benefit assessments are presented in Table 7, and the sources used in Table 9 in Appendix A.

The frequencies of the extent of inferred added benefit in limited assessments as well as in the regular benefit assessments are presented in Figure 2.

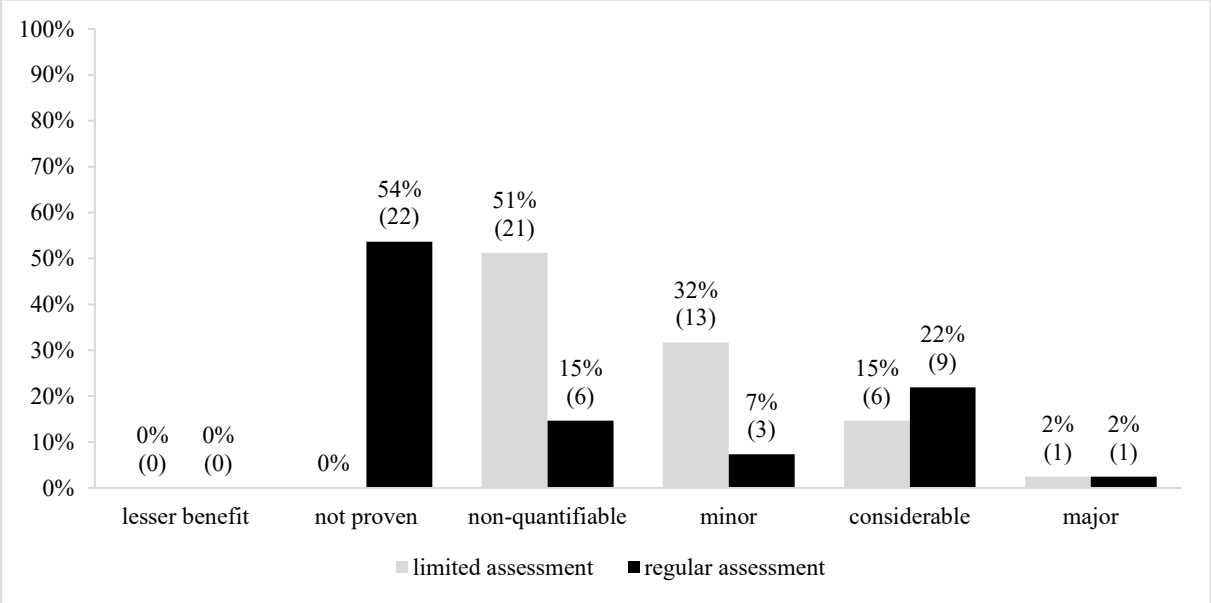

Figure 2: Primary analysis: frequency of the extent of inferred added benefit in limited assessments and regular benefit assessments of orphan drugs (n = 41); („lesser benefit“ and „not proven“ cannot be inferred in limited assessments)

In the limited assessments of the 41 research questions on orphan drugs, an added benefit with the extent “non-quantifiable” was most commonly inferred (51%; n = 21). In contrast, in the regular benefit assessments of these research questions, no added benefit (“not proven”) was most commonly inferred (54%; n = 22).

“Lesser benefit” was not inferred in any research question in the regular benefit assessments.

5.2.2 Agreement between the results of the limited assessments and regular benefit assessments

Operationalization

Based on Table 7 in Appendix A, the results on the added benefit of the limited assessment and the associated regular benefit assessment were compared at research question level. For this

purpose, the results of the limited assessment and of the associated regular benefit assessment were divided into the following categories:

- proof of added benefit: extent in limited assessment = extent in regular benefit assessment
- proof of added benefit: extent in limited assessment < extent in regular benefit assessment
- proof of added benefit: extent in limited assessment > extent in regular benefit assessment
- no added benefit in regular benefit assessment

For this analysis, the extent "non-quantifiable" was ranked between the dimensions "not proven" and "minor" ("non-quantifiable" < "minor").

Results

The results of the categorization are presented in Figure 3.

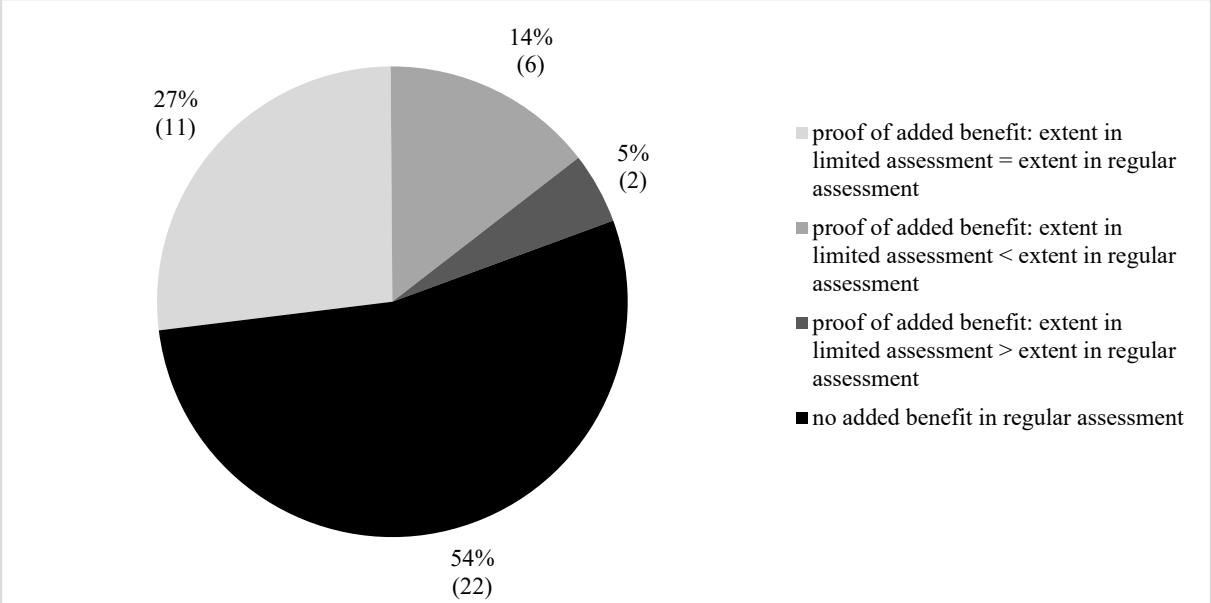

Figure 3: Primary analysis: agreement of the inferred added benefit in limited assessments and regular benefit assessments of orphan drugs (n = 41)

Overall, 27% (n = 11) of all research questions relevant for the primary analysis showed an identical extent of added benefit between the limited and the regular benefit assessments. In 73% (n = 30) of cases, the extent of added benefit deviated between the two types of assessments.

In addition, the agreement of the results between the regular benefit assessment and the limited assessment at the drug level is presented in Figure 4.

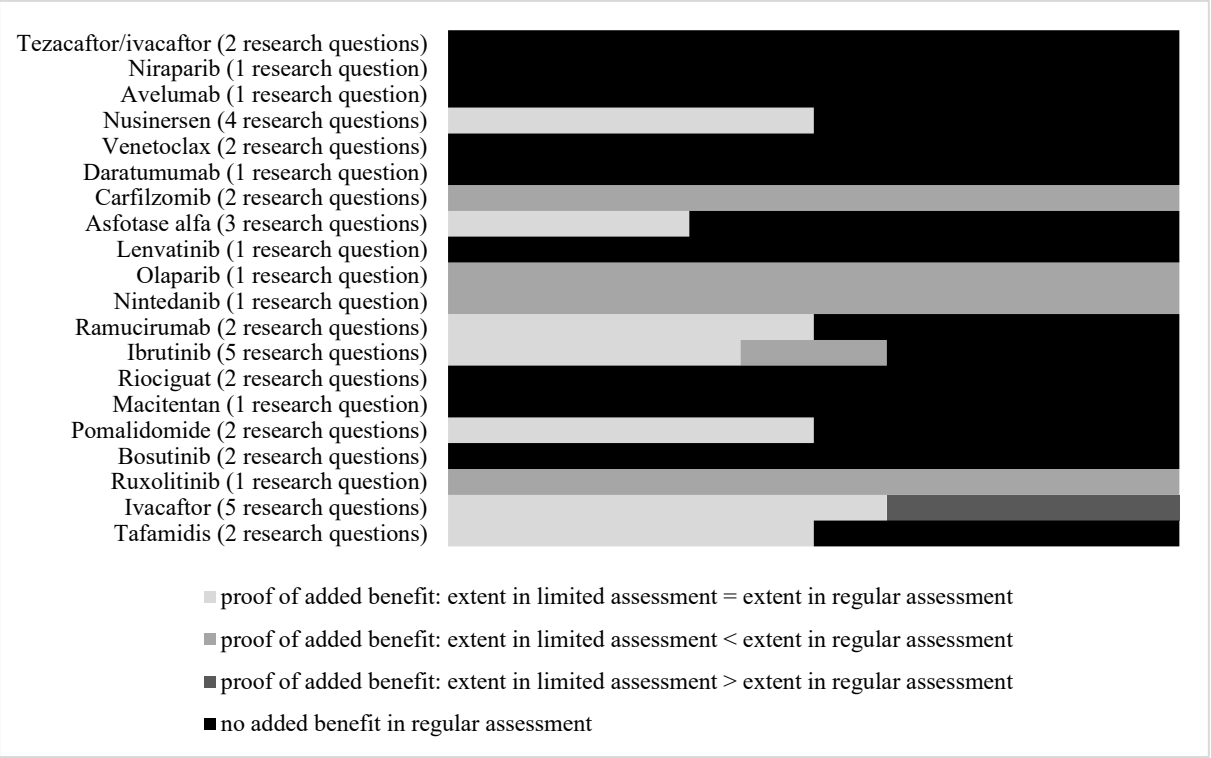

Figure 4: Primary analysis: agreement of the results between limited assessment and regular benefit assessment, separated by drugs (N = 20)

Separated by drugs, an added benefit was inferred for only 25% of the 20 orphan drugs (N = 5; ivacaftor, ruxolitinib, nintedanib, olaparib, and carfilzomib) in all research questions of the regular benefit assessment. In most cases, however, the extent of added benefit deviated between the two types of assessments. For the remaining 75% (N = 15) of orphan drugs, in each case no added benefit was shown in the regular benefit assessment for at least one research question. For 45% (N = 9) of the orphan drugs, an added benefit was not determined in any research question.

Table 1 additionally shows how often which extent of added benefit was inferred in the limited assessment and the regular benefit assessment.

Table 1: Primary analysis: cross tabulation on the added benefit in limited assessments and regular benefit assessments

Added benefit / **Limited assessment** / **Regular benefit assessment**	**Number of research questions% (n)**						
	Lesser benefit[a]	Not proven[a]	Non-quantifiable	Minor	Considerable	Major	**Sum**
Lesser benefit	**0% (0)**	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	**0% (0)**
Not proven	0% (0)	**0% (0)**	34% (14)	15% (6)	5% (2)	0% (0)	**54% (22)**
Non-quantifiable	0% (0)	0% (0)	**10% (4)**	5% (2)	0% (0)	0% (0)	**15% (6)**
Minor	0% (0)	0% (0)	2% (1)	**5% (2)**	0% (0)	0% (0)	**7% (3)**
Considerable	0% (0)	0% (0)	5% (2)	7% (3)	**10% (4)**	0% (0)	**22% (9)**
Major	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	**2% (1)**	**2% (1)**
Sum	**0% (0)**	**0% (0)**	**51% (21)**	**32% (13)**	**15% (6)**	**2% (1)**	**100% (41)**

a. „Lesser benefit“ and „not proven“ cannot be inferred in limited assessments.
n: number of research questions

The cross tabulation shows that, in the research questions where the result in the limited assessment is the same as in the regular benefit assessment (see also Figure 3), “considerable” and “non-quantifiable” were most commonly inferred. In the research questions without agreement, the largest proportion of deviations concerns “non-quantifiable” added benefit in the limited assessment. The “non-quantifiable” added benefit of the limited assessment was mostly assessed as added benefit “not proven” in the regular benefit assessment (67% [n = 14] of the 21 research questions; this corresponds to 34% [n = 14] of all 41 research questions). In the total of 49% (n = 20) of the 41 research questions where the added benefit was quantified as “minor”, “considerable” or “major” in the limited assessment, the regular benefit assessment established no proof of added benefit in 40% (n = 8) of the 20 research questions.

5.2.3 Evidence base of the results of the limited assessments and regular benefit assessments

The underlying evidence of the results of the limited assessments as well as of the regular benefit assessments on orphan drugs was aggregated from Table 7 in Appendix A.

The evidence base of the limited assessments is summarized in Table 2.

Table 2: Primary analysis: evidence base of limited assessments

Data basis / Added benefit	Number of research questions% (n)				
	RCT	**Adjusted indirect comparison**	**Non-RCT**	**Evidence transfer**	**No (usable) data**
Lesser benefit[a]	–	–	–	–	–
Not proven[a]	–	–	–	–	–
Non-quantifiable	20% (8)	0% (0)	27% (11)	0% (0)	5% (2)
Minor	32% (13)	0% (0)	0% (0)	0% (0)	0% (0)
Considerable	15% (6)	0% (0)	0% (0)	0% (0)	0% (0)
Major	2% (1)	0% (0)	0% (0)	0% (0)	0% (0)
Sum	**68% (28)**	**0% (0)**	**27% (11)**	**0% (0)**	**5% (2)**

a. „Lesser benefit“ and „not proven“ cannot be inferred in limited assessments.
n: number of research questions; RCT: randomized controlled trial

The analysis for the limited assessments shows that RCTs were available for 68% (n = 28) of the research questions. Results from non-randomized studies (non-RCTs) were available for 27% (n = 11) of the questions, and no (usable) data were submitted for 5% (n = 2) of the questions. Adjusted indirect comparisons or evidence transfers were not available in any assessment. The quantification of the added benefit by the G-BA into the categories “minor”, “considerable” or “major” was exclusively based on RCTs. In the case of non-RCTs or no (usable) data, a non-quantifiable added benefit was always inferred.

Table 3 shows the evidence base of the regular benefit assessments in analogy to the limited assessments.

Table 3: Primary analysis: evidence base of regular benefit assessments

Data basis / Added benefit	Number of research questions% (n)				
	RCT	**Adjusted indirect comparison**	**Non-RCT**	**Evidence transfer**	**No (usable) data**
Lesser benefit	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Not proven	0% (0)	5% (2)	0% (0)	0% (0)	49% (20)
Non-quantifiable	7% (3)	0% (0)	2% (1)	5% (2)	0% (0)
Minor	7% (3)	0% (0)	0% (0)	0% (0)	0% (0)
Considerable	22% (9)	0% (0)	0% (0)	0% (0)	0% (0)
Major	2% (1)	0% (0)	0% (0)	0% (0)	0% (0)
Sum	**39% (16)**	**5% (2)**	**2% (1)**	**5% (2)**	**49% (20)**

n: number of research questions; RCT: randomized controlled trial

The analysis of the evidence base of the regular benefit assessments of orphan drugs showed that for 39% (n = 16) of the research questions, direct comparative evidence from RCTs was available on orphan drugs versus the ACT. For 5% (n = 2) of the questions, an adjusted indirect comparison was used. For 2% (n = 1) of the questions, usable data from non-RCTs were available. An evidence transfer was performed for 5% (n = 2) of the questions. No (usable) data were available for 49% (n = 20) of the questions. In the regular benefit assessment, the quantification of the added benefit into the categories "minor", "considerable" or "major" was also exclusively based on RCTs.

Proportion of research questions with new evidence for the regular benefit assessment

Figure 5 shows the proportion of research questions for which new evidence was available in the regular benefit assessment in comparison with the limited assessment and whether an added benefit was inferred. If no (usable) data were provided in the G-BA decision of the regular benefit assessment, the research question was assigned to the category "no new data".

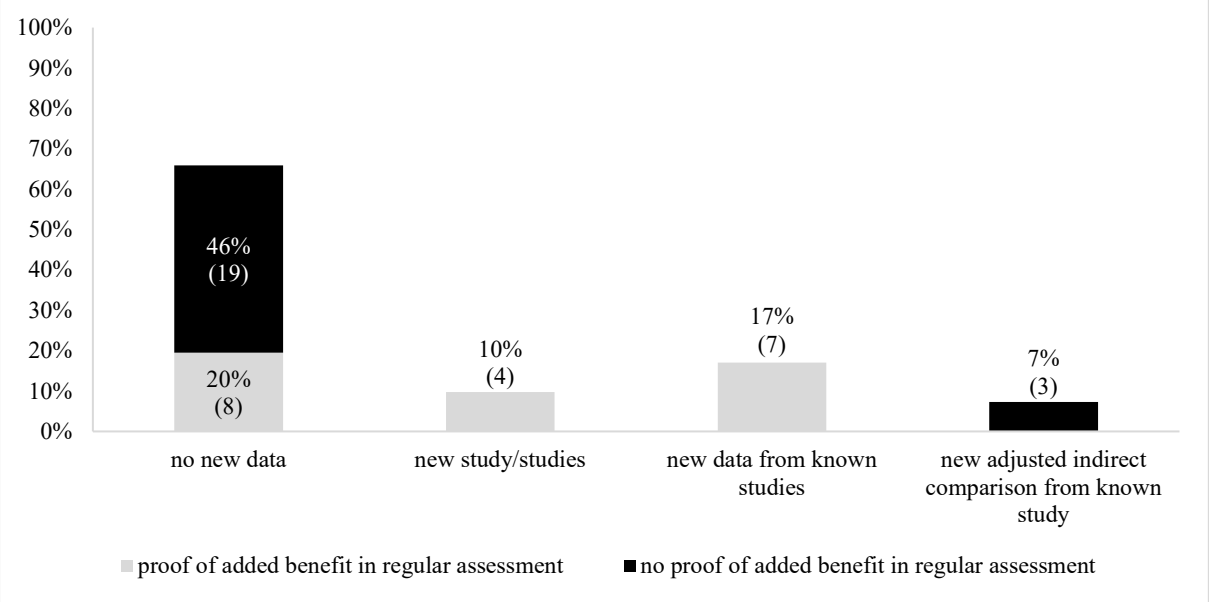

Figure 5: Primary analysis: proportion of research questions in regular benefit assessments of orphan drugs for which new data were available in comparison with the limited assessment (n = 41)

For 66% (n = 27) of the research questions, no new data were available for the regular benefit assessment versus the limited assessment. In these cases, mostly no added benefit was inferred. Data from newly conducted studies were available for 10% (n = 4) of the questions. New data cut-offs from studies already known were available for 17% (n = 7) of the questions. If new studies or new data from known studies were available, an added benefit was always inferred in the regular benefit assessment. New usable adjusted indirect comparisons were available for 7% (n = 3) of the questions; an added benefit was not inferred for any of them.

5.3 Secondary analysis

For the secondary analysis, assessments of orphan drugs were considered where only a regular benefit assessment was available. This was, for example, the case for a newly approved therapeutic indication of an orphan drug if its revenue had already exceeded the threshold of 50 million euro before approval of the new therapeutic indication.

5.3.1 Results of the regular benefit assessments

For the secondary analysis, 37 research questions were identified where only a regular benefit assessment was available (see Section 5.1). The relevant orphan drugs, the therapeutic indications assessed, the available evidence and the extent of added benefit for the regular benefit assessment are presented in Table 8, and the sources used in Table 10 in Appendix A.

The relative frequencies of the extent of added benefit of the regular benefit assessments are presented in Figure 6.

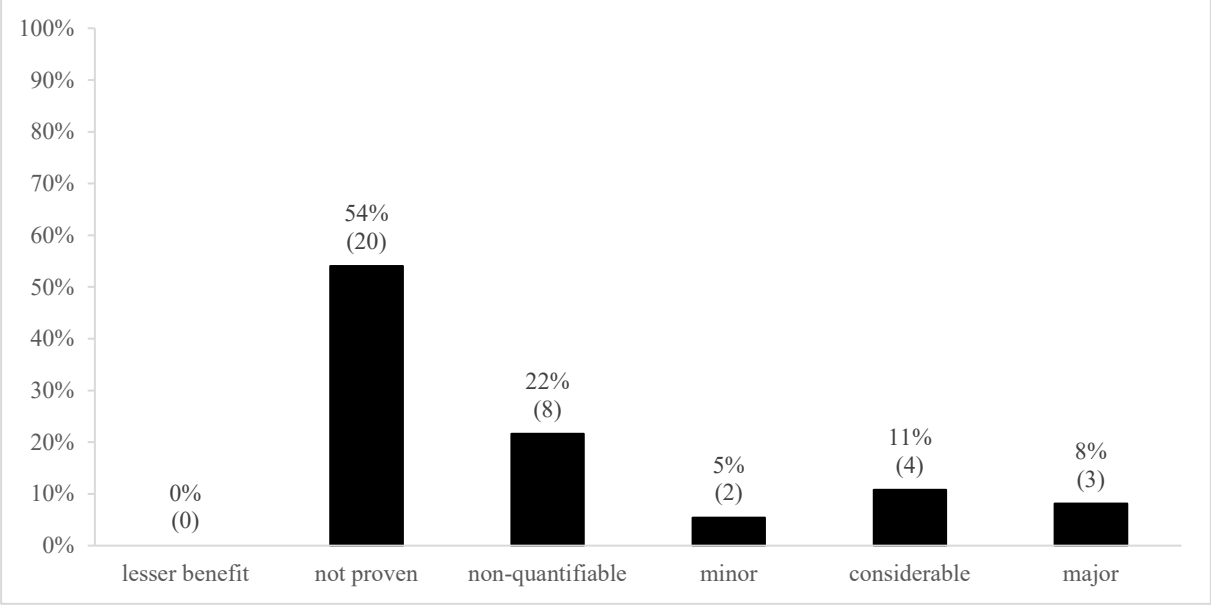

Figure 6: Secondary analysis: frequency of the extent of inferred added benefit in regular benefit assessments of orphan drugs (n = 37)

In the regular benefit assessments of the 37 research questions, the conclusion “no added benefit” was most commonly inferred (54%; n = 20).

The results are consistent with those of the regular benefit assessments from the primary analysis.

5.3.2 Evidence base of the results of the regular benefit assessments

The underlying evidence of the results of the regular benefit assessments was aggregated from Table 8 in Appendix A and summarized in Table 4.

Table 4: Secondary analysis: evidence base of regular benefit assessments

Data basis / Added benefit	Number of research questions% (n)				
	RCT	**Adjusted indirect comparison**	**Non-RCT**	**Evidence transfer**	**No (usable) data**
Lesser benefit	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Not proven	5% (2)	3% (1)	0% (0)	0% (0)	46% (17)
Non-quantifiable	5% (2)	0% (0)	0% (0)	16% (6)	0% (0)
Minor	5% (2)	0% (0)	0% (0)	0% (0)	0% (0)
Considerable	11% (4)	0% (0)	0% (0)	0% (0)	0% (0)
Major	5% (2)	0% (0)	0% (0)	3% (1)	0% (0)
Sum	**32% (12)**	**3% (1)**	**0% (0)**	**19% (7)**	**46% (17)**
n: number of research questions; RCT: randomized controlled trial					

For 32% (n = 12) of the research questions, direct comparative evidence from RCTs was available for the orphan drug versus the ACT. For 3% (n = 1) of the questions, usable data from an adjusted indirect comparison were available. Evidence transfers were used for 19% (n = 7) of the questions. No (usable) data were available for 46% (n = 17) of the questions. Non-RCTs were not considered. The quantification of added benefit into the categories “minor”, “considerable” or “major” was based on RCTs in 89% (n = 8) of the 9 questions.

The results are largely consistent with those of the regular benefit assessments from the primary analysis.

5.4 Summary of the primary and secondary analysis

In a further analysis, the results of the primary and secondary analysis on regular benefit assessments were summarized (78 questions in total). This analysis enables a view of the evidence on orphan drugs versus standard care (= ACT) in the case of a regular benefit assessment.

5.4.1 Summary of the results of the regular benefit assessments

The percentage distribution of the inferred extent of added benefit in regular benefit assessments of orphan drugs is presented in Figure 7.

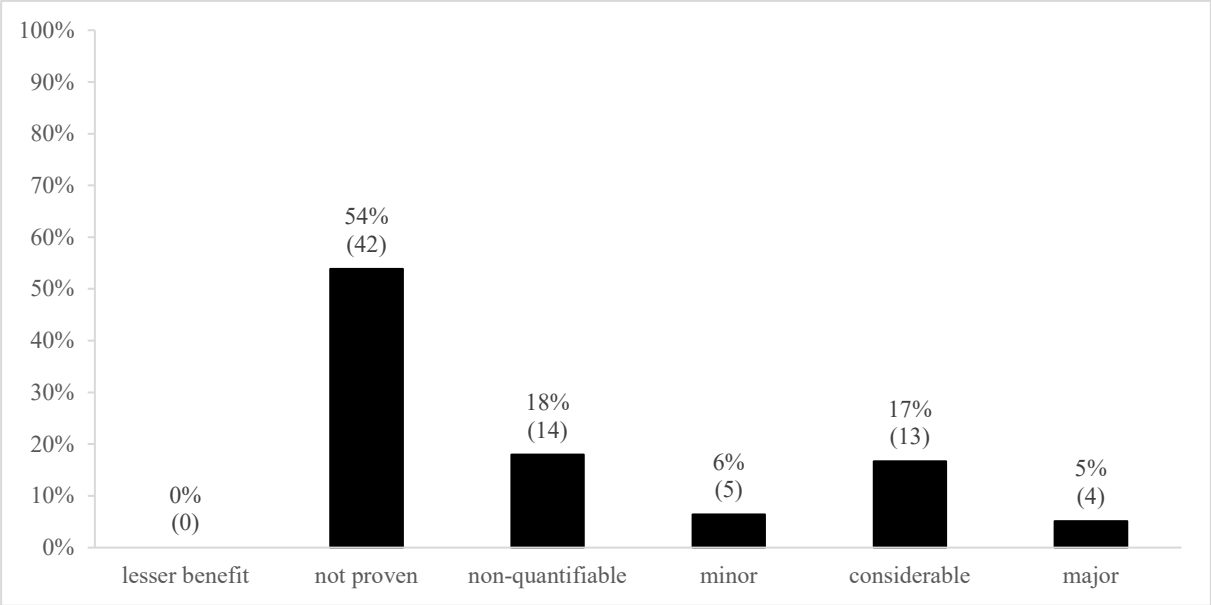

Figure 7: Summary of the primary and secondary analysis: frequency of the extent of inferred added benefit in regular benefit assessments of orphan drugs (n = 78)

The distribution of the extent of added benefit inferred is comparable to that of the primary and secondary analyses. No added benefit ("not proven") was most commonly inferred in the research questions (54%; n = 42).

The distribution of benefit assessments with and without added benefit separated by drugs is presented in Figure 8.

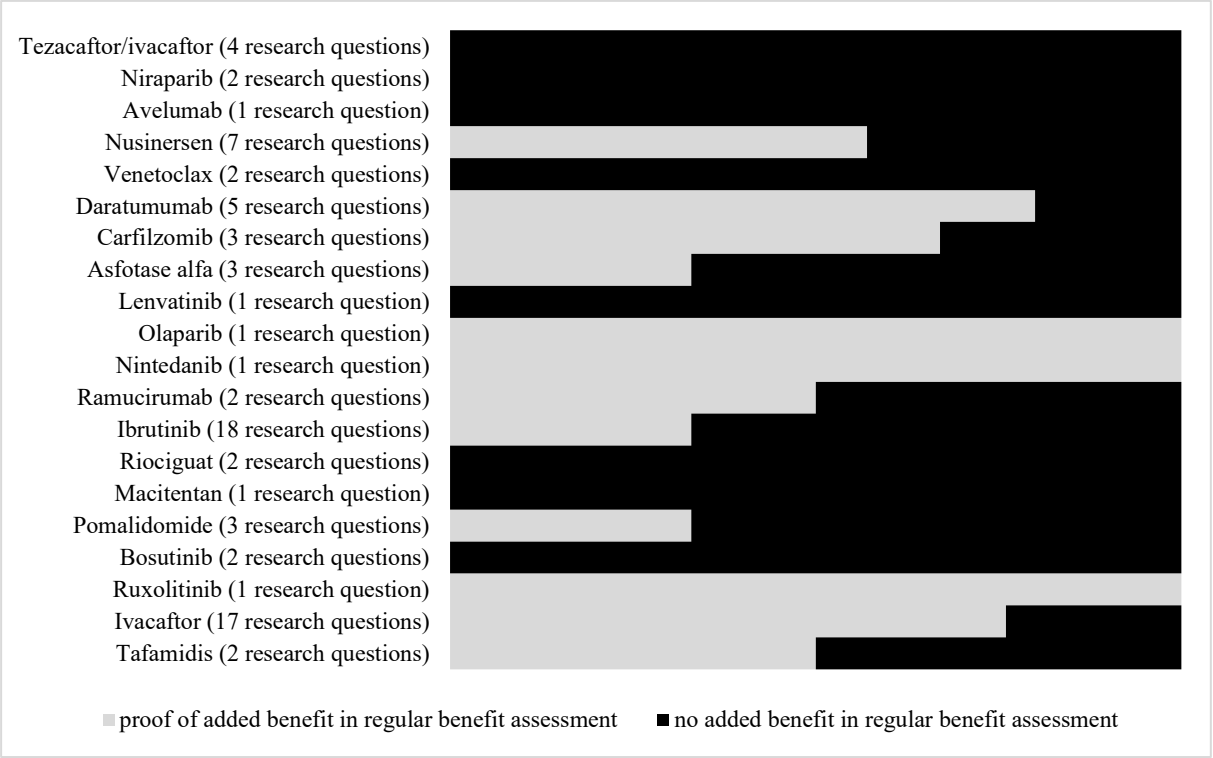

Figure 8: Summary of the primary and secondary analysis: results of the regular benefit assessments separated by drugs (N = 20)

At the drug level, an added benefit was only inferred for 15% (N = 3) of the 20 orphan drugs (ruxolitinib, nintedanib and olaparib) in all the research questions assessed during the period under review. For the remaining 85% (N = 17), no added benefit was inferred in at least one research question. In the limited assessment, at least an added benefit with the extent "non-quantifiable" was granted or would have been granted for all of these questions and thus all 20 orphan drugs.

5.4.2 Summary of the evidence base of the regular benefit assessments

Table 5 summarizes the evidence base of the 78 research questions in the regular benefit assessments.

Table 5: Summary of the primary and secondary analysis: evidence base of the regular benefit assessments

Data basis / Added benefit	Number of research questions% (n)				
	RCT	**Adjusted indirect comparison**	**Non-RCT**	**Evidence transfer**	**No (usable) data**
Lesser benefit	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
Not proven	3% (2)	4% (3)	0% (0)	0% (0)	47% (37)
Non-quantifiable	6% (5)	0% (0)	1% (1)	10% (8)	0% (0)
Minor	6% (5)	0% (0)	0% (0)	0% (0)	0% (0)
Considerable	17% (13)	0% (0)	0% (0)	0% (0)	0% (0)
Major	4% (3)	0% (0)	0% (0)	1% (1)	0% (0)
Sum	**36% (28)**	**4% (3)**	**1% (1)**	**12% (9)**	**47% (37)**

n: number of research questions; RCT: randomized controlled trial

The evidence base shows that most commonly no usable data were available for the regular benefit assessment of the orphan drugs considered here. The fact that no (usable) data were available was also the most common reason for the conclusion "added benefit not proven" (88% [n = 37] of the 42 questions with this assessment).

For 36% (n = 28) of the 78 research questions, data from RCTs were available for the assessment. The quantification of the added benefit into the categories "minor", "considerable" or "major" was almost exclusively based on RCTs, with the exception of one research question.

6 Discussion

6.1 Interpretation of the results

Results on added benefit

The primary and secondary analyses show that no added benefit was inferred in more than 50% of the research questions in the regular benefit assessment procedures for orphan drugs (see Figure 7) – for these questions, no superiority of the orphan drugs over the ACT was thus proven. In more than half of the cases, the legal stipulation of a fictitious added benefit for orphan drugs at market entry is therefore misleading, as there is obviously no scientific evidence of an added benefit (i.e. an advantage over the existing treatment options) in these cases. This discrepancy between fictitious and actual added benefit is even more pronounced at the drug level: The summarizing analysis of the current evidence on orphan drugs from regular benefit assessments shows that for 85% of the orphan drugs considered, there is no scientific evidence of an added benefit versus the ACT in at least one research question (see Figure 8). The regular benefit assessments showed an added benefit for all research questions only for 15% of the orphan drugs.

On the other hand, it can also be inferred from the available results that in 46% of the investigated research questions (see Figure 7) and for 60% of the orphan drugs in at least one research question (see Figure 8), there is scientific proof of an overall advantage of the new orphan drug compared with the previous standard therapy (ACT). In these cases, a relevant progress for patient care from newly approved orphan drugs can therefore be established.

Results on the evidence base

The analyses on the evidence base of the primary analysis show that data from RCTs were available for 68% of the research questions in limited assessments, i.e. in the first assessment on the basis of the approval studies (see Table 3). This fact reaffirms that conducting RCTs is in principle possible also in rare diseases. [9-12]. However, the subsequent regular benefit assessments of these orphan drugs revealed that only some of these RCTs investigated research questions that are directly relevant to health care (comparison with a relevant existing treatment option in respect of patient-relevant outcomes). The presented RCTs were usable as direct comparative evidence for the regular benefit only for 39% of the research questions. For the remaining research questions, other usable evidence (e.g. adjusted indirect comparisons) was only submitted in few cases. Overall, for almost 50% of the research questions, no relevant scientific evidence was available for the regular benefit assessment and thus for the assessment of the orphan drug in comparison with existing treatment options with regard to patient-relevant outcomes (see Table 3).

The results on the evidence base of the secondary analysis (research questions for which no preliminary limited assessment was conducted) confirm the results from the primary analysis: Relevant RCTs of direct comparison were only available for 32% of the research questions from the secondary analysis; for 46% of the research questions there were no usable data at all (RCTs, adjusted indirect comparisons or other evidence, see Table 4).

Finally, the analyses of the evidence base of the primary analysis show that new evidence after the market access of an orphan drug was generated only in few cases (see Figure 5). In comparison with the limited assessment at market access, new studies in the regular benefit assessment were only available for 10% of the research questions. For 24% of the research questions, new evidence on known studies was submitted (new data cut-offs or adjusted indirect comparisons using already known studies). The orphan drug privilege of the AMNOG and the time period between market access and regular benefit assessment of orphan drugs is thus not regularly used by the companies to address the lack of evidence on added benefit, i.e. on the value of the new orphan drug compared with existing treatment options.

6.2 The orphan drug privilege of AMNOG: status quo, impact on patient care and European perspective

Effects of the "fictitious added benefit" of orphan drugs on patient care

As already described in Section 1, orphan drugs have a special position in AMNOG and undergo only a limited assessment at market access, where the added benefit is already regarded as proven by the approval (§35a SGB V [1], Sentence 11).

The results of the present working paper fundamentally question this current orphan drug privilege of a fictitious added benefit at market access. This is because in more than half of the research questions, the added benefit is in fact pure fiction and not justified by scientific evidence. This misleading assessment of the fictitious added benefit is, in its consequence, not merely a procedural feature to privilege orphan drugs when determining the reimbursement price; rather, it has potentially major consequences for the quality of care for patients with rare diseases.

The rating "added benefit" from a limited assessment already differs from an actual added benefit established in a regular benefit assessment in that no data relevant to health care (comparison with available treatment options in respect of patient-relevant outcomes) have to be submitted for this limited assessment at all. The term "added benefit" alone is therefore already misleading as the result of a limited assessment. Nevertheless, in accordance with legal requirements, this regularly established result ("added benefit") is transferred to the AIS also for orphan drugs ([13], § 35a Abs. 3a SGB V). This not only suggests to the treating physicians via the practice software that the new orphan drug has an advantage over the already existing treatment options. The already existing treatment options are also at a substantial disadvantage, as the impression is created that they are inferior to the new orphan drug, without this requiring any corresponding evidence. As this working paper shows, the legal stipulation of a fictitious added benefit actually leads to a misjudgement in more than half of the research questions and thus to a discrimination against existing treatment options.

It can be argued that the treating physicians are familiar with the legislation laid down in § 35a SGB V and the associated orphan drug privilege, and that the rating "added benefit" initially assigned to orphan drugs is therefore correctly assessed as worthless because it is potentially

misleading. However, this is equally problematic because it does not allow to distinguish between orphan drugs that represent real progress for patient care from those to which this does not apply or for which the corresponding scientific evidence is lacking. Due to the current legislation, a main goal of AMNOG, namely, "separating the wheat from the chaff", is therefore missed for orphan drugs [14].

Furthermore, current legislation does not provide for a potentially erroneous assessment of the added benefit to be corrected at an early stage or at all. This is because the time point of a regular benefit assessment usually depends on how quickly and whether an annual revenue of 50 million euros is exceeded at all. Figure 9 shows for the 22 research questions of the primary analysis for which no added benefit was proven for the new orphan drug in the regular benefit assessment, with which latency period the erroneous assessment of the limited assessment was corrected in the regular benefit assessment at market access. The latency period was at least 1 year and 2 months (for the drug daratumumab) and up to 9 years (for the drug tafamidis).

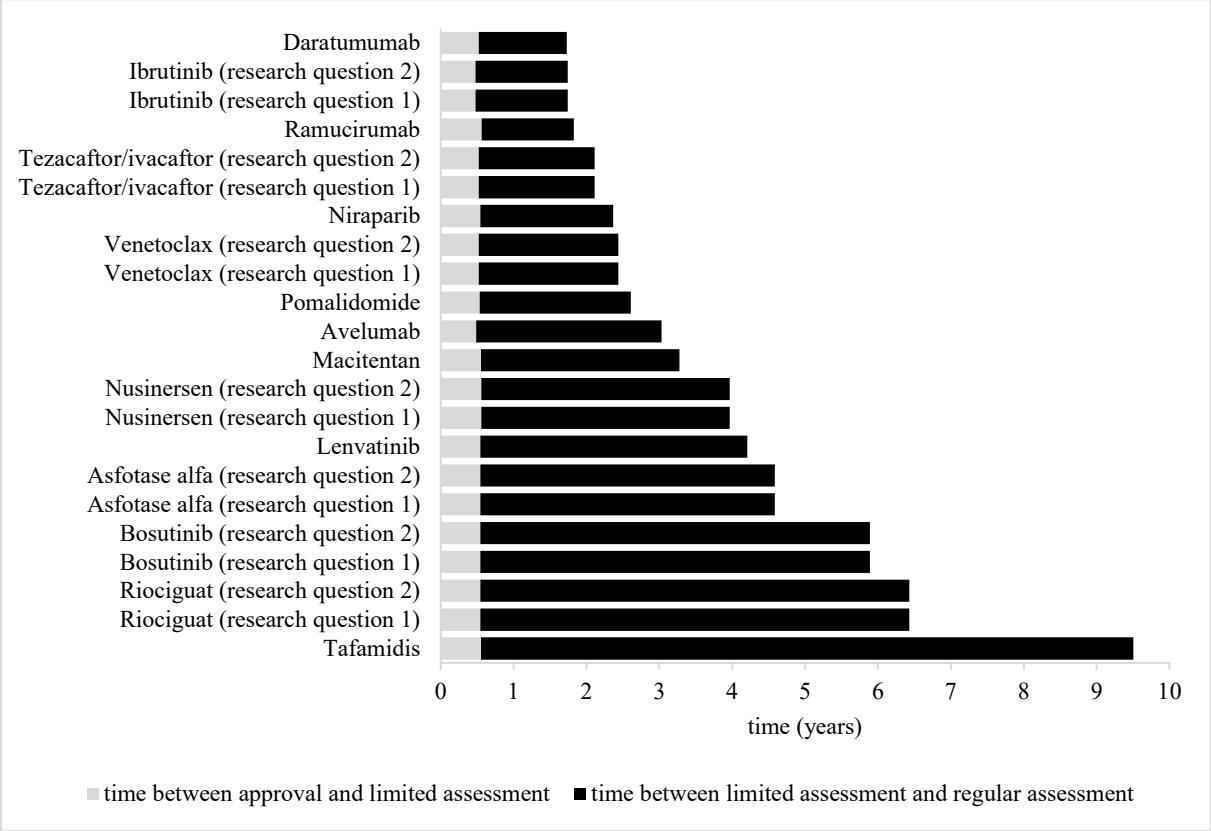

Figure 9: Time between approval, limited assessment and regular benefit assessment for research questions without added benefit (n = 22)

The potentially false communication about the added benefit has even more far-reaching implications for those orphan drugs that do not exceed the annual revenue threshold of 50 million euros, as no regular benefit assessment is carried out for these at all. An example is the first orphan drug assessed within the framework of AMNOG in 2011, the drug pirfenidone

for the treatment of mild to moderate idiopathic pulmonary fibrosis, where no advantage of pirfenidone could be inferred from the assessment of the study data [15], but a non-quantifiable added benefit had to be established in the decision of the G-BA due to the legal stipulation of a fictitious added benefit [16]. Since pirfenidone has not reached the annual revenue threshold of 50 million euros, this established added benefit has not yet been corrected by a regular benefit assessment.

Overall, it can be concluded that the privilege of a fictitious added benefit for orphan drugs leads to erroneous communication about the value of new orphan drugs in more than half of the research questions. This potentially favours treatment decisions that are not based on the actual scientific evidence and may do more harm than good to patients with rare diseases – and thus leads to a situation that AMNOG was actually supposed to prevent [14].

Evidence gaps in orphan drugs – collection of routine practice data

The results on the evidence base show that many of the studies on orphan drugs submitted for AMNOG assessments are not focused on research questions relevant to health care and are thus not suitable for answering research questions of the benefit assessments (see Section 5.2.3). This is not an isolated problem in the assessment of orphan drugs, but also concerns many therapeutic indications in the field of non-orphan diseases and is a global problem of evidence generation [17]. In the planning of studies, the focus is often not on patient-relevant and health care-related research questions, but on the criteria for approval.

Immediately after introduction of the AMNOG, the pharmaceutical industry argued that studies had been planned already years before the introduction of the AMNOG. It argued that the requirements of the early benefit assessment in Germany had not been known at the time of study planning, so that the studies could not have been designed accordingly [18,19]. On the one hand, however, this argument was already untenable at that time, as the AMNOG does not impose any requirements on study relevance that were not already known before from benefit assessments: studies of direct comparisons with existing treatment options, focused on patient-relevant outcomes [20]. On the other hand, this argument is still used today, more than 10 years after the AMNOG came into force, by representatives of the pharmaceutical industry [21,22].

Due to the focus on approval requirements instead of research questions of health care, there are regularly important evidence gaps when new drugs, including orphan drugs, enter the market. The analyses of the evidence base (see Section 5.2.3) in conjunction with the analyses of the latency period between approval and regular benefit assessment (Figure 9) show that despite the sometimes long periods after market access, new data to close these evidence gaps are rarely generated.

In order to close the evidence gaps, the first step was taken in 2019 with the GSAV in §35a (3b) SGB V, which introduced the collection of routine practice data for orphan drugs, among others [23]. Even if such a sanctionable obligation to generate evidence is to be welcomed in principle, the current legal framework does not go far enough because it stipulates that no studies with

randomization (i.e. RCTs) may be conducted as collection of routine practice data. However, it is precisely these studies that have reliable results, are easy to plan and interpret from a methodological point of view and, in the case of an appropriately set up patient registry, can also be carried out with comparatively little effort [24,25].

The exclusion of randomized studies as a possibility for a collection of routine practice data also reduces incentives to further develop the registry landscape in Germany in such a way that health care-related registry-based RCTs will be carried out regularly in future, addressing evidence gaps promptly and with high certainty of results. This restriction is thus also in contrast to the recently passed law on the pooling of cancer registry data [26]. The pooling of cancer registry data is intended to open up new application possibilities for the cancer registries in Germany, explicitly also in the context of the early benefit assessment according to AMNOG. The current exclusion of registry-based RCTs in §35a (3b) SGB V substantially limits this development of the cancer registries, especially in international comparison.

Criteria for the orphan drug status at EU level possibly not sufficiently objective

The decision on whether a drug is granted European orphan drug status is made by the Committee for Orphan Medicinal Products (COMP) of the European Medicines Agency (EMA) [1]. According to the EU regulations, orphan drugs eligible for incentives should be easily and unequivocally identified [1].

However, contrary to the above-mentioned stipulations and with the exception of the prevalence of the disease of ≤ 5 per 10 000 EU citizens, the criteria for granting orphan drug status laid down in the regulation may not be sufficiently clear and thus leave a great deal of room for interpretation. According to Article 3 [1], for example, one of the prerequisites for the orphan drug status is that without incentives it is unlikely that the marketing of the drug in the Community would generate sufficient return to justify the necessary investment, or, if a treatment method already exists, that the drug will be of significant benefit to those affected by that condition. What is meant by “sufficient return” or “significant benefit” remains unclear, however. Thus, the granting of the orphan drug status using these criteria is not comprehensible in many cases. In some cases, orphan drug status is granted for individual drugs, while orphan drug status is withdrawn from another drug in the same therapeutic indication and even with an identical mechanism of action before its approval. For example, lanadelumab has been approved as an orphan drug for the treatment of hereditary angioedema since 2019, while orphan drug status was withdrawn from berotralstat in the same therapeutic indication and with an identical therapeutic target as lanadelumab shortly before its approval in 2021 [27,28]. This ultimately also leads to unequal treatment of these drugs in the AMNOG: limited assessment with fictitious added benefit, which may only be corrected years later in a regular benefit assessment (e.g. lanadelumab [29,30]) or immediate regular benefit assessment versus the ACT, which directly establishes that an added benefit is not proven (e.g. berotralstat [31]).

6.3 Further development of AMNOG to improve the health care situation in rare diseases

It has been shown that the current legislation on the benefit assessment of orphan drugs leads to misleading communication about the added benefit of orphan drugs at the time point of their market access in Germany in more than half of the cases. This erroneous communication persists for years, sometimes even permanently. Only in exceptional cases is new evidence generated in the years after approval that addresses open research questions about these new orphan drugs with regard to the health care of patients with rare diseases. This results in an urgent need for further development of the AMNOG, particularly in the following areas:

1) The orphan drug privilege of a fictitious added benefit at market access should be abolished. Orphan drugs, like drugs for non-orphan diseases, should therefore be subjected to a regular benefit assessment directly after market access.

   From an empirical point of view, orphan drugs are not regularly superior to existing treatment options (see Sections 5.2.1 and 5.3.1). The special position of orphan drugs (assumption of a fictitious added benefit on the basis of the approval) is therefore not scientifically justified and is in fact misleading in numerous cases.

   If, due to the lower number of cases in rare diseases, an economic incentive for the development of therapies is to be maintained not only at the European level (support for the development of such drugs), but also at the national level (surcharge on the reimbursement price), this can be regulated in §130b SGB V (Agreements between the Central Federal Association of the Health Insurance Funds and pharmaceutical companies on reimbursement prices for drugs) without having to maintain the misleading fictitious added benefit. It is planned to look at the associations between result of the added benefit, patient numbers and reimbursement prices in a separate follow-up project.

2) Patient-relevant and health care-related research questions should be increasingly considered in the planning of studies. The collection of routine practice data should be expanded to include the possibility of conducting pragmatic (registry-based) RCTs with the aim of clarifying open health care questions as promptly and reliably as possible.

   RCTs are also feasible in principle for rare diseases (see Section 5.2.3). In order for data from these RCTs to also allow conclusions on the added benefit versus the current therapeutic standard in general, patient-relevant and health care-related aspects must be taken into account in the study planning. This applies in particular to the choice of the comparator, but also to the definition of outcomes and study duration. The European Pharmaceutical Strategy [5] and the introduction of the European benefit assessment [32] offer near-future opportunities to introduce or expand these collaborations and to establish Europe-wide standards for study planning. Furthermore, studies within a therapeutic indication could be coordinated in these collaborations, so that health care-related research questions can be dealt with efficiently and without duplications.

7 Conclusion

The present report shows that specifying a fictitious added benefit at market access of orphan drugs is misleading in more than half of the cases, as no proof of added benefit is shown in subsequent regular benefit assessments. This not only leads to misleading communication about the added benefit of new orphan drugs, but also discriminates against existing treatment options for rare diseases by letting them appear to be inferior through the fictitious added benefit granted to orphan drugs. Furthermore, this general fictitious added benefit prevents a distinction between orphan drugs with and without real progress for patient care. The misleading communication on added benefit is maintained for years and in some cases not corrected if the revenue threshold of 50 million euro per year is not exceeded or the company voluntarily relinquishes the orphan drug status. Overall, a main goal of AMNOG, namely, "separating the wheat from the chaff", is prevented for orphan drugs through the privilege of a fictitious added benefit.

The evidence base shows that RCTs are also possible for orphan drugs. However, many of these RCTs have so far not focused on questions relevant to health care (comparison of orphan drugs with existing treatment options in respect of patient-relevant outcomes), but in particular address the criteria for approval. Efforts must therefore be undertaken to ensure that in future, patient-relevant and health care-related questions are increasingly considered in the planning and conduct of studies. In particular, routine data collection according to the GSAV should be expanded to include the possibility of conducting pragmatic (registry-based) RCTs. This could also promote the development of the registry landscape in Germany, with the aim of clarifying open health care questions as promptly and reliably as possible in the future.

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158. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V - Ibrutinib (neues Anwendungsgebiet) [online]. 2016 [Accessed: 25.06.2021]. URL: https://www.g-ba.de/downloads/40-268-4102/2016-12-15_AM-RL-XII_Ibrutinib_nAWG_D-249_TrG.pdf.

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160. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII - Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V – Ibrutinib (neues Anwendungsgebiet: chronische lymphatische Leukämie; in Kombination mit Bendamustin und Rituximab) [online]. 2017 [Accessed: 25.06.2021]. URL: https://www.g-ba.de/downloads/40-268-4246/2017-03-16_AM-RL-XII_Ibrutinib_nAWG-Laeukemie-D-262_TrG.pdf.

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166. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Ibrutinib (Chronische lymphatische Leukämie, Erstlinie, Kombination mit Rituximab) [online]. 2021 [Accessed: 25.06.2021]. URL: https://www.g-ba.de/downloads/40-268-7422/2021-04-01_AM-RL-XII_Ibrutinib_D-598_TrG.pdf.

167. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL) Anlage XII –Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V: Carfilzomib (Neues Anwendungsgebiet: Multiples Myelom, mind. 1 Vortherapie, Kombination mit Daratumumab und Dexamethason) [online]. 2021 [Accessed: 25.06.2021]. URL: https://www.g-ba.de/downloads/39-261-4927/2021-07-15_AM-RL-XII_Carfilzomib_D-617.pdf.

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176. Gemeinsamer Bundesausschuss. Tragende Gründe zum Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Niraparib (Neues Anwendungsgebiet: Ovarialkarzinom, Eileiterkarzinom oder primäres Peritonealkarzinom, FIGO-Stadien III und IV, Erhaltungstherapie) [online]. 2021 [Accessed: 25.06.2021]. URL: https://www.g-ba.de/downloads/40-268-7544/2021-05-20_AM-RL-XII_Niraparib_D-607_TrG.pdf.

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179. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Tezacaftor/Ivacaftor (Neues Anwendungsgebiet: zystische Fibrose, Kombinationstherapie mit Ivacaftor bei Patienten ab 6 bis < 12 Jahren (heterozygot bzgl. F508del- und RF-Mutation)) [online]. 2021 [Accessed: 25.06.2021]. URL: https://www.g-ba.de/downloads/39-261-4841/2021-05-20_AM-RL-XII_Tezacaftor-Ivacaftor_D-609_BAnz.pdf.

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Appendix A – Tables

Table 6: Overview of orphan drugs that have undergone at least one regular benefit assessment (1 January 2011 to 30 September 2021) (multipage table)

Drug	Orphan drug status at EU level Yes/no (from–to)	Therapeutic indications assessed in the AMNOG procedure	Limited assessment conducted Yes/no
Tafamidis	Yes (11/2011–11/2021)	Amyloid polyneuropathy	Yes
		Amyloid cardiomyopathy	Yes
Ivacaftor	Yes (7/2012–today)	Cystic fibrosis, G551D mutation, ≥ 6 years	Yes
		Cystic fibrosis, various mutations, ≥ 6 years	Yes
		Cystic fibrosis, R117H mutation, 2–5 years, ≥ 18 years	Yes
		Cystic fibrosis, homozygous for F508del, ≥ 12 years, combination with tezacaftor	No
		Cystic fibrosis, heterozygous for F508del, ≥ 12 years, combination with tezacaftor	No
		Cystic fibrosis, R117H mutation, ≥ 18 years	Yes
		Cystic fibrosis, patients from 12 to < 24 months of age	No
		Cystic fibrosis, ≥ 6 to < 12 months of age	No
		Cystic fibrosis, patients ≥ 6 months to < 18 years of age (R117H)	No
		Cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor in patients aged 12 years and older (heterozygous for F508del and MF mutation)	No
		Cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor in patients aged 12 years and older (homozygous for F508del mutation)	No
		Cystic fibrosis, patients from 4 to < 6 months of age, gating mutations	No
		Cystic fibrosis, patients from 4 to < 6 months of age, R117H mutation	No
		Cystic fibrosis, combination therapy with tezacaftor/ivacaftor in patients from 6 to < 12 years of age (homozygous for F508del mutation)	No
		Cystic fibrosis, combination therapy with tezacaftor/ivacaftor in patients from 6 to < 12 years of age (heterozygous for F508del and RF mutation)	No
Ruxolitinib	No (8/2012–2/2015)	Myelofibrosis	Yes
Bosutinib	No (3/2013–3/2018)	Chronic myelogenous leukaemia, Ph+	Yes

Table 6: Overview of orphan drugs that have undergone at least one regular benefit assessment (1 January 2011 to 30 September 2021) (multipage table)

Drug	Orphan drug status at EU level Yes/no (from–to)	Therapeutic indications assessed in the AMNOG procedure	Limited assessment conducted Yes/no
Pomalidomide	Yes (8/2013–today)	Multiple myeloma, at least 2 prior therapies, combination with dexamethasone	Yes
		Multiple myeloma, at least 1 prior therapy, combination with bortezomib and dexamethasone	No
Macitentan	Yes (12/2013–today)	Pulmonary arterial hypertension	Yes
Riociguat	Yes (03/2014–today)	Pulmonary arterial hypertension	Yes
		Chronic thromboembolic pulmonary hypertension	Yes
Ibrutinib	Yes (10/2014–today)	Mantle cell lymphoma	Yes
		Chronic lymphocytic leukaemia	Yes
		Waldenström macroglobulinaemia	No
		Chronic lymphocytic leukaemia, first line	No
		Chronic lymphocytic leukaemia, at least 1 prior therapy, combination with bendamustine and rituximab	No
		Chronic lymphocytic leukaemia, first line, combination with obinutuzumab	No
		Waldenström macroglobulinaemia, combination with rituximab	No
		Chronic lymphocytic leukaemia, first line, combination with rituximab	No
Ramucirumab	No (12/2014–12/2015)	Gastric or gastro-oesophageal junction adenocarcinoma	Yes
Nintedanib	No (1/2015–5/2020)	Idiopathic pulmonary fibrosis	Yes
Olaparib	No (12/2014–3/2018)	Ovarian, fallopian tube or primary peritoneal cancer	Yes
Lenvatinib	No (5/2015–8/2018)	Thyroid neoplasms	Yes
Asfotase alfa	Yes (8/2015–today)	Hypophosphatasia	Yes
Carfilzomib	Yes (11/2015–today)	Multiple myeloma, at least 1 prior therapy, combination with lenalidomide and dexamethasone	Yes
		In combination with dexamethasone in multiple myeloma, at least 1 prior therapy	Yes
		Multiple myeloma, at least 1 prior therapy, combination with daratumumab and dexamethasone	No

Table 6: Overview of orphan drugs that have undergone at least one regular benefit assessment (1 January 2011 to 30 September 2021) (multipage table)

Drug	Orphan drug status at EU level Yes/no (from–to)	Therapeutic indications assessed in the AMNOG procedure	Limited assessment conducted Yes/no
Daratumumab	Yes (5/2016–today)	Multiple myeloma, monotherapy	Yes
		Multiple myeloma, at least 1 prior therapy, combination with lenalidomide and dexamethasone or bortezomib and dexamethasone	No
		Multiple myeloma, first line, stem cell transplant unsuitable, combination with bortezomib, melphalan and prednisone	No
		Multiple myeloma, newly diagnosed, patients ineligible for autologous stem cell transplant, combination with lenalidomide and dexamethasone	No
		Multiple myeloma, newly diagnosed, patients eligible for autologous stem cell transplant, combination with bortezomib, thalidomide and dexamethasone	No
Venetoclax	No (12/2016–10/2018)	Chronic lymphocytic leukaemia, monotherapy	Yes
Nusinersen	Yes (5/2017–today)	Spinal muscular atrophy	Yes
Avelumab	No (9/2017–10/2019)	Merkel cell carcinoma	Yes
Niraparib	Yes (11/2017–today)	Ovarian, fallopian tube or primary peritoneal cancer	Yes
		Ovarian, fallopian tube or primary peritoneal cancer, FIGO stages III and IV, maintenance therapy	No
Tezacaftor/ ivacaftor	Yes (10/2018–today)	Cystic fibrosis, homozygous, F508del mutation, ≥ 12 years	Yes
		Cystic fibrosis, heterozygous, F508del mutation, ≥ 12 years	Yes
		Cystic fibrosis, combination therapy with ivacaftor in patients from 6 to < 12 years of age (homozygous for F508del mutation)	No
		Cystic fibrosis, combination therapy with ivacaftor in patients from 6 to < 12 years of age (heterozygous for F508del and RF mutation)	No

AMNOG: Act on the Reform of the Market for Medicinal Products; CFTR: cystic fibrosis transmembrane conductance regulator; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; F508del: gene mutation in the 7q31.2 region on the long arm of human chromosome 7; G551D: substitution of the amino acid glycine by aspartic acid at position 551 of the CFTR protein; MF: minimal function; Ph+: Philadelphia chromosome-positive; R117H: substitution of the amino acid arginine by histidine at position 117 of the CFTR protein; RF: residual function

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Tafamidis	Amyloid polyneuropathy	1 RCT, direct comparison with placebo	Minor	Patisiran	No usable data	Not proven
	Amyloid cardiomyopathy	1 RCT, direct comparison with placebo	Considerable	BSC	1 RCT, direct comparison with placebo	Considerable (indication)
Ivacaftor	Cystic fibrosis, G551D mutation, ≥ 6 years					
	6–11 years	1 RCT, direct comparison with placebo	Minor	BSC	1 RCT, direct comparison with placebo	Non-quantifiable (hint)
	≥ 12 years	1 RCT, direct comparison with placebo	Considerable	BSC	1 RCT, direct comparison with placebo	Considerable (hint)
	Cystic fibrosis, various mutations, ≥ 6 years	1 RCT, direct comparison with placebo, crossover design	Minor	BSC	1 RCT, direct comparison with placebo, crossover design	Non-quantifiable (hint)
	Cystic fibrosis, R117H mutation, 2–5 years, > 18 years					
	2–5 years, gating mutation (class III)	1 single-arm study	Non-quantifiable	BSC	Evidence transfer from older patients; consideration of 2 single-arm studies	Non-quantifiable (hint)
	≥ 18 years, R117H mutation	1 RCT, direct comparison with placebo	Minor	BSC	1 RCT, direct comparison with placebo	Minor (hint)

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Ruxolitinib	Myelofibrosis	2 RCTs, 1 direct comparison with placebo, 1 open-label	Minor	BSC	1 RCT, direct comparison with placebo + BSC	Considerable (hint)
Bosutinib	Chronic myelogenous leukaemia, Ph+	1 single-arm study	Non-quantifiable	Not relevant[a]	Not relevant[a]	Not relevant[a]
	Chronic myelogenous leukaemia, Ph+, chronic phase	Not relevant[a]	Non-quantifiable[b]	Ponatinib	No usable data	Not proven
	Chronic myelogenous leukaemia, Ph+, accelerated phase and blast phase	Not relevant[a]	Non-quantifiable[b]	Ponatinib	No usable data	Not proven
Pomalidomide	Multiple myeloma, at least 2 prior therapies, combination with dexamethasone	1 RCT, direct comparison with high-dose dexamethasone	Considerable	Not relevant[a]	Not relevant[a]	Not relevant[a]
	Patients for whom dexamethasone (high-dose) is the individual treatment of physician's choice	Not relevant[a]	Considerable[b]	Individual treatment of physician's choice	1 RCT, direct comparison with high-dose dexamethasone	Considerable (hint)
	Patients for whom dexamethasone (high-dose) is not the individual treatment of physician's choice	Not relevant[a]	Considerable[b]	Individual treatment of physician's choice	No usable data	Not proven

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Macitentan	Pulmonary arterial hypertension	1 RCT, direct comparison with placebo	Minor	Individually optimized drug treatment specified by the physician, under consideration of the respective approval status	No usable data	Not proven
Riociguat	Pulmonary arterial hypertension	1 RCT, direct comparison with placebo	Minor	Individually optimized drug treatment under consideration of prior therapies and health status, under consideration of the following therapies: ▪ endothelin receptor antagonists ▪ phosphodiesterase-5 inhibitors ▪ prostacyclin analogues ▪ selective prostacyclin receptor agonists	No usable data	Not proven
	Chronic thromboembolic pulmonary hypertension	1 RCT, direct comparison with placebo	Minor	BSC	No usable data	Not proven
Ibrutinib	Mantle cell lymphoma	1 single-arm study	Non-quantifiable	Individually optimized treatment specified by the physician, in principle under consideration of the respective approval status	Not relevant[a]	Not relevant[a]
	Patients for whom temsirolimus is the individually suitable treatment option	Not relevant[a]	Non-quantifiable[b]	Temsirolimus	1 RCT, direct comparison with temsirolimus	Considerable (indication)

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
	Patients for whom temsirolimus is not the individually suitable treatment option	Not relevant[a]	Non-quantifiable[b]	Individually optimized treatment specified by the physician, in principle under consideration of the respective approval status	No usable data	Not proven
	Chronic lymphocytic leukaemia					
	At least 1 prior therapy	1 RCT, direct comparison with ofatumumab	Non-quantifiable	Not relevant[a]	Not relevant[a]	Not relevant[a]
	Patients for whom chemotherapy is indicated	Not relevant[a]	Non-quantifiable[b]	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated	No usable data	Not proven
	Patients for whom chemotherapy is not indicated	Not relevant[a]	Non-quantifiable[b]	Idelalisib or BSC	1 RCT, direct comparison with ofatumumab	Non-quantifiable (hint)
	First line, 17p deletion or TP53 mutation; unsuitable for chemo-immunotherapy	1 RCT, direct comparison with ofatumumab	Non-quantifiable	BSC	No usable data (evidence transfer)[c]	Non-quantifiable (hint)
Ramucirumab	Gastric or gastro-oesophageal junction adenocarcinoma					
	In combination with paclitaxel	1 RCT, direct comparison with placebo + paclitaxel	Minor	Treatment of physician's choice under consideration of the respective approval	1 RCT, direct comparison with placebo + paclitaxel	Minor (hint)

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
	As monotherapy in patients for whom treatment in combination with paclitaxel is not appropriate	1 RCT, direct comparison with placebo + BSC	Minor	BSC	No usable data	Not proven
Nintedanib	Idiopathic pulmonary fibrosis	2 RCTs, direct comparison with placebo	Minor	Pirfenidone (only for patients with mild to moderate idiopathic pulmonary fibrosis according to the approval) or BSC	4 RCTs, direct comparison with placebo	Considerable (hint)
Olaparib	Ovarian, fallopian tube or primary peritoneal cancer	1 RCT, direct comparison with placebo	Non-quantifiable	Watchful waiting	2 RCTs, direct comparison with placebo	Minor (hint)
Lenvatinib	Thyroid neoplasms	1 RCT, direct comparison with placebo	Non-quantifiable	Sorafenib	No usable data	Not proven

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Asfotase alfa	Hypophosphatasia					
	≤ 5 years	3 single-arm studies, comparison with 1 single-arm retrospective control group	Non-quantifiable	Not relevant[a]	Not relevant[a]	Not relevant[a]
	With perinatal or infantile hypophosphatasia (onset of disease before the age of 6 months)	Not relevant[a]	Non-quantifiable[b]	BSC	2 pooled single-arm studies, comparison with 1 single-arm retrospective control group	Non-quantifiable (hint)
	With juvenile hypophosphatasia (onset of disease from the age of 6 months)	Not relevant[a]	Non-quantifiable[b]	BSC	No data	Not proven
	> 5 years	▪ 5–12 years: 1 RCT, direct comparison of 2 dosing regimens ▪ > 12 years: 1 RCT, direct comparison with no treatment	Non-quantifiable	BSC	No usable data	Not proven

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Carfilzomib	Multiple myeloma, at least 1 prior therapy, combination with lenalidomide and dexamethasone	1 RCT, direct comparison with dexamethasone + lenalidomide	Non-quantifiable	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ bortezomib in combination with dexamethasone or ▪ lenalidomide in combination with dexamethasone or ▪ elotuzumab in combination with lenalidomide and dexamethasone	1 RCT, direct comparison with dexamethasone + lenalidomide	Considerable (hint)
	In combination with dexamethasone in multiple myeloma, at least 1 prior therapy	1 RCT, direct comparison with dexamethasone + bortezomib	Minor	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ bortezomib in combination with dexamethasone or ▪ lenalidomide in combination with dexamethasone or ▪ elotuzumab in combination with lenalidomide and dexamethasone	1 RCT, direct comparison with dexamethasone + bortezomib	Considerable (hint)

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Daratumumab	Multiple myeloma, monotherapy	1 single-arm study	Non-quantifiable	Individual treatment of physician's choice, depending in particular on the prior therapies and the extent and duration of the response as well as under consideration of the approval of the respective drug	No usable data	Not proven
Venetoclax	Chronic lymphocytic leukaemia, monotherapy					
	Adult patients with 17p deletion or TP53 mutation who are unsuitable for or have failed a B-cell receptor pathway inhibitor	2 single-arm studies	Non-quantifiable	▪ Ibrutinib or ▪ idelalisib + rituximab or ▪ BSC (only for patients who have failed prior therapy with ibrutinib or idelalisib + rituximab)	No usable data	Not proven
	Adult patients without 17p deletion or TP53 mutation who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor	2 single-arm studies	Non-quantifiable	▪ Ibrutinib or ▪ idelalisib + rituximab or ▪ BSC	No usable data	Not proven

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Nusinersen	Spinal muscular atrophy					
	5q spinal muscular atrophy type 1	1 RCT, direct comparison with sham intervention	Major	BSC	▪ 1 RCT, direct comparison with sham intervention ▪ (2 single-arm extension studies)	Major (indication)
	5q spinal muscular atrophy type 2	1 RCT, direct comparison with sham intervention	Considerable	BSC	1 RCT, direct comparison with sham intervention	Considerable (hint)
	5q spinal muscular atrophy type 3	No usable data	Non-quantifiable	BSC	No usable data	Not proven
	5q spinal muscular atrophy type 4	No usable data	Non-quantifiable	BSC	No usable data	Not proven
Avelumab	Merkel cell carcinoma					
	Without prior chemotherapy in the metastatic setting	1 single-arm study, comparison with retrospective control group	Non-quantifiable	Treatment of physician's choice	No usable data	Not proven
	After at least 1 chemotherapy in the metastatic setting	1 single-arm study, comparison with single-arm retrospective control group	Non-quantifiable	Was not subject of the regular benefit assessment[d]		
Niraparib	Ovarian, fallopian tube or primary peritoneal cancer	1 RCT, direct comparison with placebo	Non-quantifiable	▪ Olaparib or ▪ watchful waiting	Adjusted indirect comparison of 3 RCTs using placebo as common comparator	Not proven

Table 7: Primary analysis: results of limited assessments versus regular benefit assessments (multipage table)

Drug	Therapeutic indication Research question	Data basis for limited assessment	Extent of added benefit in limited assessment	ACT specified by the G-BA	Data basis for regular benefit assessment	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Tezacaftor/ivacaftor	Cystic fibrosis, homozygous, F508del mutation, ≥ 12 years	1 RCT, direct comparison with placebo	Considerable	Lumacaftor/ivacaftor	Adjusted indirect comparison of 3 RCTs using placebo as common comparator	Not proven
	Cystic fibrosis, heterozygous, F508del mutation, ≥ 12 years	1 RCT, comparison with placebo, crossover design	Minor	BSC	No usable data	Not proven

a. Differentiated consideration of several research questions in regular benefit assessments.
b. Results from the overall assessment of the therapeutic indication in the limited assessment.
c. According to the G-BA decision, no data are available that allow a direct assessment of the added benefit in first-line therapy. The justification of the G-BA decision describes an evidence transfer of data from the second line to the first line. The data basis is allocated to the category of evidence transfers.
d. The subgroup originally formed in the limited assessment was no longer used in the regular benefit assessment.

5q: long arm of chromosome 5; 17p: short arm of chromosome 17; BSC: best supportive care; F508del: deletion of the amino acid phenylalanine at position 508 of the CFTR protein; G-BA: Federal Joint Committee; G551D: substitution of the amino acid glycine by aspartic acid at position 551 of the CFTR protein; Ph+: Philadelphia chromosome-positive; R117H: substitution of the amino acid arginine by histidine at position 117 of the CFTR protein; RCT: randomized controlled trial; SMN: survival motor neuron; TP53: gene of the tumour suppressor protein 53

Table 8: Secondary analysis: results of the regular benefit assessments of orphan drugs for which no limited assessments were conducted (multipage table)

Drug	Therapeutic indication Research question	ACT specified by the G-BA	Data basis	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Ivacaftor	Cystic fibrosis, combination treatment with tezacaftor/ivacaftor in patients aged 12 years and older (homozygous for F508del mutation)	Lumacaftor/ivacaftor	Adjusted indirect comparison of 3 RCTs using placebo as common comparator	Not proven
	Cystic fibrosis, heterozygous for F508del, ≥ 12 years, combination with tezacaftor	BSC	No usable data	Not proven
	Cystic fibrosis, patients from 12 to < 24 months of age	BSC	Evidence transfer from patients ≥ 6 years of age; consideration of 1 single-arm study	Non-quantifiable (hint)
	Cystic fibrosis, patients ≥ 6 to < 12 months of age	BSC	Evidence transfer from patients ≥ 6 years of age; consideration of 1 single-arm study	Non-quantifiable (hint)
	Cystic fibrosis, patients ≥ 6 months to < 18 years of age (R117H)			
	Patients with cystic fibrosis from 6 months to < 6 years of age who have an R117H mutation	BSC	Evidence transfer from patients ≥ 18 years of age; consideration of 1 observational study	Non-quantifiable (hint)
	Patients with cystic fibrosis from 6 to < 18 years of age who have an R117H mutation	BSC	1 RCT, direct comparison with placebo + BSC	Non-quantifiable (hint)
	Cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor in patients aged 12 years and older (heterozygous for F508del and MF mutation)	BSC	1 RCT, direct comparison with placebo	Major (hint)

Table 8: Secondary analysis: results of the regular benefit assessments of orphan drugs for which no limited assessments were conducted (multipage table)

Drug	Therapeutic indication Research question	ACT specified by the G-BA	Data basis	Extent of added benefit in regular benefit assessment (certainty of conclusions)
	Cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor in patients aged 12 years and older (homozygous for F508del mutation)	▪ Lumacaftor/ivacaftor or ▪ tezacaftor/ivacaftor in combination with ivacaftor	1 RCT, direct comparison with tezacaftor/ivacaftor in combination with ivacaftor	Major (indication)
	Cystic fibrosis, patients from 4 to < 6 months of age, gating mutations	BSC	Evidence transfer from patients ≥ 6 years of age; consideration of 1 single-arm study	Non-quantifiable (hint)
	Cystic fibrosis, patients from 4 to < 6 months of age, R117H mutation	BSC	Evidence transfer from patients ≥ 18 years of age	Non-quantifiable (hint)
	Cystic fibrosis, combination therapy with tezacaftor/ivacaftor in patients from 6 to < 12 years of age (homozygous for F508del mutation)	Lumacaftor/ivacaftor	No usable data	Not proven
	Cystic fibrosis, combination therapy with tezacaftor/ivacaftor in patients from 6 to < 12 years of age (heterozygous for F508del and RF mutation)	BSC	No usable data	Not proven

Table 8: Secondary analysis: results of the regular benefit assessments of orphan drugs for which no limited assessments were conducted (multipage table)

Drug	Therapeutic indication Research question	ACT specified by the G-BA	Data basis	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Pomalidomide	Multiple myeloma, at least 1 prior therapy, combination with bortezomib and dexamethasone	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ bortezomib in combination with dexamethasone or ▪ lenalidomide in combination with dexamethasone or ▪ elotuzumab in combination with lenalidomide and dexamethasone or ▪ carfilzomib in combination with lenalidomide and dexamethasone or ▪ carfilzomib in combination with dexamethasone or ▪ daratumumab in combination with lenalidomide and dexamethasone or ▪ daratumumab in combination with bortezomib and dexamethasone	1 RCT, direct comparison with bortezomib + dexamethasone	Not proven
Ibrutinib	Waldenström macroglobulinaemia	Individually optimized treatment specified by the physician, in principle under consideration of the approval status and under consideration of Appendix VI of the Pharmaceutical Directive (off-label use)	No usable data	Not proven

Table 8: Secondary analysis: results of the regular benefit assessments of orphan drugs for which no limited assessments were conducted (multipage table)

Drug	Therapeutic indication Research question	ACT specified by the G-BA	Data basis	Extent of added benefit in regular benefit assessment (certainty of conclusions)
	Chronic lymphocytic leukaemia, first line			
	Patients for whom treatment with FCR is an option	Fludarabine in combination with cyclophosphamide and rituximab	No usable data	Not proven
	Patients for whom treatment with FCR is not an option	Chemo-immunotherapy specified by the physician, under consideration of the approval status	No usable data	Not proven
	Patients for whom chemo-immunotherapy is not an option and who have no 17p deletion or TP53 mutation	BSC	No usable data	Not proven
	Chronic lymphocytic leukaemia, at least 1 prior therapy, combination with bendamustine and rituximab	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated		
	Patients with ≥ 2 prior therapies for whom bendamustine in combination with rituximab is the individually optimized treatment	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated	1 RCT, direct comparison with bendamustine + rituximab	Considerable (hint)
	Patients with prior therapy and patients for whom a therapy other than bendamustine in combination with rituximab is the individually optimized treatment	Individually optimized chemotherapy specified by the physician under consideration of the approval status, preferably in combination with rituximab if indicated	No data	Not proven

Table 8: Secondary analysis: results of the regular benefit assessments of orphan drugs for which no limited assessments were conducted (multipage table)

Drug	Therapeutic indication Research question	ACT specified by the G-BA	Data basis	Extent of added benefit in regular benefit assessment (certainty of conclusions)
	Chronic lymphocytic leukaemia, first line, combination with obinutuzumab			
	Patients for whom treatment with FCR is an option	Fludarabine in combination with cyclophosphamide and rituximab	No data	Not proven
	Patients for whom treatment with FCR is not an option	▪ Bendamustine in combination with rituximab or ▪ chlorambucil in combination with rituximab or obinutuzumab	1 RCT, direct comparison with chlorambucil + obinutuzumab	Minor (hint)
	Patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib	No usable data	Not proven
	Waldenström macroglobulinaemia, combination with rituximab	Individual treatment under consideration of the general condition and possible prior therapies	No usable data	Not proven
	Chronic lymphocytic leukaemia, first line, combination with rituximab			
	Patients for whom treatment with FCR is an option	Fludarabine in combination with cyclophosphamide and rituximab	1 RCT, direct comparison with FCR	Considerable (hint)
	Patients for whom treatment with FCR is not an option	▪ Bendamustine in combination with rituximab or ▪ chlorambucil in combination with rituximab or obinutuzumab	No data	Not proven

Table 8: Secondary analysis: results of the regular benefit assessments of orphan drugs for which no limited assessments were conducted (multipage table)

Drug	Therapeutic indication Research question	ACT specified by the G-BA	Data basis	Extent of added benefit in regular benefit assessment (certainty of conclusions)
	Patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	Ibrutinib	No data	Not proven
Carfilzomib	Multiple myeloma, at least 1 prior therapy, combination with daratumumab and dexamethasone	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ bortezomib in combination with dexamethasone or ▪ lenalidomide in combination with dexamethasone or ▪ elotuzumab in combination with lenalidomide and dexamethasone or ▪ carfilzomib in combination with lenalidomide and dexamethasone or ▪ carfilzomib in combination with dexamethasone or ▪ daratumumab in combination with lenalidomide and dexamethasone or ▪ daratumumab in combination with bortezomib and dexamethasone	1 RCT, direct comparison with carfilzomib + dexamethasone	Not proven

Table 8: Secondary analysis: results of the regular benefit assessments of orphan drugs for which no limited assessments were conducted (multipage table)

Drug	Therapeutic indication Research question	ACT specified by the G-BA	Data basis	Extent of added benefit in regular benefit assessment (certainty of conclusions)
Daratumumab	Multiple myeloma, at least 1 prior therapy, combination with lenalidomide and dexamethasone or bortezomib and dexamethasone	▪ Bortezomib in combination with pegylated liposomal doxorubicin or ▪ bortezomib in combination with dexamethasone or ▪ lenalidomide in combination with dexamethasone or ▪ elotuzumab in combination with lenalidomide and dexamethasone	2 RCTs, direct comparison with lenalidomide + dexamethasone or bortezomib + dexamethasone, meta-analysis	Considerable (indication)
	Multiple myeloma, first line, stem cell transplant unsuitable, combination with bortezomib, melphalan and prednisone	Combination therapy specified by the physician	1 RCT, direct comparison with bortezomib + melphalan + prednisone	Considerable (hint)

Table 8: Secondary analysis: results of the regular benefit assessments of orphan drugs for which no limited assessments were conducted (multipage table)

Drug	Therapeutic indication Research question	ACT specified by the G-BA	Data basis	Extent of added benefit in regular benefit assessment (certainty of conclusions)
	Multiple myeloma, newly diagnosed, patients ineligible for autologous stem cell transplant, combination with lenalidomide and dexamethasone	▪ Daratumumab in combination with bortezomib, melphalan and prednisone or ▪ bortezomib in combination with melphalan and prednisone or ▪ bortezomib in combination with lenalidomide and dexamethasone or ▪ thalidomide in combination with melphalan and prednisone or ▪ lenalidomide in combination with dexamethasone	1 RCT, direct comparison with lenalidomide + dexamethasone	Minor (hint)
	Multiple myeloma, newly diagnosed, patients eligible for autologous stem cell transplant, combination with bortezomib, thalidomide and dexamethasone	▪ Induction therapy consisting of bortezomib-dexamethasone-based triple combination therapy specified by the physician ▪ followed by high-dose therapy with melphalan and subsequent autologous stem cell transplantation	1 RCT, direct comparison with bortezomib + thalidomide + dexamethasone	Non-quantifiable (hint)
Nusinersen	Pre-symptomatic patients with spinal muscular atrophy and 2 SMN2 gene copies	BSC	Evidence transfer from 5q spinal muscular atrophy type 1	Major (hint)
	Pre-symptomatic patients with spinal muscular atrophy and 3 SMN2 gene copies	BSC	Evidence transfer from 5q spinal muscular atrophy type 2	Non-quantifiable (hint)

Table 8: Secondary analysis: results of the regular benefit assessments of orphan drugs for which no limited assessments were conducted (multipage table)

Drug	Therapeutic indication Research question	ACT specified by the G-BA	Data basis	Extent of added benefit in regular benefit assessment (certainty of conclusions)
	Pre-symptomatic patients with spinal muscular atrophy and more than 3 SMN2 gene copies	BSC	No usable data	Not proven
Niraparib	Ovarian, fallopian tube or primary peritoneal cancer, FIGO stages III and IV, maintenance therapy	Treatment of physician's choice under consideration of ▪ watchful waiting (after prior therapy with carboplatin in combination with paclitaxel) ▪ bevacizumab (only after prior therapy with carboplatin in combination with paclitaxel and bevacizumab)	No usable data	Not proven
Tezacaftor/ivacaftor	Cystic fibrosis, combination therapy with ivacaftor in patients from 6 to < 12 years of age (homozygous for F508del mutation)	Lumacaftor/ivacaftor	No usable data	Not proven
	Cystic fibrosis, combination therapy with ivacaftor in patients from 6 to < 12 years of age (heterozygous for F508del and RF mutation)	BSC	No usable data	Not proven

5q: long arm of chromosome 5; 17p: short arm of chromosome 17; BSC: best supportive care; CFTR: cystic fibrosis transmembrane conductance regulator; FCR: fludarabine + cyclophosphamide + rituximab; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; F508del: deletion of the amino acid phenylalanine at position 508 of the CFTR protein; G-BA: Federal Joint Committee; MF: minimal function; G551D: substitution of the amino acid glycine by aspartic acid at position 551 of the CFTR protein; Ph+: Philadelphia chromosome-positive; R117H: substitution of the amino acid arginine by histidine at position 117 of the CFTR protein; RCT: randomized controlled trial; RF: residual function; SMN: survival motor neuron; TP53: gene of the tumour suppressor protein 53

Table 9: Primary analysis: sources (multipage table)

Drug	Therapeutic indication Research question	Decision + justification of limited assessment	Decision + justification of regular benefit assessment
Tafamidis	Amyloid polyneuropathy	[33,34]	[35,36]
	Amyloid cardiomyopathy	[37,38]	[39,40]
Ivacaftor	Cystic fibrosis, G551D mutation, ≥ 6 years		
	6–11 years	[41,42]	[43,44]
	≥ 12 years	[41,42]	[43,44]
	Cystic fibrosis, various mutations, ≥ 6 years	[45,46]	[47,48]
	Cystic fibrosis, R117H mutation, 2–5 years, > 18 years		
	2–5 years, gating mutation (class III)	[49,50]	[51,52]
	≥ 18 years, R117H mutation	[49,50]	[53,54]
Ruxolitinib	Myelofibrosis	[55,56]	[57,58]
Bosutinib	Chronic myelogenous leukaemia, Ph+		
	Chronic myelogenous leukaemia, Ph+, chronic phase	[59,60]	[61,62]
	Chronic myelogenous leukaemia, Ph+, accelerated phase and blast phase	[59,60]	[61,62]
Pomalidomide	Multiple myeloma, at least 2 prior therapies, combination with dexamethasone		
	Patients for whom dexamethasone (high-dose) is the individual treatment of physician's choice	[63,64]	[65,66]
	Patients for whom dexamethasone (high-dose) is not the individual treatment of physician's choice	[63,64]	[65,66]
Macitentan	Pulmonary arterial hypertension	[67,68]	[69,70]
Riociguat	Pulmonary arterial hypertension	[71,72]	[73,74]
	Chronic thromboembolic pulmonary hypertension	[71,72]	[75,76]
Ibrutinib	Mantle cell lymphoma		
	Patients for whom temsirolimus is the individually suitable treatment option	[77,78]	[79,80]
	Patients for whom temsirolimus is not the individually suitable treatment option	[77,78]	[79,80]
	Chronic lymphocytic leukaemia		
	At least 1 prior therapy		
	Patients for whom chemotherapy is indicated	[77,78]	[79,80]
	Patients for whom chemotherapy is not indicated	[77,78]	[79,80]
	First line, 17p deletion or TP53 mutation; unsuitable for chemo-immunotherapy	[77,78]	[79,80]

Table 9: Primary analysis: sources (multipage table)

Drug	Therapeutic indication Research question	Decision + justification of limited assessment	Decision + justification of regular benefit assessment
Ramucirumab	Gastric or gastro-oesophageal junction adenocarcinoma		
	In combination with paclitaxel	[81,82]	[83,84]
	As monotherapy in patients for whom treatment in combination with paclitaxel is not appropriate	[81,82]	[83,84]
Nintedanib	Idiopathic pulmonary fibrosis	[85,86]	[87,88]
Olaparib	Ovarian, fallopian tube or primary peritoneal cancer	[89,90]	[91,92]
Lenvatinib	Thyroid neoplasms	[93,94]	[95,96]
Asfotase alfa	Hypophosphatasia		
	≤ 5 years		
	With perinatal or infantile hypophosphatasia (onset of disease before the age of 6 months)	[97,98]	[99,100]
	With juvenile hypophosphatasia (onset of disease from the age of 6 months)	[97,98]	[99,100]
	> 5 years	[97,98]	[99,100]
Carfilzomib	Multiple myeloma, at least 1 prior therapy, combination with lenalidomide and dexamethasone	[101,102]	[103,104]
	In combination with dexamethasone in multiple myeloma, at least 1 prior therapy	[105,106]	[103,104]
Daratumumab	Multiple myeloma, monotherapy	[107,108]	[109,110]
Venetoclax	Chronic lymphocytic leukaemia, monotherapy		
	Adult patients with 17p deletion or TP53 mutation who are unsuitable for or have failed a B-cell receptor pathway inhibitor	[111,112]	[113,114]
	Adult patients without 17p deletion or TP53 mutation who have failed both chemo-immunotherapy and a B-cell receptor pathway inhibitor	[111,112]	[113,114]
Nusinersen	Spinal muscular atrophy		
	5q spinal muscular atrophy type 1	[115,116]	[117,118]
	5q spinal muscular atrophy type 2	[115,116]	[117,118]
	5q spinal muscular atrophy type 3	[115,116]	[117,118]
	5q spinal muscular atrophy type 4	[115,116]	[117,118]
Avelumab	Merkel cell carcinoma		
	Without prior chemotherapy in the metastatic setting	[119,120]	[121,122]
	After at least 1 chemotherapy in the metastatic setting	[119,120]	[121,122]

Table 9: Primary analysis: sources (multipage table)

Drug	Therapeutic indication Research question	Decision + justification of limited assessment	Decision + justification of regular benefit assessment
Niraparib	Ovarian, fallopian tube or primary peritoneal cancer	[123,124]	[125,126]
Tezacaftor/ivacaftor	Cystic fibrosis, homozygous, F508del mutation, ≥ 12 years	[127,128]	[129,130]
	Cystic fibrosis, heterozygous, F508del mutation, ≥ 12 years	[127,128]	[131,132]

5q: long arm of chromosome 5; 17p: short arm of chromosome 17; CFTR: cystic fibrosis transmembrane conductance regulator; F508del: deletion of the amino acid phenylalanine at position 508 of the CFTR protein; G551D: substitution of the amino acid glycine by aspartic acid at position 551 of the CFTR protein; Ph+: Philadelphia chromosome-positive; R117H: substitution of the amino acid arginine by histidine at position 117 of the CFTR protein; SMN: survival motor neuron; TP53: gene of the tumour suppressor protein 53

Table 10: Secondary analysis: sources (multipage table)

Drug	Therapeutic indication Research question	Decision + justification
Ivacaftor	Cystic fibrosis, combination treatment with tezacaftor/ivacaftor in patients aged 12 years and older (homozygous for F508del mutation)	[133,134]
	Cystic fibrosis, heterozygous for F508del, ≥ 12 years, combination with tezacaftor	[135,136]
	Cystic fibrosis, patients from 12 to < 24 months of age	[137,138]
	Cystic fibrosis, patients ≥ 6 to < 12 months of age	[139,140]
	Cystic fibrosis, patients ≥ 6 months to < 18 years of age (R117H)	
	Patients with cystic fibrosis aged 6 months to < 6 years who have an R117H mutation	[141,142]
	Patients with cystic fibrosis from 6 to < 18 years of age who have an R117H mutation	[141,142]
	Cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor in patients aged 12 years and older (heterozygous for F508del and MF mutation)	[143,144]
	Cystic fibrosis, combination therapy with ivacaftor/tezacaftor/elexacaftor in patients aged 12 years and older (homozygous for F508del mutation)	[145,146]
	Cystic fibrosis, patients from 4 to < 6 months of age, gating mutations	[147,148]
	Cystic fibrosis, patients from 4 to < 6 months of age, R117H mutation	[149,150]
	Cystic fibrosis, combination therapy with tezacaftor/ivacaftor in patients from 6 to < 12 years of age (homozygous for F508del mutation)	[151,152]
	Cystic fibrosis, combination therapy with tezacaftor/ivacaftor in patients from 6 to < 12 years of age (heterozygous for F508del and RF mutation)	[153,154]
Pomalidomide	Multiple myeloma, at least 1 prior therapy, combination with bortezomib and dexamethasone	[155,156]
Ibrutinib	Waldenström macroglobulinaemia	[79,80]
	Chronic lymphocytic leukaemia, first line	
	Patients for whom treatment with FCR is an option	[157,158]
	Patients for whom treatment with FCR is not an option	[157,158]
	Patients for whom chemo-immunotherapy is not an option and who have no 17p deletion or TP53 mutation	[157,158]
	Chronic lymphocytic leukaemia, at least 1 prior therapy, combination with bendamustine and rituximab	
	Patients with ≥ 2 prior therapies for whom bendamustine in combination with rituximab is the individually optimized treatment	[159,160]
	Patients with prior therapy and patients for whom a therapy other than bendamustine in combination with rituximab is the individually optimized treatment	[159,160]

Table 10: Secondary analysis: sources (multipage table)

Drug	Therapeutic indication Research question	Decision + justification
	Chronic lymphocytic leukaemia, first line, combination with obinutuzumab	
	Patients for whom treatment with FCR is an option	[161,162]
	Patients for whom treatment with FCR is not an option	[161,162]
	Patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	[161,162]
	Waldenström macroglobulinaemia, combination with rituximab	[163,164]
	Chronic lymphocytic leukaemia, first line, combination with rituximab	
	Patients for whom treatment with FCR is an option	[165,166]
	Patients for whom treatment with FCR is not an option	[165,166]
	Patients with 17p deletion and/or TP53 mutation or for whom chemo-immunotherapy is not indicated for other reasons	[165,166]
Carfilzomib	Multiple myeloma, at least 1 prior therapy, combination with daratumumab and dexamethasone	[167,168]
Daratumumab	Multiple myeloma, at least 1 prior therapy, combination with lenalidomide and dexamethasone or bortezomib and dexamethasone	[109,110]
	Multiple myeloma, first line, stem cell transplant unsuitable, combination with bortezomib, melphalan and prednisone	[169,170]
	Multiple myeloma, newly diagnosed, patients ineligible for autologous stem cell transplant, combination with lenalidomide and dexamethasone	[171,172]
	Multiple myeloma, newly diagnosed, patients eligible for autologous stem cell transplant, combination with bortezomib, thalidomide and dexamethasone	[173,174]
Nusinersen	Pre-symptomatic patients with spinal muscular atrophy and 2 SMN2 gene copies	[117,118]
	Pre-symptomatic patients with spinal muscular atrophy and 3 SMN2 gene copies	[117,118]
	Pre-symptomatic patients with spinal muscular atrophy and more than 3 SMN2 gene copies	[117,118]
Niraparib	Ovarian, fallopian tube or primary peritoneal cancer, FIGO stages III and IV, maintenance therapy	[175,176]
Tezacaftor/ivacaftor	Cystic fibrosis, combination therapy with ivacaftor in patients from 6 to < 12 years of age (homozygous for F508del mutation)	[177,178]
	Cystic fibrosis, combination therapy with ivacaftor in patients from 6 to < 12 years of age (heterozygous for F508del and RF mutation)	[179,180]

17p: short arm of chromosome 17; BSC: best supportive care; FCR: fludarabine + cyclophosphamide + rituximab; FIGO: Fédération Internationale de Gynécologie et d'Obstétrique; F508del: deletion of the amino acid phenylalanine at position 508 of the CFTR protein; G-BA: Federal Joint Committee; MF: minimal function; R117H: substitution of the amino acid arginine by histidine at position 117 of the CFTR protein; RF: residual function; SMN: survival motor neuron; TP53: gene of the tumour suppressor protein 53