# Do orphan drugs lack evidence in health technology assessments compared to non-orphan drugs?

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## Background

- Rare diseases impact a small patient population (1 in 2,000 individuals in the European Union) and often lack appropriate therapeutic options[1].
- Thus, orphan drugs (ODs) are granted special support to incentivize diagnostic and therapeutical development[1].
- During the German health technology benefit assessment (Act on the Reform of the Market for Medicinal Products, AMNOG), ODs undergo a limited benefit assessment by the Federal Joint Committee (G-BA)[2]:
  - No comparison with an appropriate comparative therapy (ACT).
  - Benefit is granted by law.
- However, a reassessment is mandatory when the turnover threshold of €30 million is reached[2] or when OD status is withdrawn[3].
- Consequently, ODs are subject to ongoing debate, particularly concerning therapeutic costs and evidence standards.

## Objectives

- This analysis aimed to compare pricing differences and evidence levels in ODs and non-ODs at initial assessment (IA) and reassessment (RA).

## Methods

- An internal AMNOG database (including G-BA data) was used to analyze benefit assessments from 2011 to May 2024.
- Data were extracted for ODs and non-ODs for the initial assessment and reassessment, including the following parameters:
  - Prices
  - Granted benefit
  - Study type
  - Number of studies and population size

## Conclusion

- Despite the persistently high costs of ODs post-assessment compared to non-ODs, evidential standards remained comparable between the two groups during re-evaluation.
- However, fewer randomized controlled trials (RCTs) were accepted for ODs, often due to a lack of evidence for the comparison with an ACT defined by the G-BA.
- The extent of the additional benefit granted when using RCTs is similar for both ODs and non-ODs and including a large patient population facilitates conducting RCTs for both groups.
- Pharmaceutical companies do not rely solely on their OD status, as reflected by the high proportion of RCTs.
- Health technology developers seem to provide the best available evidence (RCT), despite challenges like small patient populations and limitations in ACT.

## References

1. Bundesministerium für Gesundheit (BMG). Seltene Erkrankungen; 2024. [Accessed September 04, 2024]. https://www.bundesgesundheitsministerium.de/themen/praevention/gesundheitsgefahren/seltene-erkrankungen.html
2. Bundesministerium der Justiz (BMJ). Sozialgesetzbuch (SGB) Fünftes Buch (V). [Accessed September 04, 2024]. https://www.gesetze-im-internet.de/sgb_5/__35a.html
3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Preis- und Kostenentwicklung von Orphan Drugs; Arbeitspapier [online]. 2024 [Accessed September 19, 2024]. https://dx.doi.org/10.60584/GA22-01

**Abbreviations**

ACT – appropriate comparative therapy; AMNOG – Act on the Reform of the Market for Medicinal Products; G-BA – Federal Joint Committee; IA – initial assessment; No. – number; OD – orphan drug; RA – reassessment; RCT – randomized controlled trial.

## Results

- From 2011 to May 2024, 959 benefit assessments were conducted. Overall, 810 of those benefit assessments were initial assessments (**Figure 1**), whereas 149 assessments were subsequent evaluations.
- From 810 assessments, 27% evaluated ODs (**Figure 1**).
- A reassessment was mandatory for approximately 1/4 of all ODs and 1/10 of all non-ODs (**Figure 1**).

**Figure 1. Benefit assessments with and without reassessment**

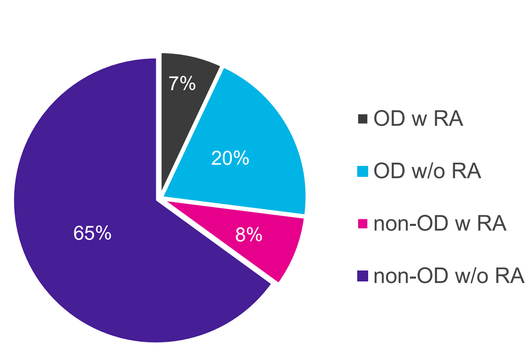
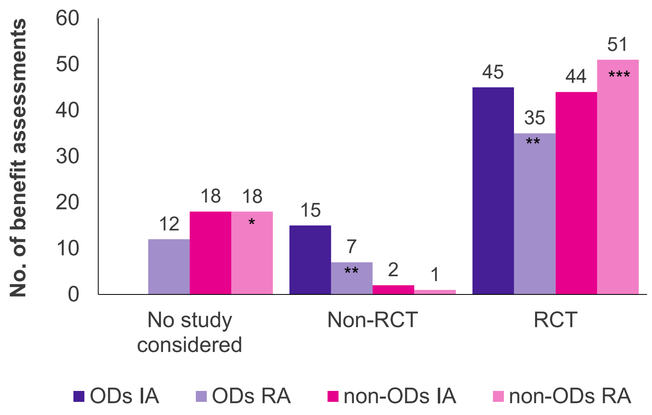



**Figure 2. Price reduction after initial assessment and reassessment**


**Reimbursement prices decrease from the initial assessment to reassessment**

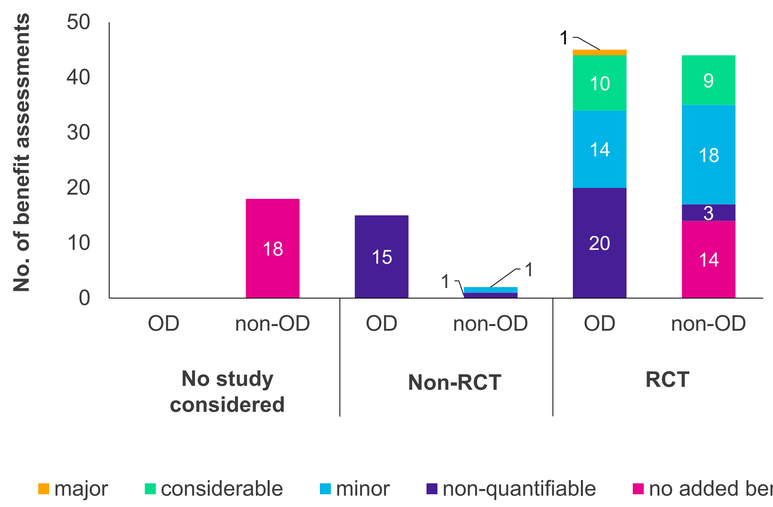
- On average, ODs were about 10.2 to 13.5 times more expensive than non-ODs (**Figure 2**).
- Generally, the benefit assessment resulted in a decrease in the reimbursement price compared to the price at the decision (**Figure 2**).
- The fall in price was greater after the initial assessment (18%–22%) than after the reassessment (8%) for both ODs and non-ODs (**Figure 2**).
- For non-ODs, the mean price decrease was 22% in the initial assessment and 8% in the reassessment, while it was 18% and 8% for ODs, respectively (**Figure 2**).

**Figure 3. Distribution of study type among ODs and non-ODs in the initial assessment and reassessment**




* Additional four former ODs, which were non-ODs in the reassessment due to loss of OD status.
** Reduced by three former ODs, which were non-ODs in the reassessment due to loss of OD status.
*** Additional two former ODs, which were non-ODs in the reassessment due to loss of OD status.

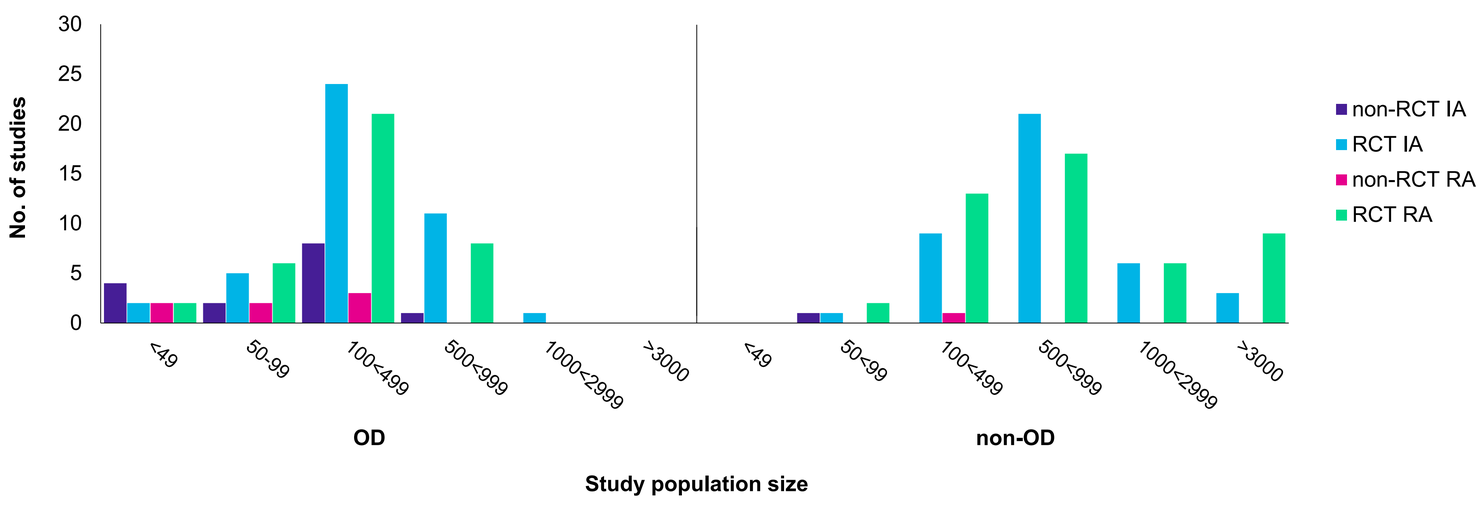
**Figure 4. Granted added benefit in initial assessments, depending on the study type**




**Comparability of evidence based on the study type**

- Randomized controlled trials (RCTs) were the predominant study type in OD and non-OD benefit assessments (**Figure 3**).
- In the reassessment, the G-BA accepted 22% fewer RCTs for ODs compared to the initial assessment. Contrarily, an increase in accepted RCTs by 16% was observed for non-ODs (**Figure 3**).
- Benefit assessments showed a similar distribution of the granted benefit among ODs and non-ODs, except in the case of "no added benefit", which is not applicable by law in limited benefit assessments of ODs (**Figure 4**).

**Figure 5. Population size distribution in study types among ODs and non-ODs in the initial assessment and reassessment**




- With larger population sizes, more RCTs were available (**Figure 5**). The quality of the provided evidence seems to be related to the prevalence of the disease.
- Generally, larger study populations were observed for non-ODs, and for those, more RCTs were considered in reassessments than for ODs (**Figure 5**).

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