Challenges and Criteria for Accepting Lower-Level of Evidence in Early Benefit Assessments (EBA) in Germany

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INTRODUCTION

BACKGROUND:

- Randomized controlled trials (RCTs) are the gold standard for regulatory approval and Health Technology Assessment (HTA).
- However, RCTs may not always be feasible or ethical in certain situations.
- As a result, consideration of single-arm trials (SATs) increased by both regulatory bodies and HTA agencies.
- In Germany, criteria for acceptance of this lower-level evidence by the Federal Joint Committee (G-BA) and the Institute for Quality and Efficiency in Health Care (IQWiG) have not been thoroughly investigated.

OBJECTIVES:

- Analysis of acceptance rates of single-arm trials (SATs), without or with external controls (externally controlled trial (ECT)), that resulted in granting an added benefit by German HTA agencies.
- Examination of conditions under which SATs/ECTs were accepted.
- Assessment of whether these criteria are transparently and consistently applied.
- Derive recommendations on how to improve the acceptance rate of SATs.

METHODS

A combined search of the AMNOG-Monitor database (as of May 1, 2024) and the G-BA website was performed.

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RESULTS

The search in the database identified:

- 1407 assessments of (sub)populations with assignment of comparators and full assessment by IQWiG & G-BA, 9.5% were evaluated based on SAT
- 222 assessments of orphan populations (without assignment of comparator and solely assessed by G-BA), 35.1% were evaluated based on SAT

SATs/ECTs were accepted for granting an added benefit (see Figure 1) in

- 21.8% of full assessments and
- 3.8% of orphan assessments (non-quantifiable added benefit based on legal grounds excluded).

81.2% of the 32 full and orphan SAT/ECT assessments with an added benefit granted by G-BA correspond to chronic Hepatitis C (CHC).

The ratio children/adolescents to adults was 1:5 for CHC and 2:1 for the other indications.

Out of 29 full assessments with an added benefit granted by G-BA, IQWiG accepted SATs only in 34.5% of the cases (N=9 for CHC & N=1 for hypophosphatasia in children (Asfotase alfa)).

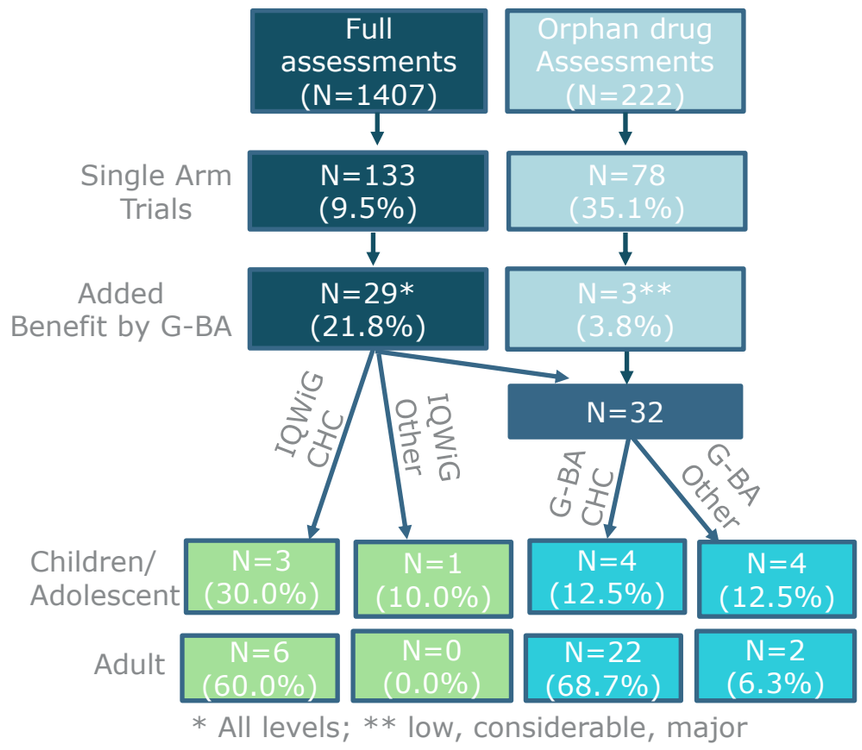

Figure 1. Acceptance of SATs/ECTs for chronic Hepatitis C (CHC) versus all other indications for adult and children/adolescent populations

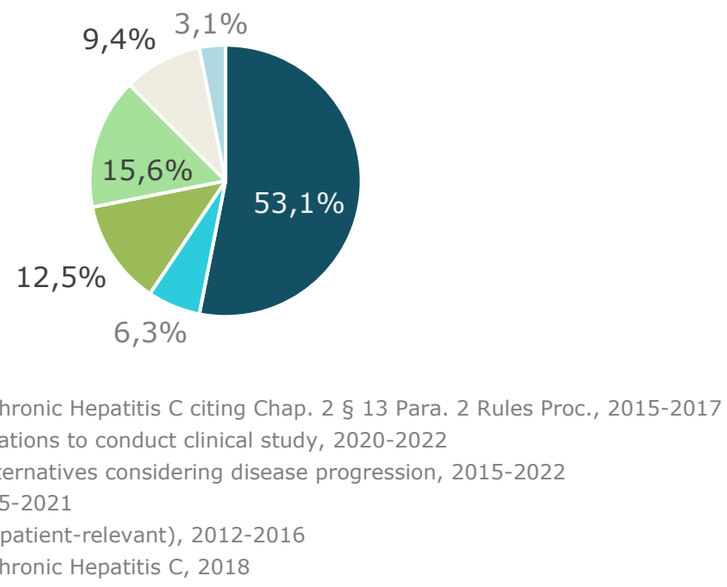

Figure 2. Reasons for SAT/ECT acceptance postulated by G-BA (N=32)

- G-BA accepted SATs/ECTs in **84%** of the cases for reasons other than a **"dramatic effect"*** (Figure 2)
- Reasons for acceptance seem to vary over time (e.g., Ledipasvir/Sofosbuvir side effects (either with or without citing Chap. 2 § 13 Para. 2 Rules Proced.))
- IQWiG refers to a "special data constellation" in the absence of "dramatic effects" in 60% of assessments.

*statistically significant result at the 1% level, with an estimated relative risk of ≥10 [3]

- The overall rate (RCT & non-RCT) to grant an added benefit for full assessments by the G-BA was 30% (Table 1).
- For small target populations, here defined as those affecting <250 patients in Germany (which can be considered "ultra-orphan"), additional benefit rate in full assessments was 19.9%. When the comparator was not active (like best supportive care) the acceptance was 54.8% (Table 1).

Table 1. Overall added benefit and added benefit for small vs large populations and for non-active vs active comparator (full assessments)

	n/N (%)	n/N (%)
	Overall	
Added benefit	422/1407 (30.0%)	
Added benefit not proven	985/1407 (70.0%)	
	<250 patients	**>250 patients**
Added benefit	44/221 (19.9%)	378/1186 (31.9%)
Added benefit not proven	177*/221 (80.1%)	808*/1186 (68.1%)
	Best supportive care	**Active Comparator**
Added benefit	80/146 (54.8 %)	333/1261 (26.4 %)
Added benefit not proven	64*/146 (43.8 %)	928*/1261 (73.6 %)

Where N= number of total assessments and n = number of respective assessments

Across all subpopulations with "added benefit not proven", no data were submitted in 27%-29%* of cases. Although a SAT was accepted in the absence of treatment alternatives considering disease progression, no data were provided in 36% (13/36) of oncological populations with a deterministic course (data not shown). Best supportive care was the appropriate comparator in these cases. E.g., for Amivantamab no data were submitted although best supportive care was deemed the appropriate comparator. It is used in locally advanced or metastatic NSCLC with activating EGFR exon 20 insertions, following the failure of platinum-based chemotherapy and when no further chemotherapy is indicated. The target population is approximately 1 to 4 patients in Germany.[1]

The fact that **no data were submitted in assessment of subpopulations with "added benefit not proven"** is notably high, with no difference between small or large populations, or between active and non-active comparators.

DISCUSSION

- G-BA acceptance rate for SATs/ECTs is low and aligns with previously reported rates.[2]
- If SATs/ECTs are accepted by G-BA and IQWiG, reasons beyond dramatic effects are more commonly cited.
- The majority of SATs/ECTs were accepted in CHC due to sustained virological response considered as a valid endpoint, leading to dramatic effects and/or fewer side effects.
- In other indications, SATs/ECTs were accepted also for rare diseases/limitations in conducting RCT, lack of treatment alternatives for progressive diseases, or complete responses predominately for children/adolescents.
- Even though Chapter 2, § 13 Para. 2 of its Rules of Procedure pertains to medical procedures rather than drugs, G-BA referenced it for accepting SAT. It remains unclear why this is restricted to 2015-2017.
- While small patient populations or the lack of treatment alternatives were used by the G-BA as reasons for acceptance of SAT, the overall added benefit rate across all full assessments appear low (19.9% and 54.8%).
- This might be caused by the fact that when added benefit was not proven in about 30% of full assessments no data was submitted, despite lower requirements. Possible reasons include:
  - Some acceptance criteria varied over time and may not have been clearly described or communicated to pharmaceutical companies.
  - Uncertainty to demonstrate a "dramatic effect" or the stringent requirements for adjustments in indirect comparisons.
- While the G-BA typically shows interest in compounds for rare diseases with no existing treatments, they do not automatically grant an added benefit when fulfilling the orphan criteria (e.g. Amivantamab subpopulation research question 2)[1]. This contrasts with EMA-designated orphan drugs, where the added benefit by the G-BA is legally mandated.

CONCLUSIONS

- RCTs remain the gold standard; however, there are specific situations its conduct may not be feasible/ethical.
- In such cases, SATs with or without external controls can serve as an alternative in order to enrich evidence.
- Submission of SATs/ECTs faces challenges in achieving additional benefit in full assessments in Germany.
- Besides the well-defined dramatic effect, other reasons for SAT/ECT acceptance seem to exit but vary over time which further complicates study planning for pharmaceutical companies.

In order to improve the acceptance rate of SATs/ECTs in Germany, we emphasize the need for binding criteria agreed with G-BA early in the drug development process when RCTs are not feasible/ethical:

Guidance on
- **small target populations**
- lack of therapeutic alternatives for **diseases with a deterministic course**
- **Consideration of Surrogates** (valid although not validated)
- Other reasons (e.g., **avoidance of side effects or complete response**)

REFERENCES

1. Amivantamab Resulution G-BA
https://www.g-ba.de/downloads/39-1464-5516/2022-07-07_AM-RL-XII_Amivantamab_D-788_EN.pdf

2 Tomeczkowski, J. et al: Real-World Data as External Controls for Single-Arm Trials: Role in Regulatory and Health Technology Assessments. November 2022Value in Health 25(12):S300-S301, DOI: 10.1016/j.jval.2022.09.1484 Poster HTA24

3. IQWiG. Allgemeine Methoden Version 7.0 19.09.2023
https://www.iqwig.de/ueber-uns/methoden/methodenpapier/

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