TRANSITION FROM ORPHAN DRUG TO FULL ASSESSMENT IN THE GERMAN AMNOG SYSTEM: KEY LEARNINGS FROM PIONEERS

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OBJECTIVES

- A specific feature of the German HTA process is the relevance of the orphan drug (OD)-status. The additional medical benefit of orphan drugs, assessed by the German HTA body (FJC, Federal Joint Committee) is already acknowledged by approval. No head-to-head data are required.
- If the revenue per annum exceeds 50 million euros or OD-status is lost, reevaluation against an appropriate comparator is mandatory.
- The aim of this study was to reveal the consequences of reevaluation.
- Acceptance of study data, patient relevant endpoints and extent of additional benefit assigned by FJC and IQWiG (Institute for Quality and Efficiency in Health Care) of reevaluated former OD-dossiers were analyzed.

METHODS

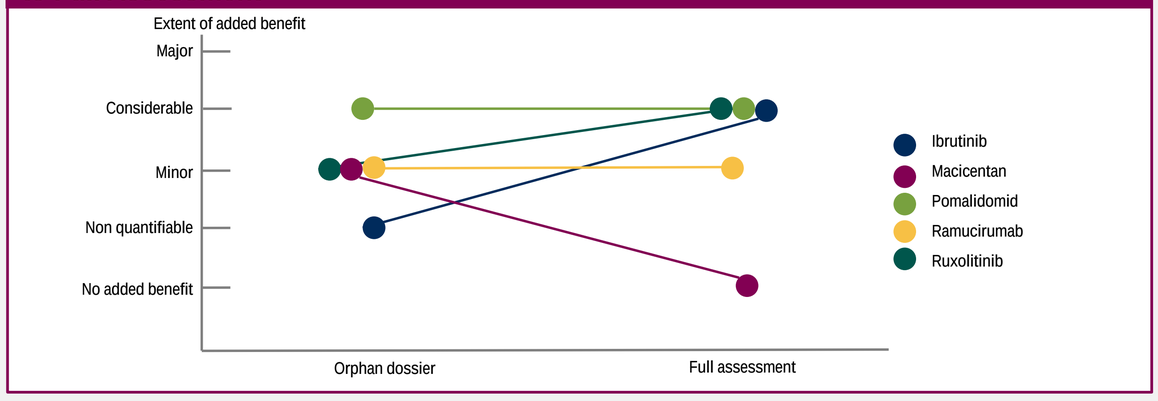
- A database containing all AMNOG dossiers assessed until June 2017 was screened for dossiers which have been assessed both under orphan and non-orphan conditions.
- Data on indication, the comparator utilized in the company's dossier, and outcome (added benefit) were collected and analyzed.

RESULTS

Table 1. Reassessed Orphan Disease Drugs in the German AMNOG System

Pharmaceutical	Reason for Reassessment	Time between 1st and 2nd evaluation	Added benefit 1st assessment	Added benefit 2nd assessment
Ibrutinib	Revenue p.a. >50 million €	14 months	Not quantifiable	A.1.1: No added benefit A.1.2: Not quantifiable A.2: Not quantifiable A.3: Considerable
Macicentan	Revenue p.a. >50 million €	32.5 months	Minor	No added benefit
Pomalidomid	Revenue p.a. >50 million €	25 months	Considerable	A: Considerable B: No added benefit
Ramucirumab	Loss of OD-status (EMA)	13 months	Minor	A: Minor B: No added benefit
Ruxolitinib	Revenue p.a. >50 million €	21 months	Minor	Considerable

Figure 1. Trend of Extend of Added Benefit After Transition from Orphan Drug to Full Assessment



- Figure 1 displays the highest extent of added benefit, which was achieved in at least one subpopulation for each drug.
- The reassessment of two drugs (Ibrutinib and Ruxolitinib) led to an increase in the added benefit in at least one subpopulation compared to OD-evaluation (Figure 1).
- Two drugs (Pomalidomid and Ramucirumab) could retain the extent of added benefit in at least one subpopulation after full evaluation (Figure 1).
- The full assessment of one drug (Macitentan) resulted in a downgrading of the added benefit in comparison to the OD-assessment (Figure 1).

Table 2. Ibrutinib - Details on Orphan Drug and Full Assessment

Label [a]	Orphan Assessment			Full Assessment		
	Pivotal Study	Added Benefit #1	Subpopulation defined by FJC	Appropriate Comparator	Additional evidence to pivotal study	Added Benefit #2
CLL, ≥ 1 prior therapy	RCT: Ibrutinib vs. Ofatumumab	Not quantifiable	r/r CLL, suitable for chemo-therapy	Patient individual chemotherapy	Yes: RCT Ibrutinib + BR vs. Placebo + BR	No added benefit
			r/r CLL , not suitable for chemotherapy	Idelalisib or BSC	Yes, indirect comparison	Not quantifiable
Firstline CLL, 17p-deletion or TP53-mutation		Not quantifiable	-	Idelalisib or BSC	No	Not quantifiable
r/r MCL	Single arm trial	Not quantifiable	-	Patient individual therapy	Yes: RCT Ibrutinib vs. Temsirolimus	No added benefit

a: Between the first and second assessment, Ibrutinib was additionaly approved for „Waldenström's Macroglobulinaemia" which was included in the full assessment. Details about this indication are not shown.

- The r/r CLL population was split into two subpopulations during full assessment (Table 2).
- In the full assessment, IQWiG and FJC accepted the pivotal trial as proxy for BSC for Patients, who are not suitable for chemotherapy (Table 2).
- In the firstline CLL Population, FJC accepted an evidence transfer from pre-treated to non-treated population based on the pivotal trial (OD-assessment and reassessment) (Table 2).
- MCL population: IQWiG proposed a major benefit for a part of the target population. FJC disagreed (considerable benefit). Temsirolimus was seen as proxy for patient individual therapy in patients with ≥3 previous treatments (Table 2).

Table 3. Macicentan - Details on Orphan Drug and Full Assessment

Label	Orphan Assessment			Full Assessment		
	Pivotal Study	Added Benefit #1	Subpopulation defined by FJC	Appropriate Comparator	Additional evidence to pivotal study	Added Benefit #2
Longterm treatment of pulmonary arterial hypertension	RCT: Macicentan vs. Placebo	Minor	-	Patient individual optimized therapy	No	No added benefit

- Full assessment: The appropriate comparator was not used in the pivotal study. Selection and dosing of concomitant medications was fixed, patient individual therapy was not possible (Table 3).
- FJC stated that the pharmaceutical company was not willing to perform an actively controlled trial and that remarkable differences between treatment groups are not expected (Table 3).

Table 4. Pomalidomid – Details on Orphan Drug and Full Assessment

Label	Orphan Assessment			Full Assessment		
	Pivotal Study	Added Benefit #1	Subpopulation defined by FJC	Appropriate Comparator	Additional evidence to pivotal study	Added Benefit #2
RRMM ≥2 prior therapies (incl. Lenalidomid+ Bortezomib) , progressive during last therapy	RCT: Pom+Dex (low dose) vs. Dex (high dose)	Considerable	-	Patient individual therapy	No	Dex (high dose) is patient individual therapy: considerable
						Dex (high dose) is not patient individual therapy: No added benefit

- FJC did not define any subpopulations with different appropriate comparators, but split the label into two subpopulations after benefit assessment (Table 4).
- In contrast to IQWiG, FJC accepted the comparator of the pivotal study (high dose Dex) as proxy for patient individual therapy in the full assessment (Table 4).

Table 5. Ramucirumab - Details on Orphan Drug and Full Assessment

Label [a]	Orphan Assessment			Full Assessment		
	Pivotal Study	Added Benefit #1	Subpopulation defined by FJC	Appropriate Comparator	Additional evidence to pivotal study	Added Benefit #2
Combination with paclitaxel, advanced gastric cancer or gastro- oesophageal junction ad-carcinoma progressive after platinum and fluoropyrimidine chemotherapy	RCT: Ramucirumab + Paclitaxel vs. Paclitaxel	Minor	-	Patient individual therapy → changed to physician's choice	No	Minor
Monotherapy, not suitable for combination with paclitaxel	Ramucirumab vs. BSC	Minor	-	BSC	No	No added benefit

a: Between the first and second assessment, Ramucirumab was additionaly approved for „colorectal carcinoma" and „lung cancer" which was separately assessed by FJC. Details about these indications are not shown.

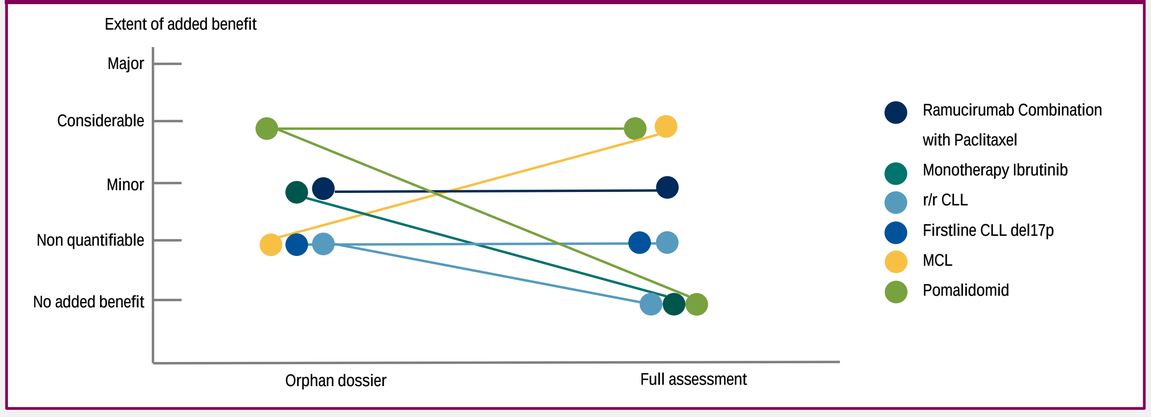
- Combination therapy: FJC changed the definition of the appropriate comparator due to experts' opinions and guidelines (Table 5).
- IQWiG assessed the dossier with regard to the former appropriate comparator → No added benefit (Table 5).
- FJC stated discrepancy between guidelines and approval status of recommended drugs and referred to a strong medical need in the indication → Paclitaxel was accepted as appropriate comparator (Table 5).

Table 6. Ruxolitinib - Details on Orphan Drug and Full Assessment

Label	Orphan Assessment			Full Assessment		
	Pivotal Study	Added Benefit #1	Subpopulation defined by FJC	Appropriate Comparator	Additional evidence to pivotal study	Added Benefit #2
Primary myelofibrosis, post polycythaemia vera myelofibrosis or post essential thrombocythaemia myelofibrosis	RCT: I. Ruxolitinib + BSC vs. Placebo + BSC II. Ruxolitinib vs. Best Available Therapy	Minor	-	BSC	No	Considerable

- Although identical evidence was base of the OD- and reassessment, the added benefit raised from minor to considerable (Table 6).
- The increase of the added benefit was based on results of the QoL instrument MFSAF v2.0 which has been validated after the OD-assessment and was subsequently accepted by FJC and IQWiG (Table 6).

Figure 2. Definition of subpopulations by FJC and resulting extent of benefit after reassessment



- Figure 2 displays all dossiers, in which FJC has defined subpopulations.
- In all dossiers the extent of benefit could be retained or improved in at least one subpopulation during reassessment (Figure 2).

CONCLUSIONS

- Following an OD assessment it is likely that FJC will split the label and define subpopulations with different appropriate comparators for the full assessment.
- FJC accepted the comparator used in the pivotal trial as appropriate in the full assessment (at least for one subpopulation) in four out of five dossiers.
- The extent of the added benefit from the OD assessment could be maintained or even increased during reevaluation (in subpopulations).
- It seems that the FJC still takes the orphan drug designation into account during full assessment. The special medical need is a strong argument in the reevaluated dossiers.

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