IMPACT OF TRIAL DESIGN ON PRICE DISCOUNTS AFTER EARLY BENEFIT ASSESSMENT (AMNOG) IN GERMANY

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BACKGROUND

- The Act on the Reform of the Market for Medical Products (AMNOG, Arzneimittelmarkt-Neuordnungsgesetz) became effective in 2011. Upon market registration, pharmaceutical companies are obliged by law to submit a benefit dossier to the Federal Joint Committee (G-BA, Gemeinsamer Bundesausschuss) in order to prove the existence of a patient-relevant medical benefit in mortality, morbidity, and health-related quality of life (HRQoL).
- Manufacturer submits and defends available evidence, usually compared to an existing appropriate comparative therapy. The acceptance of a patient-relevant medical benefit by the FJC is crucial, as only companies with proven and accepted benefit by the FJC are allowed to negotiate a premium price over existing therapies with the National Association of Statutory Health Insurance Funds (GKV-Spitzenverband).

OBJECTIVE

- The aim of this evaluation was to identify the impact on price discounts on the list price as set at market launch when supporting clinical evidence is derived from single-arm studies, which leads to only non-favorable benefit ratings as no comparative data is available.

METHODS

- A comprehensive database containing detailed information for all past assessments until August 2016 was applied.
- The official price list (Lauertaxe) was used to calculate discounts on ex-factory prices.
- Starting with a qualitative analysis of background information, descriptive statistics were employed.
- All assessments, and separately assessments with only single arm trials were analyzed with respect to:
  1. Number of assessments and completed price negotiations,
  2. Official results of the benefit assessment (major, considerable, minor, non-quantifiable or no additional benefit),
  3. Decrease in ex-factory price (prior/after negotiation),
  4. Annual treatment costs per patient.

RESULTS

1. Number of Assessments and Completed Price Negotiations

FULL ANALYSIS SET:

- Since AMNOG became effective, 161 new compounds with 430 subgroups in total went through the AMNOG process up to G-BA decision until August 2016 (including assessments with a variety of subgroups, re-assessments, new application areas etc.).
- 99 new compounds with 259 subgroups completed the AMNOG process up to a finally negotiated discount until August 2016 (Note: in total 119 assessments as 20 products were re-assessed).
- The remaining 171 assessed subgroups were still in progress (outstanding price negotiations), substances withdrawn from the market (opt-out), canceled assessments etc. **(Figure 1)**

Figure 1: Benefit assessments (until 20.08.2016)

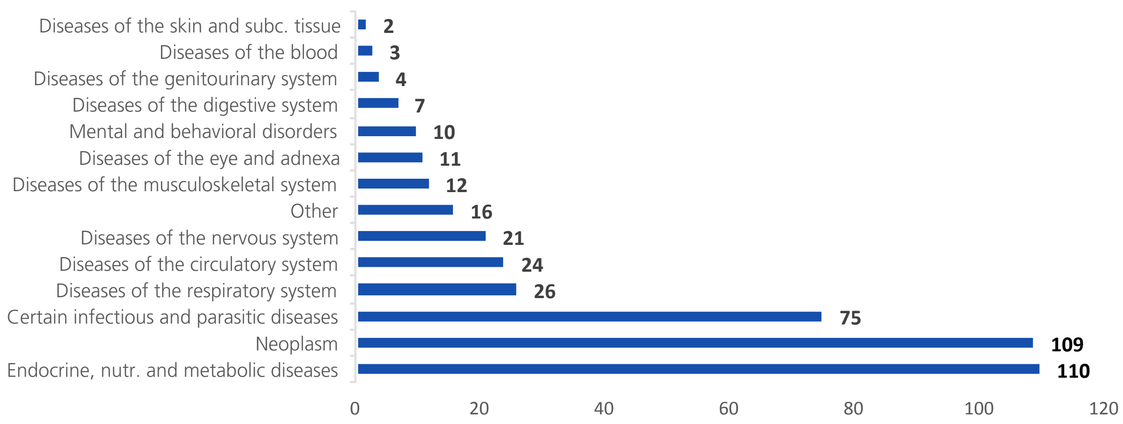
Each assessed subgroup was counted. Substances were counted once in cases of new assessments.

Finished benefit assessments (G-BA decision until 20.08.2016): N=161 substances N= 430 subgroups			
Negotiated Discounts (until 20.08.2016): N=99 substances N=259 subgroups	Discount outstanding (until 20.08.2016): N=37 substances N=75 subgroups	Opt-Out after G-BA decision (until 20.08.2016): N=26 substances N=78 subgroups	Exemptions, Fixed prices etc. (until 20.08.2016) N=18 substances N=18 subgroups

- The most frequent indication areas were metabolic diseases with 25.6% of the assessed sub-groups, 25.3% neoplasms and 17.4% infectious diseases **(Figure 2)**.

Figure 2: Subgroups and indication areas (until 20.08.2016)

Each assessed subgroup was counted.



- 14.2% of the assessed subgroups were orphan indications that fall under special regulations without a need to compare against a pre-selected comparator.

SUBGROUPS WITH EVIDENCE ONLY FROM SINGLE ARM CLINICAL TRIALS:

- In N=31 subgroups, manufacturers submitted data from single arm clinical trials, without evidence from RCT`s, meta-analyses or indirect comparisons.
- N=18 of these 31 subgroups underwent AMNOG and already finished price negotiations (for 8 different substances) **(Figure 3)**.

Figure 3: Benefit assessments in subgroups with only single arm trials (until 20.08.2016)

Each assessed subgroup was counted. Substances were counted once in cases of new assessments.

Finished benefit assessments (G-BA decision until 20.08.2016): N= 15 substances N= 31 subgroups		
Negotiated Discounts (until 20.08.2016): N=8 substances N=18 subgroups	Discount outstanding (until 20.08.2016): N=8 substances N=10 subgroups	Opt-Out after G-BA decision (until 20.08.2016): N=1 substance N=3 subgroups

- N=17 of 31 (54.9%) subgroups were in neoplasms, 9 (29.0%) in infectious diseases, 4 in metabolic diseases (12.9%) and one eye disease (3.2%) **(Figure 4)**.
- N=12 of 31 (38.7%) of these subgroups were orphan, 11 with non-quantifiable additional benefit, 1 with no additional benefit.
- N=5 of 31 (16.1%) subgroups had evidence from RCTs in another subgroup of the overall product assessment, N=26 (83,9%) had evidence from single arm trials without a RCT anywhere in the whole assessment **(Figure 5)**.
- In N=13 of 31 subgroups no HRQoL data were used, while 18 included HRQoL data
- Non-adjusted indirect comparisons were additionally included in N=14 subgroups.

2. Results of the Benefit Assessment

FULL ANALYSIS SET:

- The additional benefit rating granted by the GBA is presented in **Figure 6** (N=430).
- Over half of all assessed subgroups received a rating of "no additional benefit".

SUBGROUPS WITH EVIDENCE ONLY FROM SINGLE ARM CLINICAL TRIALS:

- 31 subgroups were included for 15 different substances and in 17 different assessments (2 re-assessments) **(Figure 7)**.

3. Decrease in ex-factory price (prior/after negotiation) (Figure 8).

- The average discount for a subgroup of the full analysis set (N=259 with final discount, without Opt-Outs) is 21.1%.
- The average final discount for those subgroups with completed price negotiations and evidence from only signle arm trials (N=18) is 16.0% (min -1.84%, max 39.65%, SD 10.96%).
- Discounts in the subgroups without HRQoL data included on average was 24.2% (SD 15.7%; N=70 subgroups) and in subgroups with HRQoL data included on average 19.1% (SD 13.1%; N=184 sub-groups)
- In subgroups with non-adjusted indirect comparisons (N=14) the average negotiated discount was 15.5% (N=9 subgroups with listed discounts).
  - Only in 4 subgroups the indirect comparison lead to a clinically relevant positive dramatic effect that might have an influence of the G-BA ruling and the final dis-count.
- Note: These 4 subgroups are from 1 assessment that consists of 7 subgroups, but no clinical data from RCT's were listed.
  - The 4 subgroups with a clinically dramatic effect in the non-adjusted indirect com-parison have a final discount of 10.1%.

Figure 4: Subgroups with only single arm trials and their indication areas (until 20.08.2016)

Each assessed subgroup was counted.

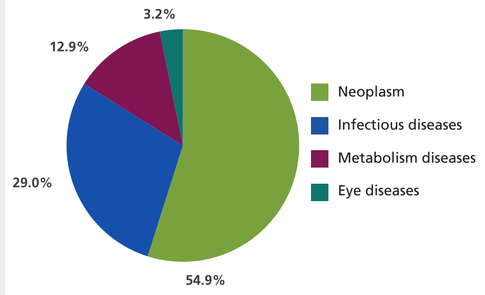


Figure 5: Subgroups with only single arm trials and assessment evidence (until 20.08.2016)

Each assessed subgroup was counted.

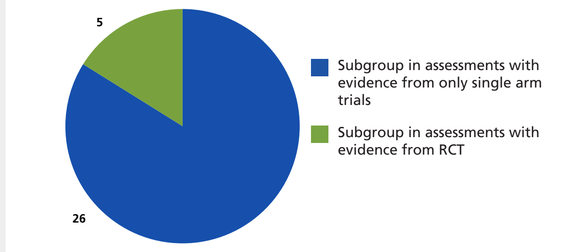


Figure 6: FJC decision on additional benefit in the assessments (N=430) (until 20.08.2016)

Each assessed subgroup was counted.

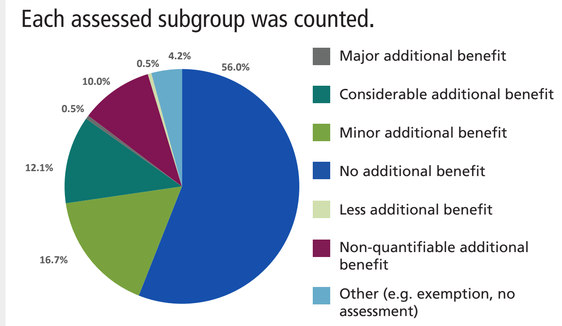


Figure 7: FJC decision on additional benefit in subgroups with only single arm trial data (N=31) (until 20.08.2016)

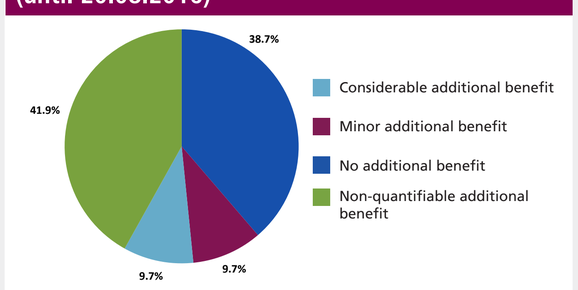
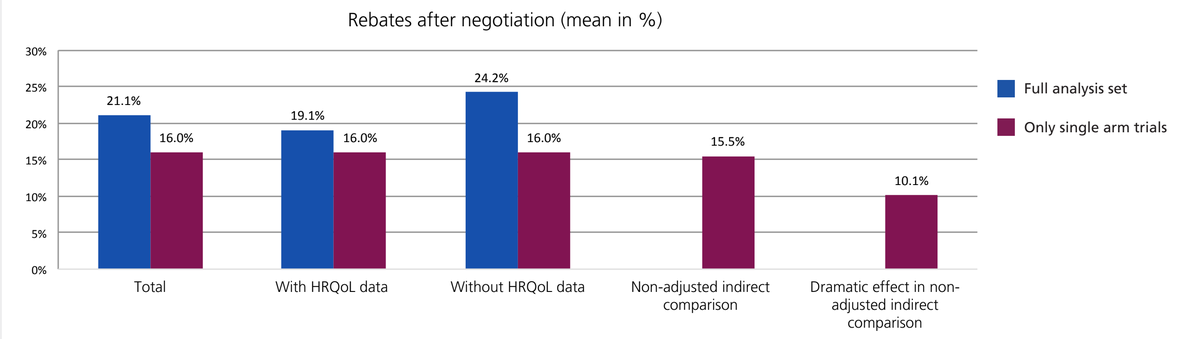


Figure 8: Average discounts of the assessed subgroups (until 20.08.2016)

Each assessed subgroup was counted.

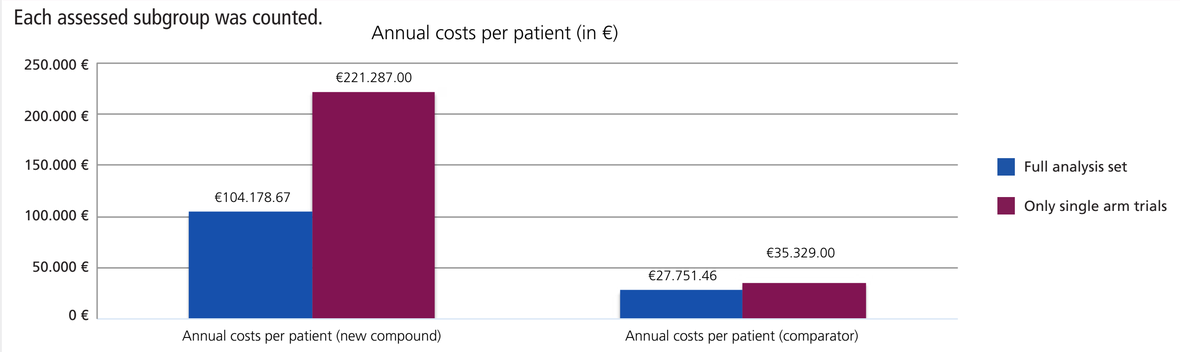


4. Annual Treatment Costs per Patient (Figure 9).

- For N=405 subgroups, annual treatment costs were reported for the new compound.
- On average annual costs came to 104.179€ (SD 401.496€; upper limit in G-BA decision) for all subgroups.
- For the comparator therapy, annual treatment costs (upper limit) on average were 27.751€ (N=327 listed annual treatment costs for the comparator therapy) (Figure 12).
- The annual treatment costs (upper limit) for the 30 subgroups with only single arm trials (1 subgroup for ceritinib was listed as individually dependent on the respective patient, hence, no value was given) were on average 221.287€ (min 648€, max 1.090.394€, SD 207.149€)
- The annual treatment costs (upper limit) of the comparator therapy on average were 35.329€ (N=14 listed annual treatment costs of the comparator)

Figure 9: Annual treatment costs per patient in assessed subgroups (until 20.08.2016)

Each assessed subgroup was counted.



CONCLUSION

- When the manufacturer can present only limited clinical evidence, e.g. only from single arm studies, it seems possible to achieve lower discounts by showing dramatic clinical effects comparing trial evidence in well-performed non-adjusted indirect comparisons. However, due to current regulation this translates as minimum into a 10-fold increase in the likelihood of relative differences in the selected patient relevant outcomes. Still, however, challenges might be encountered in the price negotiations if the perceived budgetary impact is significant.

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