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Master thesis

Market access of pharmaceuticals in Germany: Analyzing reappraisals of reimbursement decisions made by the G-BA

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Abstract

Re-evaluations of time restricted appraisals during the early-benefit assessment are an option of the G-BA products with limited evidence to request new data (DAK 2018, p. 215). Research is needed to evaluate, how the evidence, the additional benefit and the price changes in the second evaluation compared to the first early-benefit assessment.

The methods used to solve the lack of evidence are a comprehensive literature search and an analysis of two data sets. For identifying time restricted appraisals and re-evaluations, the data from the G-BA's "Tragende Gründe" were analyzed systematically. The first data set consists of all re-evaluations from 01/2011 until 12/2017. The second data set for the final analysis consists of all revaluated time restricted early benefit assessments.

The analysis of the second data set reviled an improvement of the overall quality of the clinical trials evaluated and accepted by the G-BA during the second evaluation. The benefit rating reviled different outcomes, depending on the subgroups/subpopulation. Regarding the prices, the results are not in relation with the change of the benefit rating and therefore dependent on other factors.

In conclusion, the re-valuation is an instrument for the G-BA to request new data for potentially beneficial products.

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List of abbreviations

AkdÄ	Drug Commission of the German Medical Association
ALL	Acute lymphatic leukaemia
AM	Pharmaceutical
AMNOG	Act on the Reform of the Market for Medicinal Products
AM-NutzenV	The Ordinance on the Benefit Assessment of Pharmaceuticals
ACT	Appropriate comparative therapy
AWMF	Working Group of Scientific Medical Societies
BMG	Federal Ministry of Health
BSC	Best Supportive Care
COPD	Chronic obstructive pulmonary disease
DGGÖ	German society for health economics (Deutsche Gesellschaft für Gesundheitsökonomie)
DGHO	German Society of Hematology and Medical Oncology
DKG	German hospital association
EBA	Early benefit assessment
EBM	Evidence-based medicine
EG	European Community (Europäische Gemeinschaft)
e.g.	En general
EMA	European Medicines Agency
et al.	And others
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
GKV	Statutory Health Insurance
GKV-SV	National Association of Statutory Health Insurance Funds
HAP	Ex-factory price (Herstellerabgabepreis)
HAS	Haute Autorité de Santé
HRQoL	Health-related quality of life
HTA	Health technology assessment
ibid.	In the same place
IQWiG	Institute for Quality and Efficiency in Health Care
KBV	National Association of Statutory Health Insurance Physicians
KZBV	National Association of Statutory Health Insurance Dentists

NICE	National Institute for Health and Care Excellence
NHS	National Health Services
OS	Overall survival
PFS	Progression-free survival
PZN	Pharmaceutical registration number
RCT	Randomized controlled trial
SGB V	Social code book number five
UE	Adverse events
VerfO	Rules of procedure
WHO	World Health Organization

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1 Introduction

Pharmaceuticals are an important base for treating patients in the German health care system. First, pharmaceuticals are a non-invasive method to have a (causal) effect on people's wellbeing and recovery. Second, pharmaceuticals in Germany are safe to use and third easy to distribute and sell (Häussler 2017, p. 50).

In general, health care decisions are made with multiple players. The German health care system is unique in Europe. The basis is a multi-player system consisting of statutory health insurances (SHI) and private health insurances. The SHIs have a higher body, the Federal Joint Committee, who makes all important decisions regarding reimbursement and services. The most medical services are equally reimbursed by the different SHIs but some SHI provide additional services. German citizens with a certain income, self-employed people and students can decide to "opt-out" into a private insurance. The fee payed for the SHI is a set percentage of the income. Employer and employee share the fee (Häussler 2017, p. 55).

The raising expenditures of pharmaceuticals for the Statutory Health Insurance Funds (SHI) until 2010 were due to the raising costs for new launched pharmaceuticals at that time. Those products at that time were often "me-too-preparations" with no benefit compared to the products available (Simon 2016, p.181). Figure one shows an overview about the expenditures of the SHI on pharmaceuticals in Germany from 1999 until 2017.

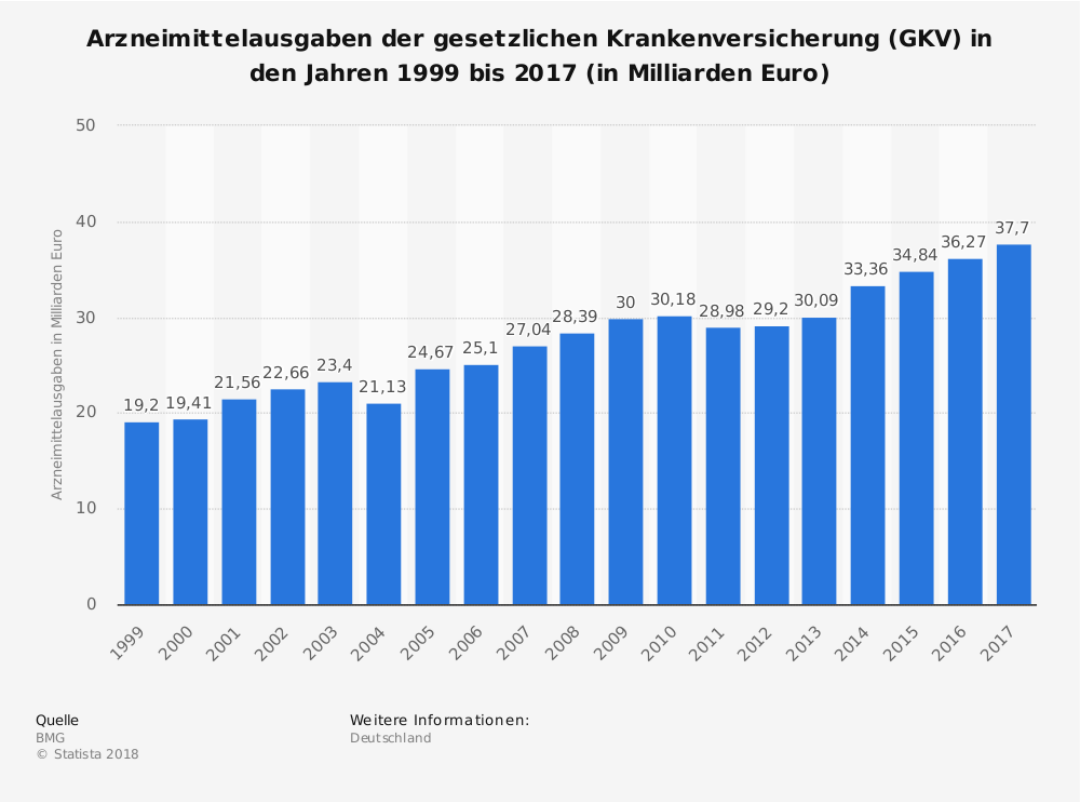

Figure 1: Expenditures of the Statutory Health Insurance for pharmaceuticals in Germany (Source: Statista 2018)

It was time to set a new system, based on valid data and evidence to help patients and to help health policy with decision making (Wegscheider et al. 2015, p. 298). Health politics and health science needed to take the common path, despite of their naturally different approaches (ibid).

In the beginning of 2011, a new law was introduced into the German Health Care system, the Act on the Reform of the Market for Medical Products (AMNOG, §35a SGB V). The aim of the law was to reduce the increasing costs for pharmaceuticals in Germany. As figure one shows, in the years 2011 and 2012, the expenditures stayed stable. AMNOG is a legally binding early-benefit assessment for every pharmaceutical, which is new launched in Germany (see chapter 5). Until 2017, the early-benefit assessment was only binding for pharmaceuticals, which were prescribed in the out-patient setting. But since 2018, even products for inpatient use only, needs to be evaluated after launch.

The evidence-based early-benefit assessment is based on scientific data. Costs or cost-effectiveness do not play a role in the decision making of the Federal Joint Committee (G-BA) (ibid. p.300).

AMNOG as a "learning system" helps with gaining new knowledge in scientific, organizational and structural health care topics. Since introduction in 2011, several legal adaptions took place and the proceeding was further adapted to the needs of the health care landscape (Skipka et al. 2015, p. 45).

Since the early-benefit assessment was introduced into the German health care systems, the number of concluded proceedings is raising constantly every year. This raising amount allows detailed analysis of special procedural provisions and problems as well as robust relations between the early-benefit assessments and care-provisions. On the other hand, the process gets more and more complex, why it is most important to keep the scientific support and evaluation of the early-benefit assessment.

The AMNOG-process allows an objective evaluation of new products, independent from the industry. It leads to more transparency and gives a fair base for the pricing afterwards (AM-Verordnungsreport 2017, p. 167). Manufacturer, who have developed an innovative product for the patients get a fair price for their product compared to existing treatment options (ibid.).

Whereas in other countries like the United Kingdom the Health Technology Agency (HTA) the National Institute for Health and Care Excellence (NICE) runs the assessment and the appraisal, the German system is different. Most often, the Institute for Quality and Efficiency in Health Care (IQWiG) conducts the assessment and the G-BA conducts the appraisal (Skipka et al. 2015, p. 44). There are two important fields, which were influenced, when AMNOG was introduced into the German health care system. On the one hand the newest and best (with additional benefit) available medicine for the patients. On the other hand, the possibility to participate in the pricing of innovative pharmaceuticals for the SHI for the first time in German history (Ärztezeitung 2015, p.6). Before 2011, the pharmaceutical companies were allowed set their prices free.

In comparison to other European countries with cost-utility analysis for reimbursement decisions like Great Britain, Germany has no maximum price limit. The concept of AMNOG is a comparator-based pricing system (Häussler 2017, p. 55).

> „The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research (Sacket, 1996)".

The results from the early-benefit assessment seem to have a direct impact on the prescriptions of the products and therefore impact on the patients. Products with no additional benefit are in average prescribed with 76.000 packages per year. Compared to that with an average of 94.000 packages per year for products with an additional benefit (AM-Verordnungsreport 2017, p. 151). That can hopefully lead to a better quality of care in the German health care system.

The first step for a new pharmaceutical after comprehensive clinical trials is to get the approval by EMA. This allows the manufacturer to sell the product in the European Union. Now, the product can be sold in Germany. For reimbursement, the early-benefit assessment is obligatory. The access to new pharmaceuticals in Germany is fast and comprehensive compared to other European countries (Busse et al. 2015). Immediate after launch, the products are available in Germany, also in long-term, independent from the results of the early-benefit assessment (Fischer et al. 2015, p. 1116).
As a result of the AMNOG-process, the derived evidence leads to a certain value and in the last step to a price (price negotiation). Therefore, the AMNOG-process is known as a value-based pricing system. In well-functioning markets, the price of a product functions as an indicator of the marginal costs of a product or the marginal added value.
For pharmaceuticals on prescription, there is no system between supply and demand to set the marginal costs. Misallocations from resources and wrong prioritization may be the consequences (Busse et al. 2015).
By approaching the topic of value-based pricing, the value itself needs to be focused on. In health care systems, how to determine a value differs a lot. It differs from country to country but also within a country. The value of medical interventions, prevention measures, psychotherapy or pharmaceuticals can be determined, by the medical benefit on the patient (Windeler, Lange 2015, p. 220). In social code book V, the medical benefit is defined as the improvement of endpoints relevant for patients, which are there operationalized in the categories mortality, morbidity and quality of life (§ 35a SGB V). Depending on the patient's situation, a different weighting of those endpoints must be done (Windeler, Lange 2015, p. 220).

Because of the fast introduction of the product after launch into the German health care market, the available evidence at the time-point of the early-benefit assessment might be limited. There is a stress ratio between patient's aiming for new treatment options and the G-BA's need for comprehensive evidence about the product and the benefit compared to existing treatment options. Therefore, the G-BA has the option to set a time-limit for the given appraisal and request new data after concluding the first early-benefit assessment (see chapter 5.1.4). The benefit ratio and negotiated price is valid until a new appraisal during the re-evaluation is published. The pharmaceutical company is able to gain new data fulfil the G-BA's request for new data. That can be either be by presenting future data cuts from ongoing clinical trials, by conducting a new trial or by analysing existing data in a new way.

In the English literature, no comprehensive wordings about those topics could be found by the author of this thesis. Therefore, when speaking of time-limited proceedings, "Zeitlich befristete Beschlüsse", are meant. And when speaking of re-evaluation or re-assessment due to expiry of the time-limit "Neubewertung nach Fristablauf" are meant.

2 Research question and objectives

The following thesis deals with the topic of re-evaluations in the early-benefit assessment of pharmaceuticals in Germany. The structure and influencing factors are not well investigated yet. There is a lack of scientific answers about pharmaceutical companies filling the gap after the first early benefit assessment being incomprehensive.
Therefore, the research question is:

To which extend has the re-evaluation after time restricted appraisals impact on the products clinical evidence, the benefit rating by G-BA and the negotiated price?

To answer the research question adequate, there are three objectives to fulfil the research question.
The general objective is to analyse the time restricted re-appraisals, that have been published from January 2011 until December 2017 and compare them to the first early-benefit assessment regarding the quality of the available data, the benefit rating and the negotiated price.

- The first objective then is to show the laws, mechanisms and concept of the early-benefit assessment in Germany in theory specializing on time-restriction of appraisals and re-evaluations
- The second objective is to present the results of analysing and comparing the time limited appraisals and the re-appraisals regarding scientific quality, additional benefit and price
- The third objective is to discuss the results in context with recent findings and themes regarding re-evaluation in early-benefit assessment

3 Materials and Methodology

In the following chapter, the methodology used to answer the research question will be explained in detail. Therefore, the used materials are presented, and the methods used for the analysis will be shown.

A scientific thesis always needs a literature review at the very beginning. The starting point of the analysis though was a systematic literature search regarding the research question. The aim of the literature search is to find out, if any other authors analysed and published data on re-evaluations of the early-benefit assessment in Germany. Furthermore, to find out if there are data available regarding time-restriction of appraisals by the G-BA. Used were the data bases "PubMed" and "Google Scholar". Regarding the languages, English and German papers are accepted by the author. The exact search terms can be found in appendix 1. The literature search on the two essential themes of this themes did not reviles any results (see Appendix 1).

The literature search reviled a lack of evidence in analysing or describing re-evaluations in the early-benefit assessment in Germany. To get a comprehensive overview about the state of the art on that topic, a google-search has been done, using the same search terms (see Appendix 1) to identify possible "grey literature[1]". The search reviled one paper by Ecker „Welche Erfahrungen gibt es mit der Befristung von Nutzenbewertungsbeschlüssen?" published 2015 at the annual meeting of the DGGÖ (Ecker and Ecker 2015).

The second part of the literature search was due to identify information material for the theoretical framework of this thesis and of the process steps at the early-benefit assessment. Legal texts as well as well as papers about the early-benefit assessment in Germany were identified. The hierarchy of the legal texts for the AMNOG-process are described further in chapter 5.1.

An intense search was conducted at the homepages at the G-BA, the IQWiG and the GKV-SV. On the IQWiG's homepage, the focus was on the method papers for defining and evaluating evidence-based medicine (see chapter 4). The paper on

1 Grey literature is literature with a background, which might not be scientific enough to be published in the key journals in that field. The information is not necessarily released by a publisher (Bortz and Döring 2006, p.360).

general methods held by the IQWiG (method paper 5.0) gives a comprehensive overview about the evaluation criteria used during the evaluation of the additional benefit.
On the GKV-SV's homepage, publications about prices and price negotiations are identified.
The focus of the hand search is on the G-BA's homepage. There, the basis for the data can be found.

As the results show, most of the legal texts and publications are written and published in German only. In this thesis, quotations cited from the SGB V chapter 5 and other regulations or legal texts are not translated in English, because the recent versions are not available in English. To prevent mistakes, the author decided not to translate the laws and rules of procedure in German by herself.

For an easier analysis, the band name and the name of the manufacturer are not included into the analysis. When speaking of the products, only the name of the substance is used.

The most important documents for the theoretical framework and the legal basis of this thesis are the AMNOG, which can be found at the Social code book number five (*https://www.bundesgesundheitsministerium.de/service/begriffe-von-az/a/arzneimittelmarktneuordnungsgesetz-amnog.html*) and the G-BA's rules of procedure (*https://www.g-ba.de/informationen/richtlinien/42/).* The information on the legal basis and the details on the process of EBA can be found in those two documents. Further important literature is the "Rahmenvereinbarung" in accordance with § 130b SGB V (*https://www.gkvspitzenverband.de/media/dokumente/krankenversicherung_1/arzneimittel/rahmenvertraege/pharmazeutische_unternehmer/Rahmenvereinbarung_130b_Abs9_SGB_V_2016.pdf),* the drug prescription report (Arzneimittelverordnungs-Report) and the pharmaceutical atlas (Arzneimittelatlas). The basis of the analysis is the information given on the homepage of the Federal Joint Committee (G-BA) (*http://www.g-ba.de/informationen/nutzenbewertung).* The documents found on this website are free-access. The information found at G-BA are always the most recent documents. The G-BA publishes twice the month all

new information and documents, which are available in context with the early benefit assessment of the product. If the proceeding for a product is still ongoing, some of the documents are online (e.g. the benefit assessment by IQWiG), even though the appraisal is not published yet. But as soon, as the EBA starts, for example the manufacturer's dossier is online available. In the case of this thesis, only concluded proceedings with published appraisals are considered.
The following documents can be found on the G-BA's homepage: The manufacturers dossier, the protocol of the commenting procedure, information on the appropriate competitive therapy (ACT), the early-benefit assessment by G-BA or IQWiG, the appraisal including the most important reasons for the decision ("Tragende Gründe") and all documents regarding any changes in the proceeding. In addition to that, possible evaluations, reports or addenda by IQWiG can be found at the G-BA's homepage.
The following things cannot be found on the G-BA's homepage: Information or protocols of beforehand consulting meetings between the manufacturer and the G-BA and all information on prices and price negotiations. That information is confidential.

For this thesis and the research question, the "Tragende Gründe" were the most important documents. There can be found a summary of the whole proceeding, a summary of the relevant trial results and a summary of the ACT. Further can be found detailed information on the additional benefit given by the G-BA and the reasons for the decision. In the case of a time-limited appraisal, the details and possible requests for further data on that are given there as well. The reason for the time-limitation and the reason for choosing the given time-limit are explained specifically.
Regarding the re-evaluation proceeding, the most important information can be found in the "Tragende Gründe" as well. In general, the same information as explained in the text above in the first proceeding can be found for the re-evaluation. Furthermore, the information on the requested scientific data or new clinical trials can be found.
In conclusion, the "Tragende Günde" were scanned carefully to identity time restricted appraisals and re-evaluated appraisals.

The next part of this chapter focuses on the prices of the products, compared at data set two. The information on prices and price negotiation can be found at the website of the National Association of Statutory Health Insurance Funds (GKV-SV) (*https://www.gkvspitzenverband.de/presse/themen/amnog verhandlungen/s them a amnog verhandlungen.jsp*).
In general, the price negotiations between GKV-SV and the manufacturer are confidential, and no protocol is published online for the public. At the GKV-SV are information regarding the process and some evaluations available. On the website of the GKV-SV can be found the following information: At first, it is possible to see if and when the price negation has ended. Second, the approximate price range for annual costs for the appropriate competitive therapy can be found.

The information on the exact prices and package sizes are available at the Lauer-Taxe® for companies or organizations with access. The prices for the products, that were used for this thesis can be found at the Lauer-Taxe® (*https://www.cgm.com/lauerfischer/loesungen lf/lauer taxe lf/webapo infosystem lf/webapo infosystem.de.jsp*). The Lauer-Taxe® is a system, in which the prices of all pharmaceuticals and medical devices in Germany are listed. It is made for health care professionals and the access is fee-based. Depending on the filters, there can be found prices and rebates for a product at an arbitrary timepoint. Furthermore, the different prices for a product depending on the package size, the different potencies of the substance and the available rebates for statutory health insurances can be found. For price identification, the Lauer-Taxe® was used. To find the right date to filter at the Lauer-Taxe®, the website of the GKV-SV was used. There, the date of the decision of the price negotiation is published. The price for the product with the highest potency and highest packaging size were used, independent from any rebate contracts with the health insurance.

For the price analysis, the ex-factory price (HAP) was taken for each product. The benefits of taking the HAP are the following: It is the net price of the product without any surcharges, discounts, rebates, taxes or other discounts (ABDA 2018). That is why it is more comparable, even between different areas of indication. To

make it even more comparable, for each product the biggest packaging size and the highest concentration of the substance was taken.
For the aim of this thesis, the prices with different dates were compared: first the prices after the negotiation after first early-benefit assessment. Second, the price after the negotiation after the second early-benefit assessment. Later, in the results, the price changes from the first to the second EBA are given in percent. The prices set free by the manufacturer during the first year after launch were not included into the analysis.

After identifying the sample, a huge overview via Microsoft Excel was done. The table included all important information on the products and the proceedings. The different and individual endpoints were put into the four categories, based on the categories used by G-BA (mortality, morbidity, adverse events (UE) and quality of life). Also included were the reasons given by the G-BA for the given additional benefit and possible changes compared to the first proceeding. Therefore, the study design was scanned precisely. In addition to that, the data source was scanned, if a new trial was conducted, if there is a new data cut or if the same data were analysed differently.
The classification of the therapeutic area of indication were used according to the information of the G-BA: Cardiovascular disorders, Infectious diseases, Metabolic disorders, Neurological disorders, Oncology, Ophthalmology, Respiratory disorders or others (G-BA 2018).

Regarding the changes of the given additional benefit from the first evaluation to the re-evaluation, a subgroup/subpopulation analysis is done. Therefore, the subgroups/subpopulations from the first- and second appraisal “Tragende Gründe” were compared, including their additional benefit ratings. Newly generated subgroups/subpopulations were marked as well. Often the subgroups/subpopulations written down by the manufacturer in the dossier and the one’s in the appraisal by the G-BA differed. In those cases, the subgroups/subpopulations from the appraisal were taken into the analysis.

An overview of the inclusion and exclusion criteria for the two conducted data sets can be found in table 1. In both data sets, included are only appraisals from the

same product being evaluated twice in the same indication. Expanses of the product in other indications (Indikationserweiterungen[2]) are not included.

Following Ruof et al., a step-wise approach was used to answer the research question (Ruof et al. 2016, p. 2). Therefore, two data sets are formed: The first data set includes every time-restricted appraisal and every re-evaluation due to any reason. The second data set is used to analyse and compare data from the second and the first early-benefit assessment. Therefore, the inclusion and exclusion criteria are stricter (see table one).

Table 1: Inclusion and exclusion criteria of datasets one and two

	Included	Excluded
First data set	• Time-restricted appraisals • Re-evaluations due to any reason • All areas of indication	• Extended areas of indication (Indikations-erweiterung)
Second data set	• All areas of indication • Re-appraisals due to expiry of the deadline set by G-BA	• Extended areas of indication (Indikations-erweiterung) • Orphan drugs (sales more than 50.000 euros per year) • Re-evaluation due to request of the pharmaceutical manufacturer • Re-evaluation due to any other reason than expiry of the deadline set by G-BA

2 „Indikationserweiterung“ means to approve the same substance in different areas of indication and is common at the moment. Especially in oncological indications, some substances have several authorizations by EMA and therefore early-benefit assessments for several indications as well.

The second data set consists only of re-evaluations due to expiry of the deadline of the first appraisal. Excluded in second data set are inter alia re-evaluations due to change of the orphan-drug state. Orphan drugs are treated different in the early-benefit assessment (see chapter 5.2.4), that's why it is difficult to compare the first and the second EBA. But orphan drugs are not excluded in general: Those orphan drugs with time-restricted appraisals and a re-evaluation are included and treated just like the other time-restricted proceedings. Further excluded are re-evaluations due to application of the pharmaceutical manufacturer.

Retroactively, two proceedings, which actual fit into the inclusion criteria were excluded: One due to the fact, that the manufacturer did not hand in a dossier during the first early-benefit assessment (Lomitapid). One more due to a change in the authorization and area of indication of the product by the European Medical Agency (EMA) (Idelalisib).

During the price analysis, Ataluren retroactively could not be analysed, because the product was withdrawn from the German market and the price is therefore not listed in the Lauer-Taxe® anymore.

To compare the quality of the evidence used in the first and the second appraisal in the second data set, the author followed a method used by Ruof et al. There are many ways to compare and measure the quality of clinical data. Therefore, is it difficult to find a system, which comprehensively gives an overview. Ruof et al., 2016 compared two different types of authorizations by the EMA. Thus, the author adapted the method to compare the qualities of the clinical trials used for the first and the second assessment.

Furthermore, the methodology to evaluate the quality of clinical data of the IQWIG were considered. But due to the limited scope of this thesis, the seven criteria mentioning underneath are considered.

The methodology is the following: Every proceeding “Tragende Gründe” and IQWiGs early-benefit assessment read carefully and then analysed regarding the following criteria:

1. If there is at least one RCT available
2. The number of trials presented in the manufacturer’s dossier (and accepted by G-BA)
3. The number of patients in the largest trial (accepted by G-BA)
4. The number of control arms in this trial
5. The usage of an active control
6. If the benefit outcome is influenced by a potential for bias
7. If a direct comparison with the appropriate comparator is available

For the second to fourth criteria, the mean was conducted, and the range was listed as well. For the fifth to seventh category, the mean was given in percent. As the criteria show, only trials accepted by the G-BA during the early-benefit assessment is analysed. In nearly every dossier handed in my manufacturer, several clinical trials are presented. But for the decision about the benefit rating, the G-BA only considers those trials with proper methodology (VerfO G-BA). If there are differences between the G-BA’s and IQWiG’s decision about including or excluding clinical trials, presented in the manufacturer’s dossier, the G-BA’s decision is considered.

4 Theoretical framework: early-benefit assessment in Germany

The following chapter starts with giving a brief overview of the German health care system and introduces the legal framework for the early-benefit assessment in Germany. Further, important stakeholders will be introduced.

The early-benefit assessment is a unique process in Germany. Other European countries and other countries wold wide, use other Health-technology-assessments (HTA's) (Angelis et al. 2018, p. 125). Even though, the European Medical Agency (EMA) approves a new product to be sold in the European Union, the decision about reimbursement by the German Statutory Health Insurances (SHI's) is made in Germany with accordance to German law.
Therefore, figure two shows the hierarchy of the different rules and laws being the basis of the proceeding in Germany.

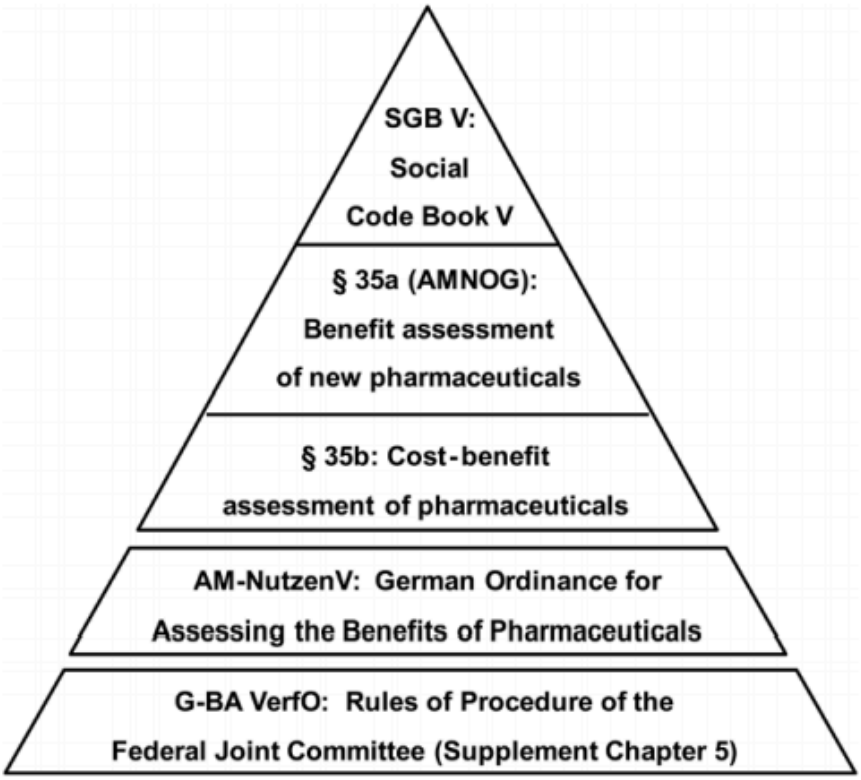

Figure 2: Hierarchy of legal texts related to early benefit (Source: Ivandic 2014, p. 3)

As figure two shows, the basis of the whole process is the SGB V.

The early-benefit assessment itself is implemented by the federal joint committee (G-BA), the central decision body in the German sickness fund system. The G-BA represents the following stakeholders in the German health care system: physicians, dentists, hospitals and SHIs.

The G-BA is the highest instance of the self-governance body of the German health care system. The legal basis for their tasks can be found in social codebook V, §91. In SGB V, the four important rules and the basis for all decisions regarding the decisions in the German health care system can be found. Due to §12 SCB V the services of the statutory health insurance have to be sufficient, practicable and economical. Furthermore, the services should not exceed what is necessary. The task of the federal joint committee now is to realize the law into practice with guidelines and regulations. The G-BA was founded in 2004 and has since then gained more and more reliability in making decisions (Pfannstiel et al. 2018, p.19). The Federal Ministery of Health (BMG), who was responsible for founding the G-BA, followed an international trend: introducing an organ responsible for evidence-based medicine (EMB) in the German health care system (Beinlich et al. 2015, p. 230).

During the early-benefit assessment, the G-BA has different tasks. After registration of a new pharmaceutical product, the G-BA has three months, whether the new product has an additional benefit compared to the competitive therapy. The basis for the decision is the dossier, handed in by the pharmaceutical company. The G-BA is also allowed to commission the IQWIG or a third party with the benefit assessment.

The G-BA can either evaluate the given information from the manufacturer's dossier itself or can commission the IQWiG with the task. In most of the cases, IQWiG is commissioned with the evaluation. They develop advices for the decision making of the G-BA regarding the additional benefit. The final decision in the appraisal is made and published by G-BA. The IQWiG publishes its own method paper (current version 5.0) with key elements on how their evaluation is done (IQWiG 2017).

The G-BA offers a fee-based consultation for the early-benefit assessment. The manufacturer can there ask for advice about planning a future clinical trial, the used endpoints, the right ACT and furthermore.

A further important stakeholder in the process is the GKV-SV. The price negotiation after finishing the early-benefit assessment by the G-BA is done between the GKV-SV and the manufacturer.

5 Early-benefit assessment in Germany

In the following chapter, the focus lies on the early-benefit assessment in Germany. In the first subchapter, the process regarding to AMNOG will be described starting with the submission of the manufacturers dossier and ending with the price negotiation.

In the second subchapter, important principles of the evaluation will be described, dealing e.g. with the appropriate competitive therapy and orphan drugs.

5.1 Act on the Reform of the Market for Medical products (AMNOG): Process

In the following chapter, the Act on the Reform of the Market for Medical products (AMNOG) will be described. Thereby topics regarding aim, history and regulations are shown. Figure three shows the separate steps of the process of early-benefit assessment.

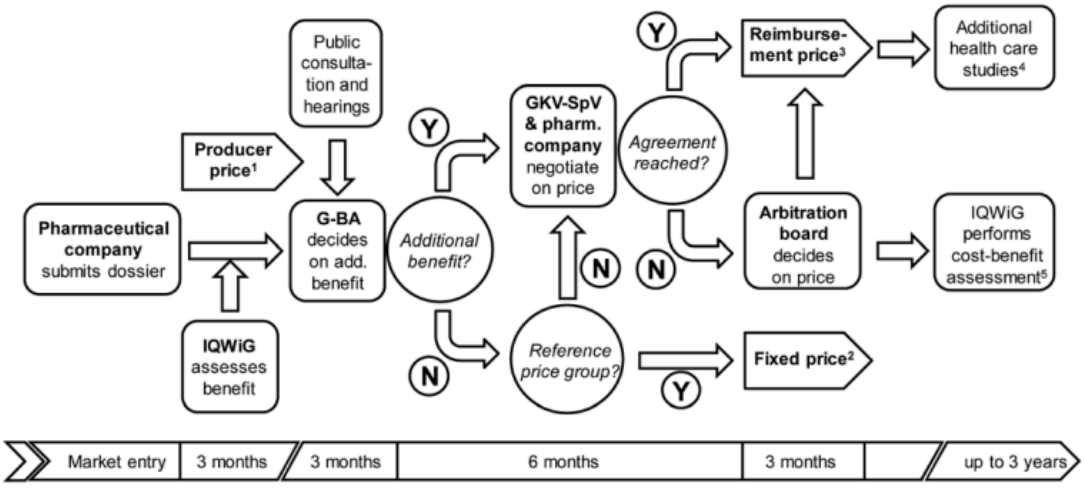

Figure 3: Early benefit assessment in Germany according to § 35a SGB V (AMNOG) (Source: Ivandic 2014, p. 2)

The Act on the Reform of the Market for Medical Products (Arzneimittelmarkt-Neuordnungsgesetz – AMNOG) of 22th December 2010 aimed to regulate prices for newly in Germany approved drugs, which are available only on prescription. Before the regulation, pharmaceutical companies were allowed to reimburse their

products for an arbitrary price for the statutory health insurance funds. In the time of 2010, the European prices for drugs were compared to Germany much lower. Thus, the first aim of the AMNOG-process was to adjust the German prices to the European prices. The AMNOG-proceeding itself is an early-benefit assessment. The product has to be authorized in the indication by the European Medical Agency (EMA) before the early-benefit assessment is conducted. The whole process starts with a dossier handed in by the pharmaceutical company to the G-BA and ends with the price negotiation with the National Association of the Statutory Health Insurance Funds (GKV-SV). The time period of the evaluation takes about twelve months.

The first question, that needs to be solved is which products need to be evaluated in the AMNOG-proceeding.
In general, every new launched product in Germany, with a new substance it is mandatory to be evaluated by the G-BA to find a reasonable price for the health care system. Evaluated must be new products as well as products from the existing market (§ 35a, section 1, SGB V). Either the substance or substance in the area of indication must be new (ibid.). It rules only for products in prescription. For generics or products with known substances, there is no early-benefit evaluation necessary After launch, those products are set in the respective reference-price-group.
Until December 2017, products used only inpatient were exempt from the evaluation. That rule changed in 2018. Since 2018, for every product with a new substance, nevertheless if it is meant for ambulant or inpatient treatment, an early-benefit assessment is mandatory (§ 4, section 3, AM-NutzenV).

5.1.1 The manufacturer's dossier

The aim of the manufacturer’s dossier is to present the available evidence for the product under evaluation. For starting the early-benefit assessment, the pharmaceutical company has to hand in a dossier for the product. The dossier is not mandatory, but if the manufacturer decides to hand it in, it has to be simultaneous with the launch in Germany (§ 35a par. 1 SGB V).

The assessment starts automatically, independent from the dossier being submitted or not. It is the manufacturers choice if and in which extend the dossier is handed in to G-BA. The G-BA has no duty to examine on its own motion (Amtsermittlungspflicht), the manufacturer has the task of presentation and proof (Dahrlegungs- und Beweislast). The failure to present the dossier means automatically no additional benefit for the product (§9 par. 3 G-BAVerfO; § 35a par. 1 SGB V).

Figure four shows the structure of a dossier handed in by the pharmaceutical manufacturer. Parts of module five may be confidential for the public.

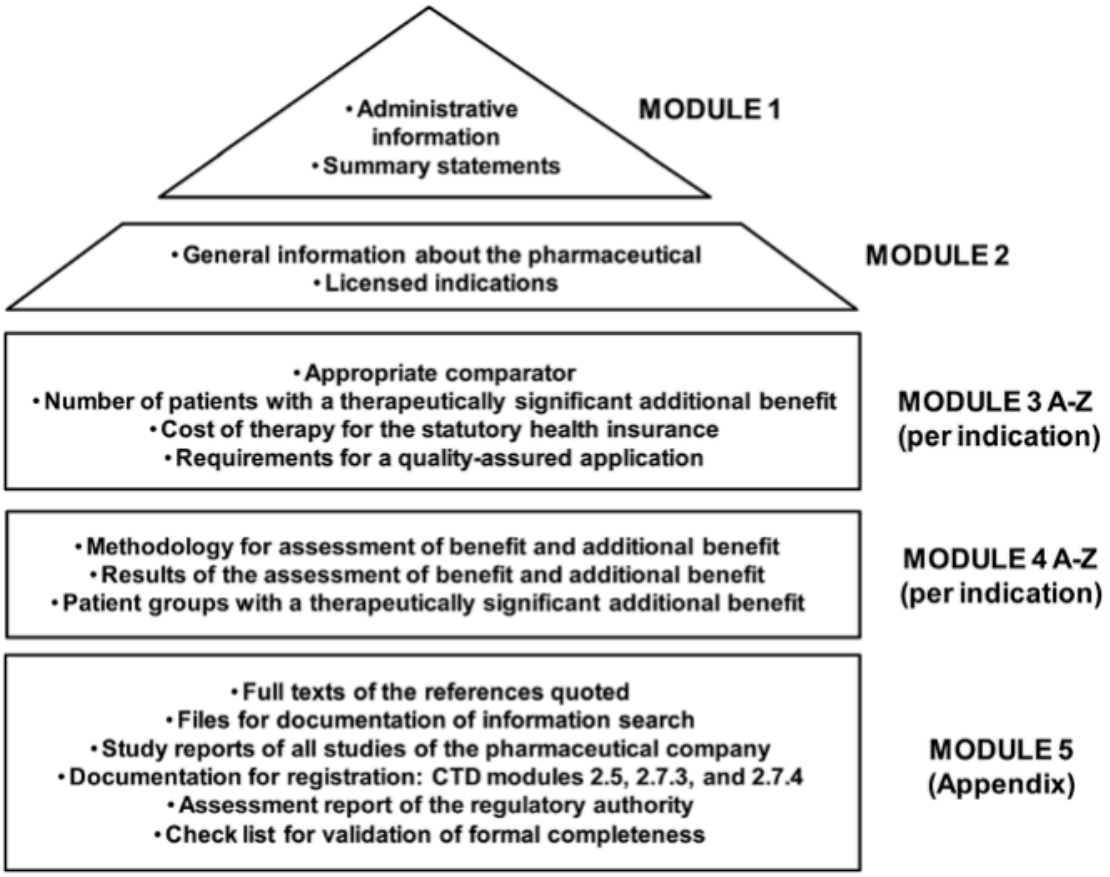

Figure 4: Structure of the dossier for early benefit assessment (Source: Ivandic 2014, p. 4)

The dossier consists of up to 20.000 pages with all information regarding the new product. The basis of the dossier are the registration studies and other available information (G-BA 2013). In addition, a systematic literature search is always required (Section 4.2.3.2 Suppl. G-BA VerfO). The purpose of the dossier is to show an additional benefit compared to the ACT. The competitive therapy can be

another drug, a medical device or other forms of treatment. In case of no other treatment option, best supportive care is taken as competitive therapy.

The dossier consists of five modules (see figure four).
In the first module information regarding administration and a summary of the key statements can be found. The orphan drug state can be found here as well.
The second module is for general information about the product itself including all authorized indications.
Module three is split into module 3 A-Z. Each authorized indication gets an own subchapter. In each of those subchapters, the authorized indication will be discribed detailed. Furthermore, the competitive therapy in this indication is specified. Further in module 3, the amount of insures from the SHI, that could be treated in the indication with the new product, must be calculated. In addition to that, all direct treatment costs for the new therapy and the competitive therapy are demonstrated. As last point in chapter 3, the quality-oriented application of the product must be described (G-BA 2013, p. 5).
Chapter four is the part of the dossier, showing the results from the clinical trials as well as epidemiological data on the area of indication. Presented are registration studies as well as all other available trials and information. The pharmaceutical company must show all results, regardless of them being good or bad. The chapter is also spit into subchapters A-Z, one for each authorized indication. For each authorized indication, the study results are shown separately. Often the results for several subgroups are shown separately to find the subgroup with the best benefit-risk ratio. The aim of chapter four in the dossier is to prove via data an additional benefit of the new product compared to the competitive ACT (ibid.).
Last chapter is chapter five. In this chapter all organization themes regarding the products' registration and the whole proceeding are shown. Here are found the trials and all other scientific sources in full text. Furthermore, tables with the description of how the used literature and sources are found. There are shown for example the search terms used for the systematic literature search the company has used (G-BA 2013, p. 6).

5.1.2 Commenting procedure

The G-BA has a given time of tree months after starting the EMA to publish the result of the benefit-assessment on their homepage. If the IQWiG was commissioned with the evaluation, the same deadline is set (35a, section 2, SGB V). After the benefit-assessment of G-BA is published online, the G-BA asks for statements. Afterwards will be an oral hearing with the G-BA and other stakeholders. It is also possible to give a written statement to the G-BA. Allowed to give a statement is the manufacturer of the product and other parties concerned. Manufacturers from similar products or in the same indication are an example. Furthermore, medical societies in the indication or a similar field can give their statements. Medical societies often give written statements (§ 19 par. 1 s. 1 G-BA VerfO). In 79% of the commenting procedures are medical societies involved (AWMF 2017, p.7). Parties from the health insurance can join the commenting procedure as well.

After the commenting procedure, the G-BA has again three months to publish the appraisal with the decision of the additional benefit. The results from the commenting procedure are considered by G-BA when evaluating the product. The decision made by the G-BA in then based on the manufacturer's dossier, the EMA by IQWiG or G-BA and the commenting procedure (§ 35a par. 3 s. 2 SGB V in connection with § 19 par. 1 p. 2 G-BA VerfO).

5.1.3 Price negotiation and pricing

When the appraisal of the early-benefit assessment by the G-BA is published, the price negotiation with the GKV-SV and the pharmaceutical manufacturer starts. The figure five shows the step in the whole process, where the price negotiation takes place (Rahmenvereinbarung due to § 130b, section 9 SGB V).

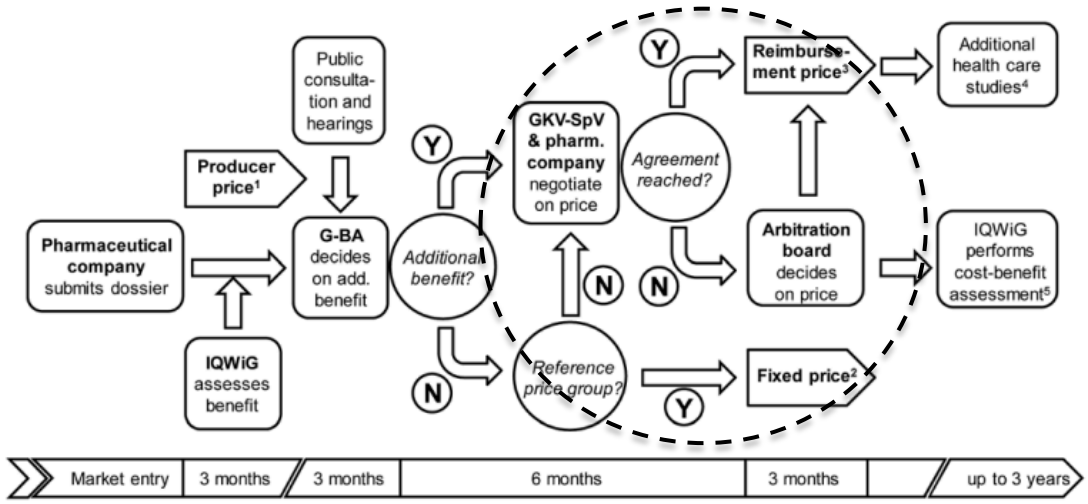

Figure 5: Early benefit assessment in Germany according to § 35a SGB V (AMNOG): Price negotiation (Source: Ivandic 2014, p. 2)

Up to four weeks after the decision of the G-BA about the additional benefit, the pharmaceutical company has the option to reject the price negotiation with the GKV-SV.

In this case, the manufacturer undertakes to exclude the product from the German market. This option is called "opt-out" (§ 4 section 7 Rahmenvereinbarung). As a consequence, there is no reimbursement price published. This option might be preferred by pharmaceutical manufacturers, because the price cannot be taken as a reference price for other European countries. A low reference price may reduce the optional price in other European countries. It is further possible to bring the product later back on the German market again, with a new pharmaceutical number (PZN) (ibid.).

In case of opt-out, a patient, who has an urgent need for the product can import the product from another country if it available there.

During the first 12 months after entering the German health care market, the pharmaceutical company can set the price for the new product free. Compared to other European countries, this process is quite unique (AWMF 2017, p.8).

In case of no additional benefit, the product is allocated to a fixed-price group (§ 35 section 1, SGB V). If the allocation to a fixed-price group is not possible, the chosen annual treatment price must not be higher than the price for the ACT chosen by G-BA (§130b SGB V). That rule is necessary to fulfil the efficiency principle (Wirtschaftlichkeitsgebot) (§ 12 SGB V) in the SHI.

The negotiation between the pharmaceutical company and the GKV-SV takes place in in Berlin in a period of six months after the G-BA publishes the appraisal. The basis of the price negotiation between the GKV-SV and the pharmaceutical company is the resolution of the G-BA and the given additional benefit.

The legal frame work for the negations can be found in §130b SGB V. The price is negotiated as a rebate on the initial list price of the manufacturer (§ 78 section 3 AMG). A high amount of rebate is not always a sign of success, because if the initial list price is set high at the beginning, the rebate is higher as well. In most cases, the price reduction is set as a duty rebate (Pflichtrabatt) for the manufacturer. This duty rebate can be split into compulsory discount (§ 130a section 1 SGB V) and benefit assessment discount (§ 130b SGB V).

In accordance with SGB V § 139b, in case of an additional, a supplement on top of the price of the ACT is negotiated. The extend of the price should be causal to the extent of the additional benefit.

Further factors influence the negotiated price: sales price in other European countries (reference prices) and price-volume agreements3 (§ 130b section 1 SGB V). Reference price and surcharge for additional benefit are valued approximately 50% each (ibid.).

The negation can take up to four rounds. If the final discount or price is arranged, the rebate is published in the Lauer-Taxe®. The negotiations themselves are confidential.

If after six months, no agreement is found, the arbitration board makes the last decision (§ 130b SGB V). The set price by the arbitration boards has a retroactive effect, from the 13th month after placing the product on the market. Thereby, delaying tactics by the manufacturer are prevented.

If the manufacturer does not agree with the price from the price negotiations or from the arbitration board, it is possible to take the product out of operation. The difference between "opt-out" and taking the product out of operation is simple: In the second case, the price is published and therefore can be taken as a reference price for the product in negotiations in other European countries. In case of "opt-

3 Price-volume agreements consist of price agreements between the GKV-SV and the pharmaceutical company. Rebates are given, if a negotiated volume of the product is prescribed within the SHI (SGB V § 139b).

out" no price at all is published, which means no reference price is set for the product (Cassel 2015, S. 36).

In most early-benefit evaluations, the evaluation of the additional benefit is split into sub groups/subpopulations (see chapter 5.2.3). The different sub groups/subpopulations might then get different additional benefits. The negotiated price will be a mixed price. It is not transparent, how the surcharges for the different additional benefits are valued and weighted within mixed prices. Those mixed prices are currently critical discussed by different stakeholders (Wasem et al. 2015, p. 5).

After the GKV-SV and the pharmaceutical manufacturer made a price agreement, the product can be prescribed to patients and reimbursed by the SHI. In general, the physician decides, which treatment option to choose for a patient, independent from the results of the EBA and the additional benefit. But the health insurances evaluate the efficiency of a product different and try to manage the physician's prescriptions, to avoid the prescription of products with no additional benefit. Due to that phenomenon, the result of the EBA affects directly the patient-care (Pfannsteil et al. 2018, p. 57).

The negotiated price is not only binding for the SHI, but also for private health insurances and out-of-pocket payers.

5.1.4 Time-limited appraisals and re-assessments

The basis of the decision made by the G-BA about the additional benefit during the early-benefit assessment is the available clinical evidence (§ 5 par. 5 s. 2 AM-NutzenV). Due to the early time-point in the life cycle of a pharmaceutical being evaluated, there might be limited evidence at the time of the early-benefit assessment. As mentioned before, the evaluation process by G-BA starts simultaneous with the launch of the product in Germany. The quote below shows the legal text of the possibility of the G-BA to ask for more evidence after a certain time.

> „Können zum Zeitpunkt der Bewertung valide Daten zu patientenrelevanten Endpunkten noch nicht vorliegen, erfolgt die Bewertung auf Grundlage der

best verfügbaren Evidenz unter Berücksichtigung der Studienqualität mit Angabe der Wahrscheinlichkeit für den Beleg eines Zusatznutzens. Sind für den Beleg eines Zusatznutzens valide Daten zu patientenrelevanten Endpunkten erforderlich, kann der Gemeinsame Bundesausschuss bei der Beschlussfassung nach § 20 eine Frist bestimmen, bis wann diese Daten vorgelegt werden sollen.“ (Source: G-BA’s rules of procedure section 5 chapter 18)

The consequence is the following: The first early-benefit assessment, starting with the launch of the product in Germany, will be finished with the a given additional benefit and a negotiated price. Just as a regular proceeding. But the negotiated price and the additional benefit expire after the time frame, predetermined by the G-BA. During that time frame, the manufacturer has to gain new evidence about the benefit and the safety of the product, compared to the ACT. Afterword’s, a second evaluation will be done, with the same steps as the first evaluation. That process will be explained later in this chapter.

There are two categories of reasons, why a product gets a time-restricted appraisal.

- The first one is due to substantive reasons regarding the available evidence.
- The second reason is the fulfilment EMA's requirements. The conditional market authorization and the impact on the appraisals of the G-BA will be discussed later I this chapter.

If substantive reasons are given to doubt the presented evidence by the manufacturer:

Table 2: Factors affecting the quality of a clinical trial (IQWiG 2018)

Study design	
	Wrong study design
	Missing blinding, randomization or control arms
	Too short study duration
	Too short follow-up
	Too many cross-over from the control into the treatment arm
	Dosage of the product under evaluation not in consensus with EMA's approval
	Wrong endpoints
	Endpoints not patient-relevant
	Non-validated instruments to measure endpoints
Study analysis	
	Final results not yet available
	Formed subgroups/subpopulations
Trial population	
	Too few participants
	Trial conduct exclusively in non-European ethnicity
	Participants with different age than the target population
	Participants with different comorbidities than the target population
	Participants with different stage of disease that the target population
	Participants with different pre-treatments than the target population
Appropriate Competitive Therapy (ACT)	
	Wrong ACT chosen
	Wrong dosage of ACT chosen
	ACT not in consent with the comorbidities or pre-treatments of the target population

In some cases, the G-BA gives in the "Tragende Gründe" explicit recommendations, how to fulfil the lack of evidence, e.g. by referring to a future

data cut of an ongoing clinical trial. In cases, where the G-BA did not give those explicit recommendations, the manufacturer has to carefully read the “Tragende Gründe” and evaluate, which lack of evidence can be fixed and how.
Generally, it needs to be distinguished, whether a set of time limitation aims to conduct a new clinical trial or to wait for results from ongoing trials. If it is necessary to gain new evidence with a newly conducted clinical trial, the G-BA often sets the deadline far more in the future.
The G-BA further has the option to extend the given period, in case of objective reasons.
Having a focus on conditional authorization by EMA: Products need to be registered by the EMA to be allowed to be sold and subscribed in Germany. But for the registration of a pharmaceutical, the safety and benefit profile of the product must be balanced. By clinical data from registration data, the balance can be proven. Bute especially for orphan drugs, it is often difficult to gain enough evidence at that time point. Thus, the benefit-safety profile, there are often not enough data in accordance with the evidence-based medicine. Therefore, there is a law from 2006 to help people with rare diseases to get as fast as possible new treatment options (art. 14 section. 7 regulation (EG) 726/2004 and art. 4 rules of proceeding (EG) Nr. 507/2006. Due to that law, the EMA is allowed to time restrict the registration for a pharmaceutical for unmet medical needs (Conditional Market Authorization[4]). The scientific results, which are needed for the registration will then be updated and checked by EMA every year (EMA 2017). If, at one time-point, the EMA sees a positive risk-benefit ratio, the product can finally be admission unlimited. In the case of a negative risk-benefit ratio, the approval will be withdrawn (ibid.). This is interesting for the analysis in this thesis, because some decisions of the G-BA to give a conditional, time-restricted appraisal, are based on EMA's decision.

The pharmaceutical manufacturer and the federal joint committee are allowed to apply for a second (or third) early-benefit assessment for a product, that was

4 A conditional market authorization due to art. 14 chapter 7 regulation (EG) 726/2004 and chapter 4 VO (EG) nr. 507/2006 products can be approved by EMA, even though there are missing data. If the benefit-risk ratio is positive and the product fulfils unmet medical needs, a conditional approval is allowed. The EMA evaluates annual the recent benefit-risk ratio. The manufacturer has to bring the required data, as far as available.

evaluated before in the same area of indication. The earliest timepoint can be one year after closing the first or last proceeding. Reasons for a second evaluation can be:

1) Application for a new EBA by G-BA due to new scientific data available for the product (§ 3 Abs. 1 nr. 4 AM-NutzenV)
2) Application for a new early-benefit assessment by manufacturer (§ 35a Abs. 5 S. 1 SGB V § 35a Abs. 5b SGB V)
3) Revaluation after expiry of the deadline (conditional authorization by G-BA or/and EMA)
4) Exceedance of 50-million-euro mark for orphan drugs (§ 35a section 1 SGB V)
5) Cancelled orphan drug-status (ibid.).

As explained in the section above, several reasons for a re-evaluation of the same product are possible.
The following quote shows the legal bases for a second evaluation of the same product.

> „Für Arzneimittel, für die bereits eine Nutzenbewertung beschlossen wurde und für das der pharmazeutische Unternehmer eine erneute Nutzenbewertung beantragt hat, innerhalb von drei Monaten nach Anforderung des Gemeinsamen Bundesausschusses, jedoch frühestens ein Jahr nach Veröffentlichung des Beschlusses gemäß § 20 Absatz 1“ (Source: G-BA’s rules of procedure section 5, chapter 8)
>
> „Für Arzneimittel, für die ein befristeter Beschluss über die Nutzenbewertung vorliegt, am Tag des Fristablaufs“ (Source: G-BA’s rules of procedure section 5, chapter 8)

Figure six shows the process of a re-evaluation. It is shown, that the same steps are made during the process, as in the first evaluation. In general, there is no different in the process between the first and the second or third appraisal. The gained data will again be evaluated by the G-BA and in some cases the IQWiG. Speaking of the number of possible re-evaluations, there is theoretically no limit. The G-BA can decide to time-limit the second appraisal as well as the first one. The price negotiation with the GKV-SV will be done again with every new

appraisal of the G-BA, independent from changes or no changes in the additional benefit. The negotiated price is than valid.

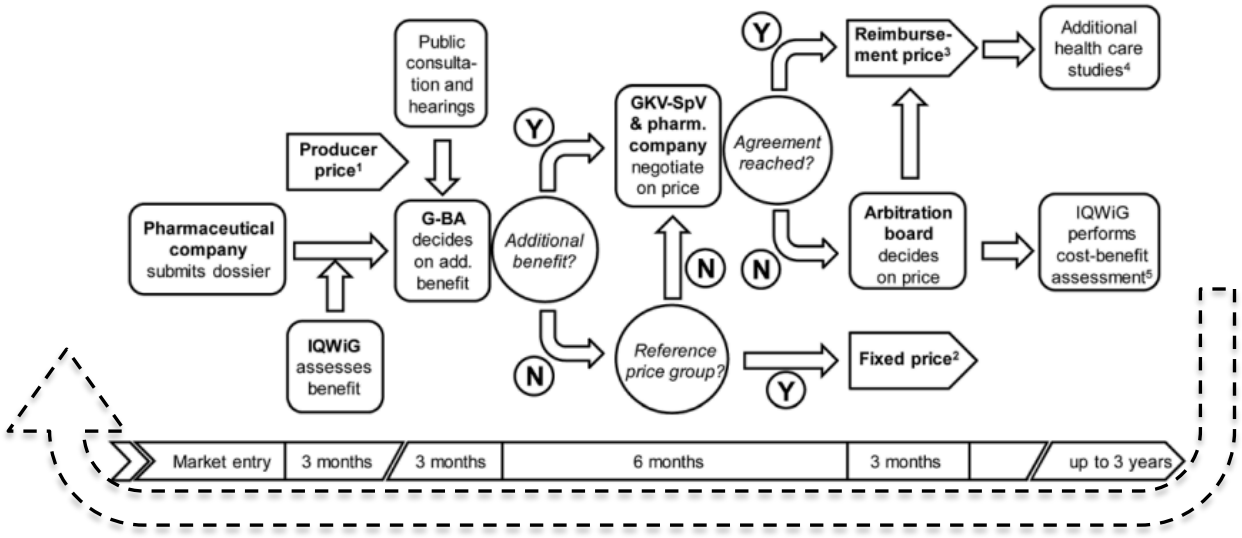

Figure 6: Re-evaluation oft he early-benefit assessment in Germany according to § 35a SGB V (AMNOG): Price negotiation (Source: Ivandic 2014, p. 2)

5.2 Act on the Reform of the Market for Medical products (AMNOG): Principles

5.2.1 Additional benefit

The additional benefit given by the G-BA is the elixir of the early-benefit assessment. Even though, the G-BA publishes a large report on the submitted evidence, the final result is the additional benefit, the conclusion of the decision, whether the product has advantages or disadvantages compared to the ACT.
The text below shows the legal definition and bases of the extend of the additional benefit.

> „Der Nutzen eines Arzneimittels ist der patientenrelevante therapeutische Effekt insbesondere hinsichtlich der Verbesserung des Gesundheitszustands, der Verkürzung der Krankheitsdauer, der Verlängerung des Überlebens, der Verringerung von Nebenwirkungen oder

einer Verbesserung der Lebensqualität. Der Zusatznutzen eines Arzneimittels ist ein Nutzen nach Absatz 1, der qualitativ oder quantitativ höher ist als der Nutzen, den die zweckmäßige Vergleichstherapie aufweist.“ (Source: G-Bas rules of procedure section 2, chapter 3)

Table three below shows differentiated the categories of the additional benefit with explanation.

Table 3: Extend and definition of additional benefit (AWMF 2017, p. 15; BMG, 2010bb, §5 (7))

Extend	Definition
Major additional benefit	Sustained and previously unequalled great improvement • Healing • Significant extension of survival • Long-term freedom of severe symptoms • Far-reached avoidance of severe side-effects
Considerable additional benefit	Previously unequaled significant improvement • Weakening of severe symptoms • Moderate extension of survival • Noticeable relief of the disease • Relevant avoidance of other side-effects • Widely avoidance of severe side-effects
Minor additional benefit	Previously unequaled moderate and not only marginal improvement • Weakening non-severe symptoms • Relevant avoidance of side-effects
Non-quantifiable additional benefit	Additional benefit extend not quantifiable
No additional benefit	No additional benefit
Less benefit	Benefit lower than the ACT

Clinical trials have different targets and therefore different endpoints. For each are of indication, different endpoints are common. For the G-BA it is always important for those endpoints to be patient-relevant.
The four patient-relevant endpoints are: mortality, morbidity, quality of life and adverse events. Every endpoint presented in the manufacturer's dossier will be sorted in one of the four categories. In the "Tragende Gründe", when the result of the early benefit assessment is published, the G-BA explicit shows the strengths and weaknesses of the product in those four categories. The factors considered for defining the extend of the additional benefit are statistical significance, clinical relevance and the severity of the disease.

Asymptomatic findings like results from blood works or radiographic progresses are not per-se patient-relevant.

- Insufficient validity of surrogate parameters (e.g. PFS)
- Insufficient patient-relevance
- Fundamental suitability of parameters for the determination of benefit
- Operationalization of endpoints
- Limitation of the study conduct (e.g. low response rate) (DAK 2017, p. 123)

The benefit rating by the G-BA can differ in the different sub-groups in the study-population.

In addition to those categories, there is another dimension in which the decision of an additional benefit is made in. The quality of evidence can be put into one of four options. proof, indication, hint and no statement (§ 5, section 4, AM-NutzenV and chapter 5 § 5 section 6 VerfO). This shows the certainty of the statement about the additional benefit. In case of no additional benefit the certainty of statement is always no statement (AWMF 2017, p. 16). Figure seven shows the requirements for deciding about the certainty of results.

	Requirement		
Conclusion	**Number of studies**	**Certainty of results**	**Effect**
Proof	≥ 2	Mostly high	In the same direction
Indication	≥ 2	Mostly moderate	In the same direction
	1	High	Statistically significant
Hint	≥ 2	Mostly low	In the same direction
	1	Moderate	Statistically significant

Figure 7: Certainty of the additional benefit (acc. to directive) (Source: Ivandic 2014, p. 7)

5.2.2 The appropriate competitive therapy (ACT)

The appropriate competitive therapy (ACT) is the therapy, against which the new product has to perform better to get an additional benefit and then probably a higher price.

The appropriate comparator is determined by the G-BA beforehand the early-benefit assessment. Therefore, there are defined criteria by law (§ 6 der AM-NutzenV, chapter 5 § 6 VerfO). In the dossier, the manufacturer presents the chosen ACT. The G-BA choses the ACT in its own opinion. Therefore, the ACT can differ between the dossier and the early-benefit assessment.

The following quote shows the legal basis of the ACT.

> „Bei der Bestimmung der zweckmäßigen Vergleichstherapie sind insbesondere folgende Kriterien zu berücksichtigen:
>
> 1. Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.
> 2. Sofern als Vergleichstherapie eine nichtmedikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der gesetzlichen Krankenversicherung erbringbar sein.
> 3. Als Vergleichstherapie sollen bevorzugt Arzneimittelanwendungen oder nichtmedikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.

4. Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.“ (Source: G-BA’s rules of procedure, section 5 chapter 6)

Priority one for choosing the right ACT has the licensed product in the indication (off-label-use[5] is not allowed). In case of a licensed product in the indication, that has to be chosen as ACT (G-BA’s rules of procedure, section 5 chapter 6).
Priority two is the standard of care. If there is no licensed product for the indication, but a commonly used and well-known treatment option, it has to be taken.
Priority three has the best evidence, in case there is no standard of care.
In case of no treatment option in Germany, best supportive care is taken as ACT. That can be palliative care as well (ibid.).

The ACT chosen by the manufacturer can differ from the comparator used in the clinical trial. In that case, the manufacturer has to justify the decision. In case that the pharmaceutical company is not sure, which ACT is right, it can be requested within a consultation with the G-BA.
The ACT can be another pharmaceutical as well as a medical device, surgical proceedings or other treatment options.
In the scenario, that there are several treatment options in the indication fitting with the criteria, the G-BA can choose to more than one ACT (§ 6 (2a) AM-NutzenV). Until now, in approximately 50% of the assessments, the G-BA recommended more than one ACT (Theidel and von der Schulenberg 2016, p.6).
In case of subgroups/subpopulations, the right ACT for every single group must be chosen separately. In some cases, there can be several ACT’s for one product being evaluated.

5 Off-lable use means the prescription of a pharmaceutical by a physician to a patient in an area of indication, for which the product has no commission from the EMA. It is possible, when there is no adequate alternative therapy for the patient (AWMF 2018, p. 4).

5.2.3 Subgroups/Subpopulations

In accordance with the rules of procedure by the G-BA, creating subgroups/subpopulations should be used to identify the extend of the additional benefit more detailed (section 4.2.5.5 Suppl. G-BA VerfO).

In the literature, two different wordings are used: subgroups and subpopulations. A subpopulation is a subset of the target population in the same area of indication. The treatment plans in those subpopulations than differ and can be analysed separately (AWMF 2018, p. 11). As mentioned in the chapter before, different subgroups/subgroups may have different ACT's and therefore different treatment effects and benefit-risk profiles.

In the following section, the possible reasons for creating subpopulations/subgroups within a clinical trial will be explained.

A typical reason for creating subpopulations, are different pre-therapies before being part of the trial for the new product. Pre-treatments can be either other medications, stem-cell-transplantation, radiotherapy or other forms of therapy. Especially for relapse therapy, the patients are often pre-treated with several medications.

Other subpopulations in a clinical trial are due to the health states of the participants. For example, for some oncology treatments, some people's health status allows a chemotherapy. Others need different treatment options. And some of the new products, like immunology therapy, can be given in combination with a chemotherapy, if possible. For not mixing the effect the new treatment, different subpopulations are formed.

A recent trend focuses on the genetical testing of trial participants. In cancer patients, genetically changes in the cancer-cells can be found, as there are allocations, additions or modifications of the chromosomes. Those genetically differences may influence the treatment response. Therefore, the trial participants are split into groups with genetically similarities (ibid.).

Furthermore, subgroups are partly populations of a clinical trial, who might differ in their effect modification[6]. Due to the law of AMNOG, the pharmaceutical manufacturer has to check their trail results for effect modifications and run

6 Effect modification is a statistical instrument. Typical effect modifications are sex, age and socioeconomic status. By integration them into the regression model, possible interactions between the factors can be identified.

separate analyses. Typical effect modifications for pharmaceutical trials are sex, age, disease severity / disease stage, centre- or country effects (AMNOG). Regarding those subpopulations/subgroups the pharmaceutical manufacturer shows separate analysis in the dossier.
The subgroups/subpopulations should fit with the real target population for the area of indication. The G-BA and/or IQWiG often forms other subgroups/subpopulations from the same data. That can be the case, if, in the G-BA's opinion, the chosen groups do not fit with the reality of care. The new generated subgroups/subpopulations than represent the target patients better (ibid.).

5.2.4 Orphan drugs

Orphan drugs are medical products for treating rare diseases. Rare diseases are defined as a disease, which affect less than 5 per 10.000 people in the European union (EG 1999). Due to the EMA, 30.000.000 people in the EU are affected by a rare disease.
For pharmaceutical companies, it is more profitable to develop products for widespread diseases than for orphan diseases. Therefore, fewer treatment options for people with rare diseases are available. This affects unmet medical needs in the European union. To promote the development of new medications for rare diseases, the European Union passed a law with the regulation 141/2000 „Orphan Medicinal Products" (EG 1999). It gives incentives for pharmaceutical companies to develop products for orphan diseases. The conditional authorization (earlier chapter, EMA 2006) is a further development of that law.
In the early-benefit assessment in Germany, a special framework for orphan drugs was integrated in accordance with the EU-laws.
Due to incentives offered by the European union, the German legislator guaranteed orphan drugs a positive additional benefit (EMA 2015). The proof of the additional benefit is the EMA-authorization of the product. Therefore, the G-BA only evaluates the extends of additional benefit. No additional benefit or less benefit must not be used for products with orphan-status.

The registration by EMA as an orphan drug is sufficient. It might be the case for orphan drugs, not to be supported by a RCT. But as analysis show, many orphan drugs can be examined in RCTs (Schulz et al. 2017, p.5).
Those regulations exist, as long as the product's value of sales at GKV expenses stays below 50 million € per 12 months and keeps the state of an orphan drug (Schwabe et al. 2017, p. 55).

6 Results

In the following chapter, the results of the analysis will be presented. Starting with some general overview about the AMNOG-proceedings in the last years. Than going on to some statistics on the conditional authorizations by G-BA. The analysis of the re-appraisals is followed, including the price analysis.

6.1 Time-restricted appraisals from 01/2011 – 12/2017

In 2017, there are 48 concluded early-benefit assessments. During the last six years, the number of AMNOG-processes per year raised constantly. In 2017, for the first time, the number dropped to the level of 2015. For 2018, a raise of proceedings is expected (AWMF 2018, p.8). In total since 2011, 277 early-benefit assessments are concluded. Figure eight shows an overview of the concluded AMNOG-proceedings from January 2011 – December 2017.

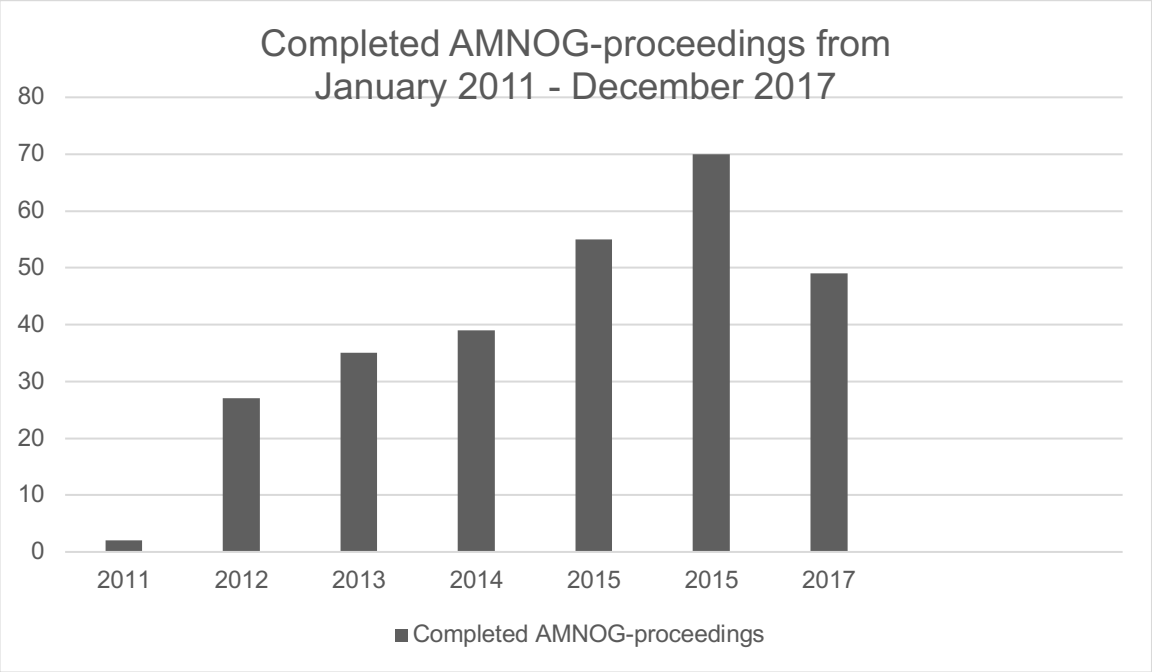

Figure 8: Completed AMNOG-proceedings from January 2011 – December 2017

Taking a closer look at 2017, there are several indications represented in the AMNOG-processes. With 28 concluded proceedings, the Oncology was obviously overrepresented.
Talking about orphan drugs, a trend can be found that shows a constantly raise of orphan drugs over time. In 2017, 29 percent of all products evaluated by the G-BA are products for orphan diseases. 50% of those orphan drugs are located in the oncological indication. The other 50% are spread widely over many other indications.
Extensions of market approvals (Indikationserweiterungen) are raising in the past years. As an example, the active substance Nivolumab has been launched for seven further indications (Pfannstiel 2018, p.61).
In all 277 concluded EBAs, 57% of the proceedings had at least one subgroup/subpopulation with an additional benefit.
Taking a closer look at orphan drugs, every fourths product in the EBA has an authorization as an orphan drug by EMA (n=46, 25%).
The range on rebates negotiated from the two parties is between 2% and 96% (AM-Versorgungsreport 2017, p. 150). For products with additional benefit, the average rebate is 23% compared to products with no additional benefit with 31% (ibid.). The medium price premiums on the ACT are 181% (DAK 2017, p. 139).

The analysis has shown, in 22 % (n=56/260) the G-BA decided to time-restrict the appraisal and thereby the given additional benefit and negotiated price. The relative number of time-restricted appraisals by G-BA is raising over time. In 2016 17% (n=12/70) are time-restricted and in 2017 29% (n=14/49). But, when taking an overview of the total amount of early-benefit assessments, there is no linear trend seen between the raise of all proceedings and the raise of time-limitations. Therefore, no trend for time-limiting the appraisals can be seen. The range for the time given by G-BA to gain new data lasts from 6 months to 7 years. This different is due to the higher effort by conducting a new trial. If proper reasons are presented, the G-BA can prolong the time-limit for gaining new data.

As the analysis showes, in approximately 60% of the time-restricted proceedings, the G-BA gave concrete recommendations, how to fill the gap of evidence. In case of concrete recommendations, the manufacturer knows how to solve the problem.

The predominant way for the manufacturer is to gain the missing evidence from future results from ongoing trials. Concrete, new data cuts or the final analysis, are expected in the “Tragende Gründe” by G-BA. As a consequence, the mean time-frame for gaining new data are in average 2.5 years for proceedings with existing, ongoing clinical trials.
Another option for gaining new data, which was used less frequent, is by conducting a new clinical trial. In those cases, the G-BA allows in average 3.5 years to gain new data.
In case of Nivolumab, an innovative option for treating inter alia melanoma, the proceeding affected all other treatments for melanoma. There are some time-restricted proceedings still going. Bute due to the promising effects of Nivolumab, the ACT for melanoma changed. The time-restriction was cancelled, and the negotiated price is valid without limitation (DAK 2018, p. 120).

If an early-benefit assessment is introduced into a healthcare market, there is always the worry of products not being available at the market afterwards. In worst case, there could be missing treatment options, a supply gap for some people. Time-limitations and re-evaluations might be a further hurdle for manufacturers in Germany. Therefore, it might be interesting to see, if time-restricted proceeings are more prone to be withdrawn from the market. Therefore, in this thesis, the number of opt-outs and market withdrawals for time-restricted products will be presented.
In total, 31 products, which have been evaluated since AMNOG in Germany have been taken from the German health care market. 13 of those are opt-outs (opt-out directly after the end of EBA) and 18 due to market withdrawals (market withdrawal after unsatisfied price-negotiation). Besides Bosutinib, Pomalidomid and Sipuleucel-T, none of them got an additional benefit by the G-BA during the first assessment. In general, the risk for the product been taken off the market, is 6-times higher with no additional benefit compared to those with additional benefit (DAK 2018, p. 131)

Products taken from the German market with time-limited appraisals (opt out and market withdrawals). For a full list of market withdrawals and opt-outs see Table 18 Appendix 3.

1. Lomitapid

Indication: familial hypercholesterolemia
First appraisal (time-limited): 05.06.2014
Second appraisal: 27.11.2015 (new area of indication)
Opt-out: 01.08.2014 (G-BA, 2014)

2. Ataluren

Indication: Duchenne muscolar dystrophy
Appraisal: 21.05.2015
Market withdrawal: 01.04.2016 (G-BA, 2016)

3. Regorafenib

Indication: Colorectal carcinoma
Appraisal: 17.03.2016
Opt-out: 15.05.2016 (G-BA, 2014a)

4. Sipuleucel-T

Indication: Prostate carcinoma
Appraisal: 19.03.2015 (G-BA, 2015)
Withdrawal of EU-market authorization

As the list above shows, time-limited appraisals or re-evaluations are not further affected by opt-outs or market withdrawals. Two of the withdrawals and opt-outs are due to approval reasons: One lost the approval by EMA and the other changed the area of indication. For the two others, there is no explicit explanation.

6.2 Re-evaluated early benefit assessments

6.2.1 Re-evaluations due to any reason (Dataset number 1)

In the following subchapter of the results, the re-evaluations in the early-benefit assessment will be described. This chapter comprehensively shows the second evaluation of the same product in the same indication due to any reason. The chapter includes re-evaluations due to time-limitations, orphan drugs with sales per year of more than 50.000 million € and because of request of the pharmaceutical manufacturer.

Re-evaluations can have different reasons, as mentioned in chapter 5.1.4. From January 2014 – December 2017, there are in total 29 second early-benefit assessments of pharmaceuticals. In the years 2011 - 2014 are no re-evaluations. In 2014, the percentage of second evaluations in the total of early-benefit assessments are 11%. The number of re-evaluations had its plateau pro rata in 2015 and 2016 with 19%. In 2017 the rate dropped to 15%.
In three cases, the revaluations resulted in an additional benefit, even though the first assessment concluded no additional benefit for the product (Ceritinib, Fingolimod, Osimertinib). Table four shows an overview of all re-evaluations until December 2017.

Table 4: Reasons for Re-evaluation (State: 12/2017)

Substance	Expiration of deadline	Orphan drug > 50 million EUR	Requested by manufacturer	Change of market-authorization
Aclidiniumbromid			x	
Afatinib	x			
Ataluren	x			
Axitinib	x			
Belatacept	x			
Blinatumomab	x			

Ceritinib				
Crizotinib				
Empagliflozin	x		x	
Eribulin	x			
Fingolimod	x			
Ibrutinib		x		
Idelalisib	x			
Lomitapid	x			
Macitentan		x		
Nivolumab	x			
Osimertinib	x			
Pomalidomid		x		
Regorafenib	x			
Retigabin				x
Ruxolitinib		x		
Saxagliptin	x			
Saxagliptin/ Metformin	x			
Secukinumab			x	
Sitagliptin	x			
Sitagliptin/ Metformin	x			
Vemurafenib	x			
Vildagliptin			x	
Vismodegib	x			
Total	20	4	4	1

Looking at the distributions of the four categories for revaluations, a trend can be seen. One revaluation was due to amendment of the authorisation of the product (Retigabin). Four re-evaluations (14%) are due to a request by the pharmaceutical manufacturer (Aclidiniumbromid, Empagliflozin, Secukinumab and Vildagliptin). Four of the re-evaluations (14%) are orphan drugs, after exceeding the 50 million turnover limit (Ibrutinib, Macitentan, Pomalidomid and Ruxolitinib). The twenty

other revaluations (69%) are due to the end of the deadline given by G-BA. The instrument of re-evaluation due to a request was used by pharmaceutical manufacturers four times until now, the payers or service providers or G-BA did not make use of this option until now.

6.2.1.1 Distribution and analysis: Areas of indication

The predominant area of indication in re-evaluated proceedings are is the oncology with 15 products. Seven products are located in the area of indication of metabolic diseases. Six of them are for treating diabetes mellitus and one for treating hypercholesterolemia (Lomitapid). In the area of indication for treating diseases in the nervous system are located two products (Retigabin and Fingolimod). The other areas of indication are represented with one product. Diseases of the musculoskeletal system with Ataluren, illnesses of the respiratory system with Aclidiniumbromid, Diseases of the genitourinary system with Belatacept, cardiovascular diseases with Macitentan and diseases of the skin with Secukinumab.

6.2.1.2 Distribution and analysis: Additional benefit

From January 2011 – December 2017, in total 80 subgroups/subpopulations in 29 proceedings are identified. Table five shows the 80 subgroups/subpopulations and the benefit rating by G-BA. The categories describe the comparison of additional benefits in the second evaluation by G-BA compared to the first evaluation. In two cases there is both a better and a worse additional benefit within the subgroups/subpopulations in the new evaluation. In those two cases, the proceeding was categorized due to the predominance of the subgroups/subpopulations. As mentioned beforehand, the subgroups/subpopulations are set by the G-BA. The groups shown in the manufacturer's dossier can differ from those chosen by the G-BA. Further can the subgroups/subpopulations set by IQWiG differ.
In the legend underneath table five, the different colourings are explained.

Table 5: Changes in subgroups/subpopulations from the first appraisal and the re-appraisal (Adapted from AWMF 2018, p. 23)

Substance	No additional benefit	Non-quantifiable additional benefit	Minor additional benefit	Considerable additional benefit
Aclidiniumbromid	xx			x
Afatinib	xxxx			x
Ataluren			x	
Axitinib	x		x	
Belatacept			x	x
Blinatumomab				x
Ceritinib	x			x
Crizotinib	x			x
Empagliflozin	xxxxx		x	xxxx
Eribulin	x			x
Fingolimod	x		x	
Ibrutinib	xx	xx		x
Idelalisib	xx	x		
Lomitapid	xx			
Macitentan	x			
Nivolumab	x			
Osimertinib	xx			x
Pomalidomid	x			x
Regorafenib	x			
Retigabin	x			
Ruxolitinib				x
Saxagliptin	xxx			
Saxagliptin/ Metformin	x		x	
Secukinumab			x	x
Sitagliptin	xxx		x	

Sitagliptin/ Metformin	**xx**		**x**	
Vemurafenib				**x**
Vildagliptin	**x**			
Vismodegib	**x**		**x**	
X= Same subgroup, same result; **x**= same subgroup, better results **X**= Same subgroup, worse result; x= new subgroup				

Looking closely at the orphan drugs, six out of those 29 re-appraisals are orphan drugs. One of them (Ataluren) had no changes in the given additional benefit in the different subgroups. Two of them (Blinatumomab and Ruxolitinib**)** got in the revaluation process at least at one subgroup/subpopulation a higher additional benefit than at the first appraisal. And finally, three of them (Ibrutinib, Mecitentan and Pomalidomid) (50%) got at least at in one subgroup/subpopulation a worse result regarding the additional benefit at the second EBA.

Whereas looking at the reason for the re-appraisal, for orphan drugs two reasons can be found. The first reason is due to sales of the product of more than 50 million euros per twelve months for orphan drugs. Four of them are due to that reason in a re-appraisal (Ruxolitinib, Ibrutinib, Mecitentan and Pomalidomid). The other two orphan drugs had a second EBA due to a time-limitation at the first appraisal given by the G-BA (Blinatumomab and Ataluren).

Table six shows the changes in additional benefit in the different subgroup.

Table 6: Changes in subgroups/subpopulations from the first appraisal and the re-appraisal (Source: AWMF 2018, p. 23)

Comparing first- and second evaluation	Subgroups/subpopulations in percent
No change (n=44)	55%
Changing the definition of the subgroup/subpopulation (n=11)	14%
Worse additional benefit (n=8)	10%
Better additional benefit (n=17)	21%
Total (n=80)	100%

In 36 out of 80 subgroups/subpopulations (45%), the result from the first and second evaluation by the G-BA differs. Differences are shown in both directions: better or worse changes in the given additional benefit. In 55% of the proceedings, the result does not differ from the rating of the first evaluation.

There is a link between the area of indication and a change in the given additional benefit. Therefore, table 7 to 9 shows the amounts of proceedings in the area of indication in relation with the change of the additional benefit. Further information about changes in the additional benefit can be found earlier in this chapter.

Table 7 Proceedings with additional benefit in the second evaluation (at least in one subgroup/subpopulation)

Respiratory disease	1
Oncological disease	6
Urogenital disease	1
Metabolic disease	1
Skin disorder	1

Table 8: Proceedings with no change in additional benefit in the second evaluation (at least in one subgroup/subpopulation)

Oncological disease	5
Metabolic disease	2
Diseases of the musculoskeletal system	1
Disease of the nervous system	2

Table 9: Proceedings with worse additional benefit in the second evaluation (at least in one subgroup/subpopulation)

Oncological disease	4
Metabolic disease	4
Cardiovascular disease	1

As the tables above have shown, two areas of indication are most of interest: The oncology and the one with metabolic diseases. The products for treating metabolic diseases (i.e. diabetes mellitus) seem to be more likely to get a worse benefit in the second evaluation.

6.2.1.3 Analysis and distribution of the endpoint mortality

Figure nine shows the frequency of the endpoint mortality. In general, it is interesting to see, which endpoints are most important for the G-BA's decision on the additional benefit. Here can be seen, if the endpoint mortality is decisive due to G-BA's "Tragende Gründe".

The analysis show, for those products with a better additional benefit at the second appraisal, a high impact of the endpoint mortality (50%). Which means, in 50% of those proceedings the G-BA made the decision and the endpoint mortality had a high impact on their decision. Next, coming to those products with no change in additional benefit, the rate drops tremendously. Only in 10% (n=1/10) of the proceedings, the endpoint mortality had a positive impact on the given additional benefit.

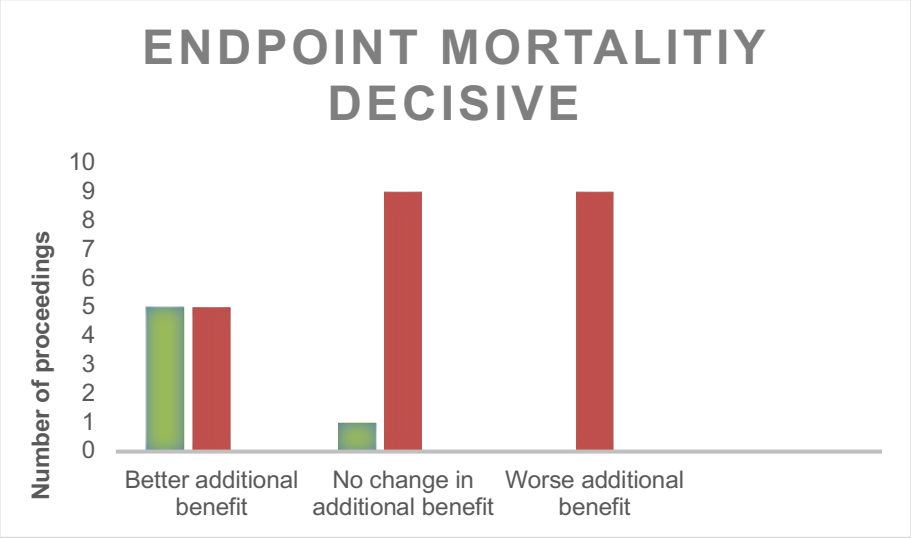

Figure 9: Decisive of endpoint mortality (green bar: endpoint mortality decisive, red bar: endpoint mortality not decisive)

Figure nine shows, if the data in the manufacturer's dossier include analysis of the outcome "mortality". For some areas of indication, the reduction of the mortality during the clinical trial, might be unnecessary (i.e. most skin disorders). During other clinical trials, the prevention of patient's death is decisive while evaluating, if the treatment is successful. As an example, for people with life-limiting, incurable kidney cancer, the survey of prolong survival rates is most important.

6.2.2 Analysis and distribution of re-evaluations due to expiry of the deadline (Dataset number 2)

In the following subchapter of the results, the focus will be on re-evaluations of a product due to the expiry of the appraisal of the first early-benefit assessment. As described clearer in the methodology in chapter three especially the for orphan drugs with a sales volume above the limit of 50 million € per years, the comparison of the first and the second early-benefit assessment is highly biased. The requirements for the evaluation of the additional benefit and of the data for orphan drugs differ tremendously. Therefore, in the following data set and analysis, orphan drugs and re-evaluations due to request of the pharmaceutical manufacturer will be excluded. In this data set, only data from re-evaluations due to expiry of the first appraisal will be considered.

In the first subchapter, the changes in the quality of the available evidence of the product, will be described and analysis further and will be compared with the first evaluation of the G-BA. The second subchapter deals with the same, but the focus here is on the comparison of the additional benefit. In the third and last subchapter of the results, the negotiated prices will be compared, thus the final result of the whole proceeding. Table ten shows gives an overview of all re-evaluations due to the expiration of the deadline from the first early-benefit assessment.

Table 10: Overview re-evaluations after expiry of the deadline

Substance	Date of second appraisal	Duration of time-restriction	New data available	Change in additional benefit
Vemurafenib	06.03.2014	1 year	New data cut	No change
Eribulin	22.01.2015	2,5 years	New data cut	Positive
Fingolimod	01.10.2015	3 years	New analysis, same study	Positive
Afatinib	05.11.2015	1 year	New data cut	Positive, negative
Belatacept	07.01.2016	3 years	New data cut	Positive
Regorafenib	17.03.2016	1.5 years	New study, new analysis same study	Negative

Vismodegib	04.08.2016	2 years	New data cut	No change
Ataluren	01.12.2016	1 year	New study	No change
Crizotinib	15.12.2016	2 years	New data cut	No change
Sitagliptin	15.12.2016	3 years	New study	No change
Saxagliptin	15.12.2016	3 years	New study	Negative
Saxagliptin/ Metformin	15.12.2016	3 years	New study	Negative
Sitagliptin/ Metformin	15.12.2016	3 years	New study	Negative
Ceritinib	16.03.2017	0.75 years	New study	Positive
Axitinib	21.09.2017	4 years	New study	No change
Osimertinib	19.10.2017	0.5 years	New study	Positive
Blinatumomab	07.12.2017	1 years	New study	Positive
Nivolumab	07.12.2017	0.5 years	New data cut/new analysis same study	Negative

6.2.2.1 Comparison and analysis: Quality of the clinical data

As presented in table ten, during every second early-benefit assessment, the manufacturer conducted new clinical data. In seven evaluations, the pharmaceutical manufacturer decided to take new data cuts from ongoing clinical trials, to present the benefit of the new product compared to the ACT.

In three cases, the manufacturer used data, that are theoretically already available during the first evaluation. But on purpose for the re-appraisal, the data held by the manufacturer, are analysed again to gain new knowledge.

In ten cases, the manufacturer decided to present data of a clinical trial, which are not mentioned or conducted during the first evaluation.

Table 11: Changes in quality of data from the first tot he second EMA

	First evaluation (n=18)	Second evaluation (n=18)
RCT available	10/18	13/18
Number of trials accepted by the G-BA, mean (Range)	0.72 (0-2)	1.1 (0-2)
Number of patients in the largest trial, mean (Range)	301 (104-860)	440 (104-860)
Number of control arms in the largest trial, mean (Range)	0.67 (0-2)	1.17 (1-2)
Use of an active control (n, %)	9 (50%)	12 (67%)
Benefit outcome influenced by potential bias	7 (39%)	4 (22%)
Direct comparison to ACT available	7 (39%)	14 (78%)

Table eleven shows the change in the quality of data accepted by the G-BA. The analysis only includes those trials, which are accepted by the G-BA for evaluating the additional benefit. In most dossiers, the manufacturer presented much more trials or indirect comparisons from other trials. An overview of the detailed analysis can be found in appendix 3.

As the results show, the quality of the overall clinical evidence was in average higher in the second early-benefit assessment compared to the first one. When looking at the chosen categories, it can be seen that the number of proceedings with an accepted RCT raised from 10 to 13 from those 18 proceedings. Furthermore, the number of patients in the biggest clinical trial raised from 301 to 440.

A further improvement of the clinical data can be seen at the usage of an active control group in the clinical trial, raising from 50% to 67%. During the first

evaluation, 50% of the manufacturers used placebo as the ACT, which is most times not accepted by the G-BA or IQWiG.
Another aspect, which has changes positively at the second evaluation is the usage of the right ACT, hence the ACT preferred by the G-BA. During the first assessment, only 39% of the accepted trials are comparing the substance under evaluation with the ACT preferred by the G-BA. Compared to that, in 78% of the second evaluation, the right ACT was chosen. In conclusion regarding the chosen categories for evaluating the development of the quality of the evidence can be said, there is better quality during the Re-evaluations.

Another aspect that can be said here are the basis for the new gained data and evidence. 12 dossiers presented new clinical trials, which are accepted by the G-BA. 7 manufacturers decided to present the new data cuts from trials, which were already available during the first evaluation. 3 dossiers presented the same data as in the first evaluation but analysed them differently.

6.2.2.2 Comparison and analysis: Additional benefit

Table twelve shows the differences in the given additional benefit of the subgroups/subpopulations by G-BA in the first appraisal compared to the result of the second appraisal. The legend below the table explains the different colourings.

Table 12: Changes in additional benefit of re-evaluations by subgroup/subpopulation

Substance	No additional benefit	Non-quantifiable additional benefit	Minor additional benefit	Considerable additional benefit	Change overall in additional benefit
Vemurafenib				x	No change
Eribulin	xx			x	Positive
Fingolimod	xx		xx		Positive
Afatinib	xxxx			x	Positive
Belatacept			x	x	Positive
Regorafenib	x				Negative
Vismodegib	x		x		No change
Ataluren			x		No change
Crizotinib	x			x	No change
Sitagliptin	xxxx		x		No change
Saxagliptin	xxxx				Negative
Saxagliptin/ Metformin	x		x		Negative
Sitagliptin/ Metformin	xx		x		Negative
Ceritinib	x			x	Positive
Axitinib	x		x		No change
Osimertinib	xx			x	Positive
Blinatumomab				x	Positive
Nivolumab	**x**				Negative
X= Same subgroup, same result; **x**= same subgroup, better results **X**= Same subgroup, worse result; x= new subgroup					

As shown in the table above, there are many changes in the additional benefit comparing the subgroups if the first and the second appraisal. Overall, seven products get a positive change during the evaluation. Noticeable often, substances for treating Diabetes mellitus get worse results in some subgroups during the second evaluation (i.e. Sitagliptin, Saxagliptin, Saxagliptin/Metformin and Sitagliptin/Metformin). Overall, five of the substances got a worse benefit rating during the second assessment.
Eight substances had no change in the evaluation of the additional benefit.

6.2.2.3 Comparison and analysis: Prices

In the following subchapter, the analysis of the prices will be done. As mentioned before, this chapter consists only of data from data set 2. Therefore, the data show only re-evaluations due to time-restrictions in the first place.
The prices can be found at the Lauer-Taxe®, as mentioned in the methods. For all products, the ex-factory price was taken (HAP) for the biggest package size with the highest concentration of the substance. Taking always the same basis, makes the data more comparable.

Table 13 shows the prices of those products, which got a better result in the second appraisal by G-BA. The table also shows the area of indication and the dates of the first and the second appraisal. In case of different changes within the subgroups, the most frequent change was taken. The initial price at launch, set free by the manufacturer was not considered in this analysis, as well as the rice of the ACT.

Table 13: Price-changes of products with better rated additional benefit in the re-evaluation compared to the first evaluation (Lauer-Taxe®)

Substance	Area of indication	Date of first appraisal	Price, HAP (date)	Date of second appraisal	Price, HAP (date)	Price change in percent
Afatinib	Onkological disease	08.05.2014	2235,50€ (15.11.2013)	05.11.2015	2276,67€ (15.06.2016)	+2%
Belatacept	Urogenital disease	05.07.2012	868,42€ (15.07.2012)	07.01.2016	955,26€ (15.07.2016)	+10%
Blinatumomab	Onkological disease	02.06.2016	2261,11€ (01.04.2017)	15.06.2017	2215,89€ (15.06.2018	-2%
Ceritinib	Onkological disease	17.12.2015	4366,44€ (01.11.2016)	16.03.2017	4977,74€ (01.10.2017)	+14%
Eribulin	Onkological disease	19.04.2012	332,58€ (01.04.2014)	22.01.2015	332,58€ (15.08.2017)	0%
Osimertinib	Onkological disease	15.09.2016	5763,70€ (16.06.2017)	19.10.2017	6900,00€ 01.11.2017	+20%
Fingolimod	Disease of the nervous system	29.03.2012	1300,32€ (01.04.2014)	01.10.2015	1400,00€ (01.11.2015)	+7%

As table 13 shows, there is no direct link between the better result during the second evaluation and a guaranteed increase of the negotiated price. The analysis shows in five proceedings price increases from 2 - 20%. Compared to that, Blinatumomab got a worse price rating after the second price negotiation, even though the rating of the benefit improved. Eribulin did not had any price change at all, even though the rating of the benefit by G-BA improved.

Table 14 shows the prices for those products with the same benefit rating at the first and the second appraisal

Table 14: Price-changes of products with the same additional benefit in the first evaluation and the re-evaluation (Lauer-Taxe®)

Substance	Area of indication	Date of first appraisal	Price, HAP (date)	Date of second appraisal	Price, HAP (date)	Price change in percent
Ataluren	Diseases of the musculoskeletal system	*21.05.2015*	Market withdrawal 01.04.2016			
Axitinib	Oncological disease	21.03.2013	2887,96€ (01.04.2014)	21.09.2017	2887,96€ 15.05.2018	0%
Crizotinib	Oncological disease	02.05.2013	4920,00€ (01.04.2014)	15.12.2016	4443,90€ (15.08.2017)	-10%
Vemurafenib	Metabolic disease	06.09.2012	1500,00€ (01.04.2014)	06.03.2014	1497,00€ (15.09.2014)	-1%
Vismodegib	Oncological disease	06.02.2016	4465,85€ (01.09.2014)	04.08.2016	4465,85€ (15.08.2017)	0%

Table 14 shows the price differences of the product after the first and after the second evaluation and price negotiation. Ataluren had to be excluded retroactively, because the product is not sold in Germany anymore. The manufacturer decided to withdraw the product from the market. Therefore, the product cannot be found at the Lauer-Taxe® anymore. It cannot be taken as a reference for other price negotiations.

As the analysis showed, two products had no price change after the second price negotiation. The other two products got both a decrease of the price. Even though, the rating of the benefit by G-BA stayed the same, the price decreased.

Table 15 shows the price changes in those products with a worse rating of the additional benefit after the second evaluation.

Table 15: Price-changes of products with worse rating of the benefit in the re-evaluation compared to the first evaluation (Lauer-Taxe®)

Substance	Area of indication	Date of first appraisal	Price (date)	Date of second appraisal	Price (date)	Price change in percent
Regorafenib	Oncological disease	20.03.2014	4538,50€ (15.01.2015)	17.03.2016	2735,61€ (01.09.2015)	-40%
Saxagliptin	Metabolic disease	01.10.2013	106,21€ (01.04.2014	15.12.2016	82,26€ (15.07.2017)	-23%
Saxagliptin/Metformin	Metabolic disease	02.05.2013	106,21€ (01.04.2014	15.12.2016	82,26€ (15.07.2017)	-23%
Sitagliptin	Metabolic disease	01.10.2013	117,60€ (01.04.2014)	15.12.2016	93,10€ (01.08.2017)	-21%
Sitagliptin/Metformin	Metabolic disease	01.10.2013	117,60€ (01.04.2014)	15.12.2016	93,10€ (01.08.2017)	-21%

Table 15 shows the prices of those proceedings with a worse benefit rating by G-BA after the second appraisal.

As the analysis shows, every product in this category decreases in the negotiated price. The range is shows decreasing from -21 to -40% compared to the first price.

As a conclusion of this chapter, the results are not always predictable in relation to the benefit rating of the G-BA.

7 Discussion

The aim of this thesis is to analyse in the first-place time-restricted appraisals. As the analysis showed, time-restrictions are an instrument for the G-BA to request further data for an innovative product to improve health care for the German population. Time-restrictions are approximately 20% of all appraisals during the last four years. There is no trend of an increasing ratio visible. The reasons for the G-BA to request further data are a conditional appraisal by EMA or other reasons for doubt of the presented evidence. The mean duration of the time-limitations are 2.5 years. In approximately 60% of the appraisals, the G-BA requested further data and specified how to fulfil the lack of evidence until the second evaluation. Often, the request of the G-BA was to show the final result of an ongoing clinical trial or to present a future planned data cut of an ongoing clinical trial. Further can be said, not all time-restricted appraisals conclude in a second early-benefit evaluation. In some cases, the G-BA decides to cancel the time-restriction and change the appraisal and the negotiated price into a regular appraisal. In other cases, the G-BA decides to prolong the time-frame for the manufacturer to gain new data.

The second data set and the final analysis consist of data comparing the re-evaluated appraisals due to the expiry of the time-limit given by G-BA. Those proceedings are analysed regarding changes in quality of evidence, changes in the benefit-rating and changes in the negotiated prices. The analysis has shown for the quality of the data accepted by G-BA an overall improvement. There are more RCTs with more trial participants and active control groups. Furthermore, the amount of proceeding using the adequate RCT improved up to 78%.

Regarding the changes of the benefit-rating, the results are various. There are better, worse and the same benefit rating. No direct trend could be found. Apart from products for treating diabetes mellitus, which are presented continues with a worse benefit rating. The analysis also reviled the different rating in the different subgroups/subpopulations.

For the manufacturer, the most interesting result is the price change from the first appraisal and the following price negotiation and the second appraisal and price negotiation. As the analysis shows, the benefit rating does not predict the outcome

of the price negotiation. In the analysis, the products with a better benefit rating at the second appraisal did not always show an improvement of the price. In one case the price even decreased. The analysis of those products with no change of the benefit rating reviled the following results: for two products, the manufacturer negotiated the same price and for two products the price decreased.
Regarding the products with a worse rating, the results of the price negotiations are all the same and decreased tremendously.

During the price analysis, several questions occurred.
In general, the price negotiation between the manufacturer and the GKV-SV is confidential. Therefore, for the author of this thesis it is not possible to analyse the whole pricing procedure.
The results differed from the expectations. There are lower prices after the second price negotiation, compared to the first negotiation, even though the benefit rating increased. One possible explanation is the widely discussed topic in the field of health sciences: mixed prices. As mentioning in chapter 5.2.3, there are different subgroups/subpopulations with different benefit ratings. The price itself, negotiated by the GKV-SV and the manufacturer combines and considers the results of every subgroups/subpopulations accepted by G-BA. Therefor one price for the product, including all subgroups/subpopulations is negotiated.
At the moment, there are many stakeholders from the pharmaceutical industry and the SHI complaining about the system of mixed prices. In case of Idelalisib, the SHI is complaining about the price set by the arbitration board. In this case, the positive benefit rating occurs only for a few patients (few subgroups/subpopulations) within the area of indication. In contrast, the high price, because of the positive benefit rating, must be paid by the SHI for every patient in that area of indication. The court decided, that mixed prices need to be more arithmetical transparent (Pharmazeutische Zeitung 2017). The judge also said, that there are doubts as to the lawfulness of the past proceedings of mixed-prices.
In conclusion, mixed prices result in difficulties to make a link between the given additional benefit and the negotiated price (Greiner 2017, p. 20).
The price discount negotiated depends on the initial price at launch set by manufacturer, the price of the ACT, the reference prices of other European countries and the rating of the additional benefit. Other research has shown further

aspects, that influence the result of the price negotiation, i.e. the soft-skills of the negotiation partners, other ongoing early-benefit assessments by the manufacturer in the same indication and many other aspects. Therefore, it is difficult for the author to find a final explanation and a comprehensive overview about the pricing system in Germany. The analysis did not show any aspect regarding the rating of the additional benefit to predict the outcome of the price negotiation. Just in case of a worse rating, the prices in the analysis always massively decreased. Greiner et al. made an analysis to compare the benefit ratings and prices of regular appraisals during the early-benefit assessment in Germany (Greiner 2017, p. 20). Greiner et al. ended up in concluding, there is no statistical significant ore predictable link between the benefit rating and the negotiated price (ibid.).

The AMNOG-proceeding itself has binding and strict rules for the manufacturer as well as for the HTA bodies G-BA and IQWiG. Compared to that, the subsequent price negotiations are still unpredictable. Negotiation tactics as well as political needs and regulations affect the prices of pharmaceuticals tremendously (Theidel and von der Schulenberg 2016, p. 1). There has been research, trying to find the factors that influence the pricing in the negotiation process. Hard facts as well as soft skills are tried to analyse. But there is more research needed to find out more about the influencing factors. Until now, the pricing system in Germany is opaque (ibid.).

A further finding of the thesis is the worse outcome during the early-benefit assessment for products treating Diabetes Mellitus (e.g. Sitagliptin, Saxagliptin). Those products got a high decrease of the price after the second evaluation by G-BA. Taking a closer look at the “Tragende Gründe”, the G-BA requests long-term data for cardiovascular security of the products. The four affected products in this analysis are all from the same manufacturer. For the author, it is not possible to find an explanation, why the manufacturer is not able to present the requested data for the second evaluation. Maybe, the results were not positive and that is why the manufacturer did not show an analysis.

The results showed the analysis of time-restricted in the first hand and re-evaluated appraisals in the second hand. Therefore, results of this analysis should be interpreted as a trend and starting point for further research.

The results, which are described above solve some question regarding the evolution of the additional benefit, the quality of the clinical trials and the

negotiated price. But taking a close look at the topic, some question still remain unclear.

Until now, it is not clear what happens, after expiration of the deadline, if the pharmaceutical company is not able to deliver the missing data. The legal basis for that scenario is not available yet. If there is an adequate explanation by the manufacturer, the G-BA is allowed to extend the deadline for gaining new data. But it is not clear yet, which explanation adequate is. Further options for sanctioning are not available as well. The G-BA has no legal basis or guidance paper, which makes those cases clear (DAK 2017, p.69). Even though, the case has not been there yet, the early-benefit assessment in Germany is a quite restrictive proceeding and some manufacturers may therefore decide not to start the process in Germany or to opt-out after an unsatisfying result of the proceeding. But until now, as the results show, no trend towards that can be seen.

Due to Ruof et al., the practice of issuing time-restricted appraisals and requesting additional data has a clear legal basis and is not questioned per se, key shortcomings in the current G-BA approach such as a lack of rationale for time-restricted appraisals, a lack of methodological guidance from the G-BA and a lack of flexibility and pragmatism within the G-BA (Ruof et al. 2016, p.8).

Due to that authors, the reasons for issuing time-limited appraisals are not transparent. Due to that, an analysis of G-BA appraisals concerning products with conditional approval by EMA showed that clear reasons for issuing time-restricted or regular appraisals are not always reported in the documentation of the assessment procedure. Data asked for by the G-BA are issued without any methodological framework to help the manufacturer in aiming acceptable data (ibid.).

Other European HTA bodies also provide guidance regarding their preferred methodology. The French authority, the Haute Autorité de Santé, can request additional data, which may require new studies, during its assessment procedure. In order to make sure the agency’s requirements are met, a guidance document regarding general methodological considerations has been published, and the study protocol has to be submitted for evaluation prior to the start of the study (HAS 2011).

The re-assessment of the additional benefit after the expiry of the first appraisal for Vemurafenib illustrates the consequences of the absence of such guidance or method paper by the G-BA. During the first evaluation, the G-BA had suggested a comparison of dacarbazine vs. vemurafenib to evaluate the differences in overall survival (OS). Although this was provided by the manufacturer during the second evaluation, the G-BA decided that it was no better evidence due to methodological reasons and the first given additional benefit was not changed (ibid.).
According to Ruof et al., a less restrictive approach explicitly accepting non-RCT data is used by the NICE in the United Kingdom. NICE's requests modelling data by the manufacturer in case of a lack of evidence. Modelling is a great way, to evaluate data, which are itself not the best quality and do not fulfil the standards e.g. surrogate outcomes, a short study duration or a study population that is not representative of patients within the NHS (Ruof et al. 2016, p. 9).
The aim of NICE in those cases to get the best information, even on limited data results. Compared to NICE, the G-BA most times does not accept data from lower quality and therefore does not use modelling as an instrument to fill the lack of evidence (Ruof et al. 2016, p. 10). In conclusion, the German system to evaluate twice the additional benefit of pharmaceuticals may be extended with modelling data. As far as the research of the author of this thesis goes, there are no ambitions from decision makers to change the legal basis or the process itself.

An important factor, when looking at the value and benefit of a product or procedure is the determinant time. The given medical benefit must always be seen in the current situation. Situation in different areas. Taking a look at the patient's perspective. Patient's life changes over time automatically. Life circumstances and progression of a disease differs over time and leaved its trace (Wegscheider et al. 2015, p. 304). The given benefit always has to be seen as a snapshot in context with the current state of the research, the market of innovations and the care landscape (ibid.).
Future challenges for AMNOG as a "learning system" will be further participation of patients into the process and the harmonization of European HTA-decisions (Pfannstiel 2018, p. 48).
Therefore, the topic, which is recently often discussed is the wide topic of quality of life data used for evaluating the benefit of a product (Bender et al. 2018, p. 133). In

the opinion of some authors, the quality of life should be more in focus when talking about patient-relevant treatment effects. Due to Bullinger et al., the quality of life is the overall measurement of treatment's practical effect on patients (Bullinger et al. 2015, p. 285). Many of the new therapy options, which have been developed recently, prolong patient's life and have positive effects on their morbidities. Uncurbable disease are slow downed in their progress to give the patients a few more months to live. Often those treatments provide a prolong of the overall survival but have a negative influence on the adverse effects of the product. The prolonging of the lifespan is associated with more side effects. Quality of life world be an endpoint of a clinical trial to measure this effect. There are thoughts in the scene to gain data from later assessments to measure the long-term quality of life on treatment options (Blome et al. 2017, p. 185).

Wasem, the head of the G-BA has started a discussion on quality of life data in cancer patients. In his opinion, every product in the oncological are of indication should be evaluated twice: The first time regularly and the second time at a far later time-point on quality of life findings (Wasem et al. 2018). Therefore, the second early-benefit assessment could be used to further evaluate the patient's quality of life after receiving the treatments for a longer time. Right now, it might be difficult to introduce a frequent evaluation of the patient's quality of life due to methodological issues. Generally, to measure the change in patient's quality of life is tricky. By IQWiG and G-BA only two questionnaires are valid and accepted to evaluate the quality of life. Furthermore, only few dossier show quality of life data (Dabisch et al. 2014, p. 36). Therefore, a methodological approach and guideline regarding quality of life data and their measurements must be provided by G-BA or IQWiG.

Due to Dabish et al., the general discussion about patient-relevant endpoints in the oncology is important to measure the right treatment effects (Dabisch et al. 2014, p. 35). The Drug Commission of the German Medical Association recommends in general a conditional appraisal by G-BA and a revaluation for oncological products after two to three years. The fraction "Die LINKE" asks in 2018 the German government for a statement regarding that topic. In their answer, they referred to the current law. The G-BA has the option to revaluate a product of their choice at the earliest, one year after the first EBA (Deutscher Bundestag, 2018, p. 13.). The written comment shows, in the nearer future will be no law change.

Taking a closer look at the methodology of this thesis, there are some aspects that must be discussed further:

Due limits in time and scope of this thesis, various aspects of the early-benefit assessment are not further analysed, discussed or considered either in the first, nor in the second data set. In chapter 3, the methodology and materials, an explanation can be found, why which aspects of the early-benefit assessment are included into the evaluation. In the following few sentences, the chosen method will be critical discussed.

The certainty of results regarding the additional benefit given by G-BA are descripted in the process but are not further analysed. Due to Pfannstiel et al., analysing these categories as well as the additional benefit, is not expedient (DAK 2018, p. 350).

Another aspect found in literature, was not considered during the analysis: The differences of the evaluation of the G-BA and the IQWiG. Due to Pfannstiel et al., the rating of the presented evidence and clinical trials and the given additional benefit, differs. In many cases, the IQWiG gives more critical recommendations to the G-BA about a product. Those differences are not considered in this thesis. There is research, that can be found at PubMed, that focuses only on the different ratings and decisions of the IQWiG and G-BA.

Furthermore, two similar aspects, the prevalence of the disease and the assumed number of patients affected by the treatment option in the SHI, are not evaluated. Due to the literature, there is link between those two aspects and the G-BA's result of the early-benefit assessment (Schwabe 2017, p. 345).

The next aspect of the AMNOG-process, that has not been taken into the analysis are the appearance of medical societies in the oral hearing during the evaluation. Further, the orientation of the therapy options in context with the available and published guidelines of the medical societies are omitted.

In context with that, in general the protocols of the oral hearings are omitted as well.

One last aspect from the early-benefit assessment, that was not analysed, is the question if the population in the clinical trial of the product, represents the affected population in the SHI regarding age, multimorbidity, stage of the disease, ethnicity and furthermore characteristics.

Regarding the analysis of the included data, limitations can be found as well:
One fact, that limits the results, are due to the different subgroups/subpopulations. As mentioned before, some of the prices are higher or lower as expected. The different additional benefits in the different subgroups could cause the changes in the price. The author did not weight the subgroups/subpopulations or looked at the number of patients in the subgroups/subpopulations. Maybe there could have been found an explanation. In general, can be said, mixed prices lead non-transparent price-constructs. Pfannstiel et al. mentioned in a paper, that there is no causal relation between the additional benefit and the negotiated price.
The whole pricing procedure in Germany with the differences factors as there are negotiation skills, reference prices, mixed-prices, subgroup-analysis, relations between parallel negotiations and the in-transparency of the pricing, leads to difficulty in drawing a comprehensive picture.

8 Conclusion and Limitations

Summarizing, the EBA is a system in to find the most appropriate price for innovative pharmaceuticals in Germany. The HTA system is based on the new product being compared to the ACT and results in benefit ratings. In case of uncertainties of the clinical results of the product, the G-BA has the option to set a time-limit for the given additional benefit. The given benefit rating is the base for the following price negotiation with the GKV-SV. This time-restricted appraisal than leads to a re-evaluation of the product. Other reasons for revaluation can be due to an orphan drug overriding 50 million sales per 12 months or due to an application of the manufacturer or the G-BA. The aim of this thesis is to analyse those re-evaluations towards changes in the quality of the clinical trials, the evolution in the benefit rating and the negotiated price.

In conclusion, the results reviled, the system of re-evaluation and time-restricted appraisals aims for an improvement of the rules and laws. There is still a gap of evidence, to give a comprehensive overview of that topic.
The following themes need to be further investigated by research:

1. How is the proceeding, if the manufacturer does not bring the requested data by G-BA. Until now, no legal basis for restrictions or consequences are available.
2. No data from models are incorporated or accepted by G-BA or IQWiG during the early-benefit assessment. Seeing NICE as a role model, in case of missing data, the available data are incorporated in a scientific model to gain better evidence.
3. The future evaluation of the quality of life gained by a product, might be expanded at second or third evaluation timepoints. Thereby, the patient-relevant and long-term treatment effects could be measured and evaluated.
4. The pricing of pharmaceuticals in Germany are opaque and due to mixed prices difficult to analyse and set in relation with the benefit rating. A more transparent pricing would be preferable.

The landscape of health sciences, the pharmaceutical manufacturers as well as the decision makers would benefit from having more certainty about the regulation itself and the consequences of re-evaluations.

Even thought, the methods of this thesis are chosen in accordance with recent papers in the field of health economics, the limitations of this thesis must be mentioned as well. To confirm the findings, the sample of the first data set for the analysis is a full-survey. All re-appraisals ever made in Germany are include. Due to that, no selection or recall bias can be considered. Further positive impact of the analysis' quality is the chosen price: the ex-manufacturers price. This price is free of any discounts, agreements or other regulatory fees, that influence the price. The methods used for the analysis are in accordance with recent papers from scientific research and further in accordance with IQWiG's recent method paper (version 5.0).

A limitation regarding the analysis and the evaluation of the results are the chosen categories to measure the quality of the clinical evidence in dataset number two. The categories are chosen due to the "Tragende Gründe" published by the G-BA. The IQWiG's method paper gives a much more comprehensive system to evaluate the quality of the data.

A limitation regarding the price-analysis could be, if there is parallel with the revaluation or the following price negotiation an expansion of indication for the substance. In those cases, the two parallel proceedings with the same substance but different indications, can affect the price negotiation between the GKV-SV and the manufacturer (Greiner and Witte 2018, p. 58). For the author of this thesis, those agreements cannot be considered. In addition to that, the price negotiation itself or the protocol is not available for the public. For the author, it was not transparent to reproduce the exact pricing for the products.

As mentioned in the methodology and materials (see chapter 3), the literature search did not revile any results. Only one paper by Ecker was found, dealing with the wrong focus of the topic. Thus, it is not possible for the author to compare and discuss the findings of the thesis, with the current research.

In the last sentences of this thesis, the focus is on answering the research question and considering the objectives mentioned in chapter three:

“To which extend has the re-evaluation after time restricted appraisals impact on the products clinical evidence, the benefit rating and the negotiated price?”
The general objective is to analyse the time restricted re-appraisals, that have been published from January 2011 until December 2017 and compare them to the first early benefit assessment regarding the quality of the available data, the benefit rating and the negotiated price.

- The first objective then is to show the laws, mechanisms and concept of the early-benefit assessment in Germany in theory specializing on time-restriction of appraisals and re-evaluations
- The second objective is to present the results of analysing and comparing the time limited appraisals and the re-appraisals regarding scientific quality, additional benefit and price
- The third objective is to discuss the results in context with recent findings and themes regarding re-evaluation in early benefit assessment

The author fulfils the first objective in chapter five of this thesis by giving a comprehensive overview about the recent processes and principles of the early-benefit assessment in Germany. The second objective fulfils by chapter six, by presenting the presenting the relations between the benefit rating, the quality of the clinical trials and the negotiated price during the first and the second evaluation. Chapter seven fulfils the third objective to discuss the findings and sets the relation between the results and recent topics, that are discussed in the landscape of health care supply.
To answer the research question, the findings are not comprehensive. The quality of the data generated by the manufacturer for the second evaluation, has a positive extend. Overall, by using the methods described in chapter three, in average, the quality increased. The findings of the benefit ratings, in contrast, did not show any trend. Neither did the prices, which revile no predictability.

In conclusion, the thesis showed the legal framework for re-evaluations in the German health care system. As the analysis showed, the outcome of the second evaluation differs regarding the rating of the additional benefit, the quality of the data held by manufacturer and the reimbursed. Due to opaque’s during the

proceedings, missing methodological standards and opaque pricing, it is not possible to predict the outcome of the proceeding. Many themes still remain unclear and must be evaluated in further research.

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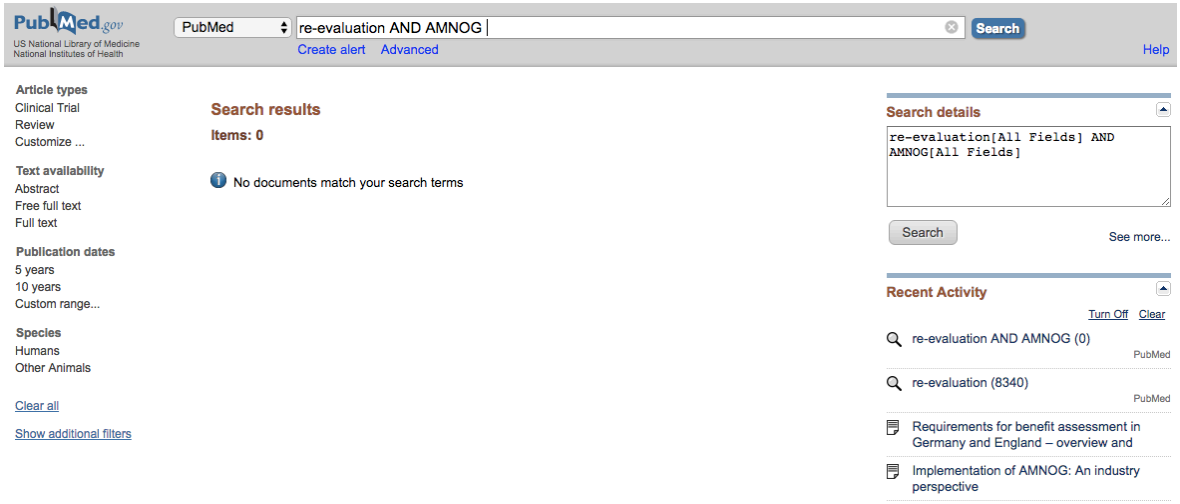
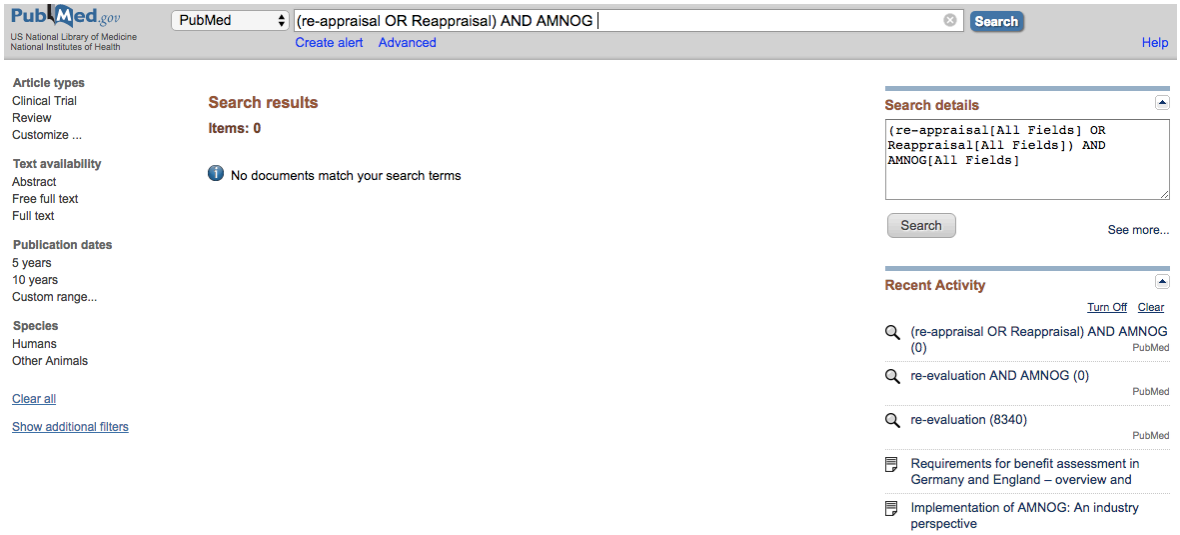
10 Appendix I: Literature search

Literature search on re-appraisals of AMNOG-proceedings

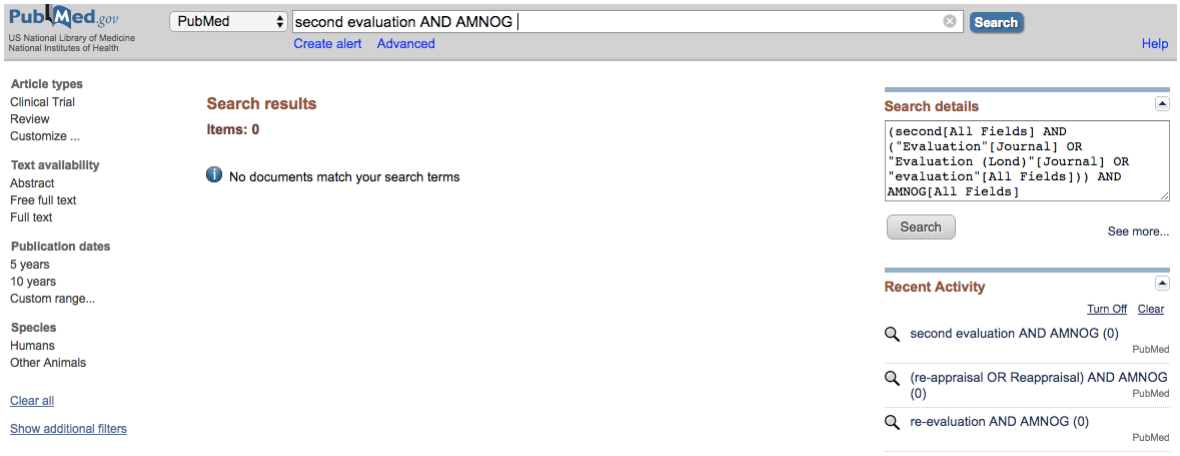
Search term: Re-evaluation AND AMNOG



(Re-appraisal OR Reappraisal) AND AMNOG



Second evaluation AND AMNOG



11 Appendix 2: Quality of data

Table 16: Quality of data at first EBA

Substance	RCT Yes/ No	Number of trials presented in manufacturer's dossier (mean ± SD)	Number of patients in largest trial (mean ± SD)	Number of control arms (mean ± SD)	Use of an active control (**n**, %)	Benefit outcome influenced by potential for bias	Direct comparison to appropriate comparator available
Vemurafenib	yes	1	675	1	yes	no	yes
Eribulin	yes	1	762	1	yes	yes	no
Fingolimod	yes	1	860	1	yes	no	no
Afatinib	yes	1	345	1	yes	no	yes
Lomitapid (EMA: conditional authorization)	No dossier submitted during the first assessment						
Belatacept	yes	2	461	1	yes	yes	yes
Regorafenib	yes	1	760	1	no	no	yes
Vismodegib	no	0	104	1	yes	yes	no
Idelalisib	Change in the area of indication between the two assessments						
Ataluren (EMA conditional authorization)	yes	1	185	2	no	yes	yes
Crizotinib (EMA	yes	1	347	1	yes	no	yes

conditional authorization)							
Sitagliptin	yes	2	303	1	yes	yes	yes
Saxagliptin	None of the trials were accepted by G-BA						
Saxagliptin/ Metformin	None of the trials were accepted by G-BA						
Sitagliptin/ Metformin	None of the trials were accepted by G-BA						
Ceritinib (EMA conditional authorization)	None of the trials were accepted by G-BA						
Axitinib	None of the trials were accepted by G-BA						
Osimertinib (EMA conditional authorization)	None of the trials were accepted by G-BA						
Blinatumomab (EMA conditional authorization)	no	1	189	0	no	yes	no
Nivolumab	yes	1	429	1	yes	yes	no

Table 17: Quality of data at re-assessment

Substance	Date of second appraisal	RCT Yes/No	Number of trials presented in manufacturer's dossier (mean ± SD)	Number of patients in largest trial (mean ± SD)	Number of control arms (mean ± SD)	Use of an active control (**n**, %)	Benefit outcome influenced by potential for bias	Direct comparison to appropriate comparator available	New data available	Change in additional benefit
Vemurafenib	06.03.2014	yes	1	675	1	yes	no	yes	New data cut	No change
Eribulin	22.01.2015	yes	2	1102	2	yes	no	yes	New data cut, new study	Positive
Fingolimod	01.10.2015	yes	3	843	3	yes	no	yes	New analysis, same study	Positive
Afatinib	05.11.2015	yes	1	345	1	yes	no	yes	New data cut	Positive, negative

Lomitapid	27.11.2015	No dossier submitted during the first assessment							Yes, dossier was analysed for the first time	No change
Belatacept	07.01.2016	ja	2	461	2	yes	no	yes	New data cut	Positive
Regorafenib	17.03.2016	ja	2	760	1	no	yes	yes	New study, new analysis same study	Negative
Vismodegib	04.08.2016	no	0	104	1	no	yes	no	New data cut	No change
Idelalisib	15.09.2016	Change in the area of indication between the two assessments							-	No change
Ataluren	01.12.2016	yes	2	230	2	no	no	yes	New study	No change
Crizotin	15.12	yes	1	347	1	yes	no	yes	New	No

ib	.2016								data cut	change
Sitagliptin	15.12.2016	yes	1	850	2	yes	yes	yes	New study	No change
Saxagliptin	15.12.2016	no	None of the trials were accepted by G-BA						New study	Negative
Saxagliptin/ Metformin	15.12.2016	no	None of the trials were accepted by G-BA						New study	Negative
Sitagliptin/ Metformin	15.12.2016	no	None of the trials were accepted by G-BA						New study	Negative
Ceritinib	16.03.2017	yes	1	228	1	yes	no	yes	New study	Positive
Axitinib	21.09.2017	yes	2	723	1	yes	no	yes	New study	No change
Osimertinib	19.10.2017	yes	1	419	1	yes	no	yes	New study	Positive
Blinatumomab	07.12.2017	no		405	1	yes	no	yes	New study	Positive
Nivolumab	07.12.2017	yes	1	429	1	yes	yes	yes	New data cut/new anal	Negative

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12 Appendix 3: Market withdrawals

Table 18: Market withdrawals of AMNOG-substances (State 12/2017)

Substance	Additional benefit	Appraisal	Status	Market withdrawal
Aliskiren/Amlodipin	No	03.05.2012	Opt-Out	01.09.2011
Linagliptin	No	29.03.2012	Opt-Out	01.01.2012
Mikrobielle Collagenase	No	19.04.2012	Opt-Out	16.05.2012
Retigabin	No	03.05.2012	Opt-Out	01.07.2012
Lixisenatid	No	05.09.2013	Market withdrawal	01.04.2014
Bromfenac	No	19.01.2012	Market withdrawal	01.05.2014
Linaclotid	No	17.10.2013	Market withdrawal	01.05.2014
Vildagliptin	No	01.10.2013	Market withdrawal	01.07.2014
Vildagliptin/ Metformin	No	01.10.2013	Market withdrawal	01.07.2014
Lomitapid	No	05.06.2014	Opt-Out	01.08.2014
Canagliflozin	No	04.09.2014	Opt-Out	15.10.2014
Canagliflozin/ Metformin	No	05.02.2015	Opt-Out	17.02.2015
Lurasidon	No	16.04.2015	Opt-Out	01.03.2015
Colestilan	No	01.10.2013	Market withdrawal	01.04.2015
Living larvae Lucilia sericata	No	20.11.2014	Market withdrawal	15.06.2015
Tafluprost/Timolol	No	18.06.2015	Opt-Out	01.08.2015
Insulin degludec	No	16.10.2014	Market withdrawal	15.01.2016
Gaxilose	No	04.02.2016	Opt-Out	01.03.2016

Ataluren	Yes	21.05.2015	Market withdrawal	01.04.2016
Regorafenib	No	17.03.2016	Opt-Out	15.05.2016
Boceprevir	Yes	01.03.2012	Market withdrawal	15.07.2016
Insulin degludec/ Liraglutid	No	15.10.2015	Market withdrawal	01.08.2016
Vortioxetin	No	15.10.2015	Market withdrawal	15.08.2016
Telaprevir	Yes	29.03.2012	Market withdrawal	01.09.2016
Ospemifen	No	20.10.2016	Opt-Out	01.01.2017
Dasabuvir	Yes	16.07.2015	Market withdrawal	01.09.2017
Ombitasvir/ Paritaprevir/ Ritonavir	Yes	16.07.2015	Market withdrawal	01.09.2017
Sipuleucel-T	Yes	19.03.2015	Cancelled EU-market authorization	

13 Declaration of Academic Integrity

Hereby, I declare that I have composed the presented paper independently on my own and without any other resources than the ones indicated. All thoughts taken directly or indirectly from external sources are properly denoted as such. This paper has neither been previously submitted to another authority nor has it been published yet.

Hamburg, 17.12.2018