




ARTICLE

Ten years of German benefit assessment: price analysis for drugs with unproven additional benefit

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(Received 26 August 2022; revised 2 May 2023; accepted 21 June 2023; first published online 14 August 2023)

Abstract

Introduction. Since 2011, the prices for all new drugs in Germany are negotiated based on a benefit assessment. The purpose of this study was to analyze the price regulation of drugs with unproven additional benefit.

Methods. Benefit assessment procedures from 2011 to 2020 were reviewed and selected through AMNOG Monitor and Lauer Taxe. Negotiated annual therapy costs, the annual costs of the most cost-efficient appropriate comparative therapy (ACT) and the potential budget impact for 33 included procedures were calculated.

Results. 55% of the included drugs achieved a negotiated price higher than the most cost-efficient ACT, 3% were identified as equal and 42% showed lower negotiated prices. The potential savings exceeded expenditures by around EUR 523.5 m. After price flexibility was adopted by the legislator in 2017, the overall potential savings still outweighed the expenditures by around EUR 62 m.

Conclusions. Our analysis shows that making price negotiations more flexible by law does not undermine the fundamental aim of the AMNOG, which is to avoid additional expenditure without increased patient benefit. The regulation can thus fulfill the objective provided by the legislature of keeping drugs without proven additional benefits in the German healthcare system.

Keywords: AMNOG; drugs; Germany; pricing; statutory health insurance

1. Introduction

1.1 Pharmaceutical expenditure in Germany

High-income OECD countries, such as Germany, are key markets for the health care industry. In 2019, per capita retail spending on pharmaceuticals (prescription drugs and over-the-counter products) in OECD countries averaged US\$ 571 (adjusted for purchasing power differentials). Spending in Germany was almost double the OECD average at US\$ 935. The majority of OECD countries were within a relatively narrow expenditure range of $\pm 15\%$ of the average (OECD, 2021). Total sales of drugs in the German pharmacy market amounted to EUR 56.7 bn in 2020 at the pharmacy retail price level, excluding value added tax (Federal Union of German Associations of Pharmacists, 2021). The German healthcare system has various cost-saving measures. For the patent-protected pharmaceutical sector, the early benefit assessment

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is the most important measure to regulate pharmaceutical prices. The savings target of EUR 2 bn defined in the draft legislation was achieved or exceeded by EUR 2.65 bn from 2018 at the latest (Bundesanzeiger, 2010; Schwabe *et al.*, 2020). The long-term permanent average annual saving is estimated at EUR 3 bn (Wörmann *et al.*, 2021). International price differences for patent-protected drugs are often the result of nationally different healthcare systems with their different reimbursement regulations, as well as due to social and economic determinants (Wagner and McCarthy, 2004). The German reimbursement amount is used as an international reference price for reimbursement of the same drug in other countries (e.g., in the European Union). Accordingly, reductions in the original market entry price can lead to an international price reduction spiral (López-Casasnovas and Puig-Junoy, 2000; Houy and Jelovac, 2015; Maini and Pammolli, 2020). Thus, changes in the legal framework regarding pricing and reimbursement can have a global impact.

1.2 The German HTA-system

1st January 2021 marked the tenth anniversary of the Act to Reorganise the Pharmaceuticals' Market in the Statutory Health Insurance (AMNOG) taking effect (Bundesanzeiger, 2010). AMNOG introduced the 'early benefit assessment', the German version of a Health Technology Assessment (HTA). According to this procedure, the prices for new, patent-protected drugs are determined based on a benefit assessment (Bundesanzeiger, 2010). The AMNOG procedure consists of two parts – first the benefit assessment followed by the price negotiation (Henschke *et al.*, 2013; Ruof *et al.*, 2014). The Federal Joint Committee (G-BA) plays a crucial role in this procedure because it is the highest decision-making body of the joint self-management of physicians, dentists, hospitals and health insurance funds in Germany. Submitted evidence for non-orphan drugs is first evaluated by the Institute for Quality and Efficiency in Health Care (IQWiG). Taking into account the results of the IQWiG benefit assessments, written statements and the oral hearings, the G-BA decides on the added benefit of the drug. The G-BA determines additional benefits in six categories major, considerable, minor, non-quantifiable, no benefit and less benefit (Henschke *et al.*, 2013; Ruof *et al.*, 2014). A key factor in the entire AMNOG procedure is the selection of the appropriate comparative therapy (ACT), which is determined according to criteria set by G-BA (Leverkus and Chuang-Stein, 2016). The pharmaceutical company must prove the additional benefit of its new drug compared to the ACT. At the same time, the annual therapy costs of the specified ACT play a central role in the subsequent price negotiations between the National Association of Statutory Health Insurance Funds (GKV-SV) and the pharmaceutical company. Negotiations must be completed twelve months after market entry or, if the Arbitration Board is invoked, 15 months after market entry (Leverkus and Chuang-Stein, 2016; Ludwig and Dintsios, 2016; Lauenroth and Stargardt, 2017). For drugs with an additional benefit, the pharmaceutical company and GKV-SV agree on a negotiated price i.e. intended to reflect the 'value' of the drug for the corresponding patient population (Lauenroth and Stargardt, 2017; Gandjour *et al.*, 2020; Dintsios and Chernyak, 2022). Drugs without proven additional benefit are strictly capped in price or placed in a 'fixed reference price group' with comparable drugs for which a fixed amount (upper reimbursement limit) already applies (Lauenroth and Stargardt, 2017). In Germany, a uniform pharmacy dispensing price is prescribed by law for prescription-only drugs. Since AMNOG was introduced, the price is to be based on the demonstrated additional benefit compared to the standard of care specified by G-BA. However, a drug can receive several disparate additional benefit assessments from G-BA. This may be the case if a drug is approved for different indications, or if it was assessed in different patient groups (subpopulations) within an indication. In such cases, GKV-SV and the pharmaceutical manufacturer negotiate a mixed price. This price is intended to factor in different levels of additional benefit and prices for indications/subgroups to define a single price for the drug across all patient populations.

1.3 HTA (AMNOG) as a learning system

After ten years of AMNOG implementation, the question of the need for adjustment and improvement, in particular, is controversial among stakeholders (Greiner *et al.*, 2020; Bartol *et al.*, 2022). Criticism of excessively high drug costs is voiced at regular intervals, particularly by the health insurance funds. E.g., the Prescription Drug Report 2021 on behalf of AOK, Germany's largest group of health insurance funds, estimated for 2020 pharmaceutical expenditures in Germany to be around EUR 45.6 bn. Spending on patent-protected drugs in particular increased sharply by more than 10%. With sales of EUR 24.16 bn, patent-protected drugs accounted for 45.2% of the total market in 2020 (Ludwig and Mühlbauer, 2021). A key element for market penetration, and thus for the supply of drugs, is the pricing of drugs with unproven additional benefit. The pharmaceutical company has the legal right to terminate price negotiations no later than two weeks after the first meeting and to withdraw its drug from the German market; this is called an opt-out (Associations of Pharmaceutical Entrepreneurs and National Association of Health Insurance Funds, 2016). During the early AMNOG years, in particular, a significant number of drugs were withdrawn from the market due to several opt-outs from price negotiations. Staab and colleagues analyzed drugs withdrawn from the German market between January 2011 and June 2016 in more detail (2018). Among 139 drugs investigated, 10 opt-outs and 12 discontinuations of supply were identified. With the exception of one drug, G-BA determined that 'an additional benefit is not proven' (Staab *et al.*, 2018). Of particular importance is the fact that 68% of the 22 drugs withdrawn were specifically recommended in medical guidelines (Staab *et al.*, 2018). After the period analyzed by Staab and colleagues, four additional opt-outs have occurred by the end of 2021. However, in two cases, an additional benefit within a single patient subpopulation was demonstrated (National Association of Health Insurance Funds, 2022).

Based on the experiences described above and the resulting potential limitations on therapy alternatives, in May 2017 the German legislator enhanced the regulations for price negotiations on the basis of a benefit assessment with the Act to Strengthen the Supply of Medicines in the Statutory Health Insurance (AMVSG) (Bundesanzeiger, 2017). As before, new patent-protected drugs with unproven additional benefit should in principle not lead to higher annual therapy costs than the most cost-efficient ACT set by G-BA. However, the legislator intended to provide more flexibility for price negotiations by changing the wording in the legislation (Social Code Book V Section 130b Paragraph 3). This amendment softened the previous formulation that a drug with unproven additional benefit 'must not' lead to higher costs than the most cost-efficient comparative therapy named by G-BA and replaced it with the wording 'shall not'. Thus, once the new regulation took effect, it was possible to deviate from the price cap of the most cost-efficient ACT in justified individual cases (German Bundestag, 2016; Bundesanzeiger, 2017). The legislature made further AMNOG modifications by introducing the SHI Financial Stabilization Act, which came into force in November 2022 (Bundesanzeiger, 2022). With regard to the validity of the negotiated price, there is now a retroactive application of the negotiated price from the seventh month. This retroactivity applies to newly launched drugs, for all new indications as well as for the price set by the arbitration board. In addition, new requirements for price negotiations are valid which also affect drugs with unproven additional benefit and are presented in the discussion.

The purpose of our study was to determine the negotiated price level of drugs with unproven additional benefit compared to the most cost-efficient ACT and to analyze the resulting budget impact for the Statutory Health Insurance (SHI). The questions to be examined are whether the option of being more flexible in negotiating a price above the costs of the most efficient comparative therapy was used, and whether additional financial burdens have arisen for SHI as a result of the amendment to the legislation. Therefore, the negotiated prices of AMNOG-rated drugs with unproven additional benefit are compared to the price of the corresponding most cost-efficient

ACT set by G-BA. The corresponding results are collected for the periods prior to (January 2011 to April 2017) and after (June 2017 to December 2020) the effective date of the AMVSG regulation and compared. This analysis evaluates for the first time, for a ten-year timespan, the negotiated prices of AMNOG-rated drugs with unproven additional benefit compared to their most cost-efficient ACT. By comparing negotiated prices prior to and after AMVSG, the impact of this regulation and the corresponding potential budget impact on SHI is analyzed.

2. Methods

2.1 Selection of drugs and benefit assessment procedures

For our price analysis, we analyzed all AMNOG procedures in the period prior to (2011 to April 2017) and after (June 2017 to 2020) the effective date of the AMVSG regulation. Since the AMVSG regulation went into effect in May 2017, that month was omitted as a transition period. To minimize potential bias and to create a homogeneous database for the subsequent analysis, various inclusion and exclusion criteria were defined. The analysis was carried out using an external commercial database (AMNOG-Monitor, 2021). The results were then verified against a database developed internally at Janssen. This validation step confirmed the previously identified procedures. Two additional procedures were identified by the internal database; these were therefore included in the selection process. A concise overview of the individual steps as well as the inclusion and exclusion criteria is available in [Figure 1](#).

(A) Firstly, all completed and ongoing AMNOG procedures were identified during the initial search as of 21 July 2021 (702 AMNOG procedures). (B) Secondly, only the completed procedures were allocated to the periods 2011–April 2017 and June 2017 until the end of 2020. (C) Next, we only included AMNOG procedures of launched products and drugs that exceeded the EUR 1 m threshold (by law, drugs exceeding EUR 1 m in revenues must go through the AMNOG assessment). In addition, the AMNOG procedure for each drug had to be fully completed. Accordingly, all aborted AMNOG procedures (e.g. opt-outs or drugs directly included in a fixed reference price group) and procedures based on expanding the indications for an already marketed product are excluded. (D) In the third selection step, only drugs that showed an unproven additional benefit across all subpopulations were included in the price analysis. Consequently, we excluded all products that showed an additional benefit for at least one subgroup. Hence, orphan drugs were also excluded, since, according to AMNOG regulation, the additional benefit is a given based on the European Medicines Agency's orphan drug designation and subsequent marketing authorization (Worm and Dintsios, 2020). By excluding expansions of indications and disparate additional benefit assessments across different subpopulations, we prevent the analysis from being biased by negotiated prices (mixed price) whose composition cannot be calculated accurately. In case of an additional benefit, in addition to the cost of the ACT, monetization of the additional benefit, actual selling prices in specified EU countries and prices of comparable drugs must be considered according to the framework agreement pursuant to Section 130b (9) SGB V. These named components are freely negotiated and cannot be determined precisely. (E) To analyze whether the intended price flexibility was leveraged during price negotiations, we only included AMNOG procedures in which the G-BA named a single ACT or several ACTs that only had an OR connection. According to G-BA, ACTs that include drugs with an OR connection are seen as interchangeable. Excluding ACTs such as 'patient individual drug therapy', 'therapy according to doctor's instructions' and 'best supportive care' further reduces uncertainties, since in such cases, the most cost-efficient component of ACT does not necessarily constitute the sole price ceiling for the price negotiations with SHI.

(F) In the penultimate step, we excluded all AMNOG procedures that were ultimately decided by the Arbitration Board. This exclusion criterion was chosen to further ensure a uniform data basis and to avoid uncertainties due to different Arbitration Board chairpersons. (G) Lastly, market withdrawals and drugs for the therapy of coagulation disorders in hemophilia (a total of seven

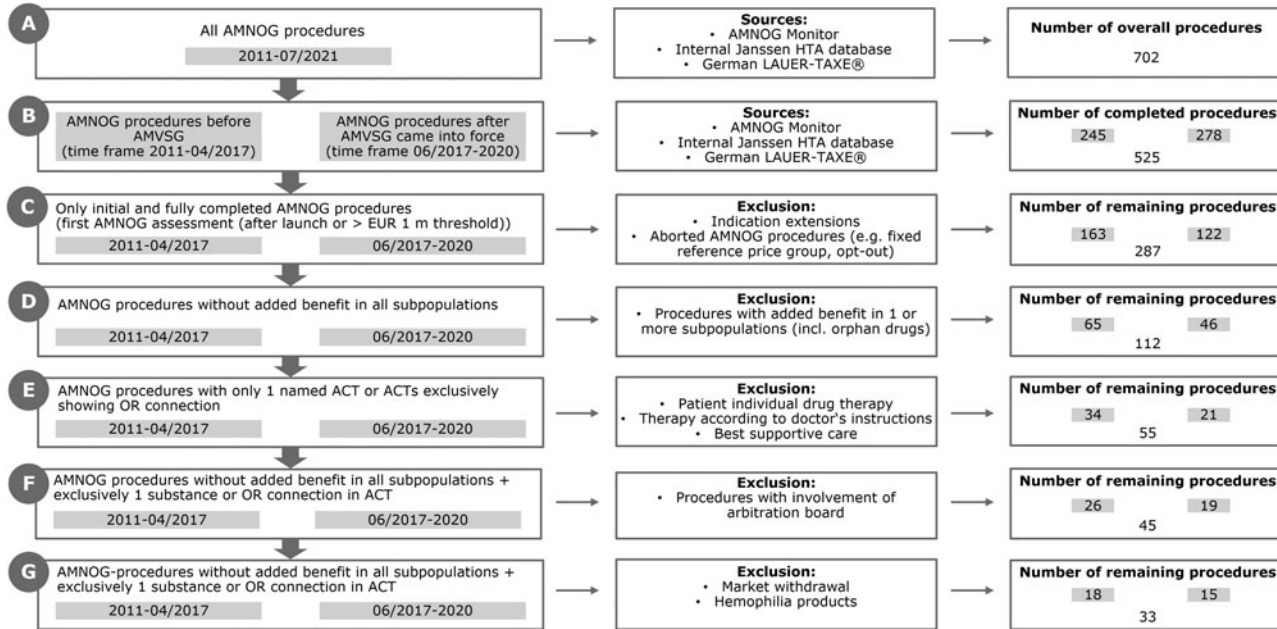


Figure 1. Flowchart with the defined analysis steps as well as sources, inclusion and exclusion criteria (search performed on 21 July 2021); differences in totals compared to the split between procedures may be due to the transition period.

drugs) were excluded from the subsequent price analysis. In Germany, the pharmaceutical market for the therapy of coagulation disorders in hemophilia is characterized by various peculiarities. With the German Act for More Safety in the Supply of Pharmaceuticals (GSAV), the legislator decided to regulate the sale of hemophilia drugs exclusively via pharmacies starting 1 September 2020 (Bundesanzeiger, 2019). Previously, plasma and genetically engineered coagulation factor preparations were excluded from the distribution channel via pharmacies, associated uniform pricing (wholesale and pharmacy surcharges) and mandatory public price listing. Due to possible direct distribution to clinical centers or physicians, in some cases, price information is missing or is highly uncertain. A case in point is the fact that the re-organization of prices in the existing market by law also provided for a re-negotiation of reimbursement amounts in the patent-protected AMNOG sector (Bundesanzeiger, 2019).

Based on the inclusion and exclusion criteria described above, we ultimately analyzed 33 remaining AMNOG procedures for the research question (see Supplement 1).

2.2 Annual treatment costs of the ACT

For the AMNOG benefit assessment, a pharmaceutical company must submit a value dossier with evidence demonstrating the additional benefit of the drug in the therapeutic indication newly approved by the regulatory authorities. Such a dossier contains all relevant studies and information from drug development and approval, specially prepared to meet AMNOG requirements (Federal Joint Committee, 2023). The AMNOG dossier is divided into five different modules. Module 3 contains the determination of the ACT, quantifies the number of patients in the corresponding therapeutic indication and the therapy costs for SHI, including the drug to be assessed as well as the ACT (Ivandic, 2014; Federal Joint Committee, 2022). Annual therapy costs were taken from module 3 written by the pharmaceutical company and reviewed in the associated G-BA resolution. In case of discrepancies between the information stated in module 3 and the G-BA resolution, we used the data on method of administration, treatment duration and costs provided by G-BA. The reason for this is the fact that the G-BA resolution is binding for the subsequent price negotiations between the pharmaceutical company and SHI. A validation of the prices stated in module 3 and the G-BA resolution was conducted using the official German drug directory (Lauer-Taxe[®]) (Lauer-Fischer GmbH, 2022). Price information in Lauer-Taxe[®] is updated twice a month (on the first and on the fifteenth of each month). Since the first price negotiation between the pharmaceutical company and SHI should take place no later than four weeks after the publication of the corresponding G-BA resolution, we gathered the price information in Lauer-Taxe[®] as follows: For G-BA resolutions published between the first and fourteenth of a month, the prices of the corresponding ACTs in Lauer-Taxe[®] from the fifteenth day of that month were considered. If the G-BA resolution was published between the fifteenth day and the end of a month, the prices of the ACTs from the first day of the following month were verified. The price histories of the ACTs were reviewed during the six-month negotiation period between issuing of the G-BA resolution and agreement on the negotiated price between the pharmaceutical company and SHI to identify potential price changes. If that was the case, the most recent price was used for the subsequent analysis. Annual costs were calculated on the public discounted ex-factory price (PD-EF) level. Annual costs on the PD-EF level reflect the costs of the drug for one year (365 days) based on the ex-factory price of the pharmaceutical company after deduction of mandatory rebates according to SGB V Section 130a. No assumptions about confidential rebates that may result e.g., from rebate contracts with health insurance funds were made in this analysis. Thus, beyond the mandatory rebates according to SGB V Section 130a, no further rebates were considered for the calculation of annual treatment costs.

To achieve a transparent, conservative and comprehensible basis for our price calculations, the following criteria were established: I. Common dosage range: use of average costs to reflect

minimum and maximum costs. II. In case of initial and maintenance doses: only the costs of the maintenance dose are reflected in the analysis. III. Dosage for non-responders and special populations: determination of costs for regular dosage/patients only. IV. Dosage depending on the patient's weight and/or height: use of the German 'micro census' applicable at time of the corresponding G-BA resolution. V. Change in ACT costs during the 6-month negotiation period: previous and new annual costs are reflected in the analysis. For further calculations, the most recent costs are used. VI. In case of a fixed reference price group: since the fixed reference price reflects the maximum amount i.e. Reimbursed for the corresponding active substance, this price was used instead of that of the most cost-efficient generic drug. This approach is in accordance with G-BA resolutions, since they also refer to the fixed reference price in such cases.

2.3 Negotiated price of the drugs to be assessed

In accordance with the procedure for determining the ACT costs as described in the previous section (Annual treatment costs of the ACT), module 3 as well as the corresponding G-BA resolution were considered when calculating the negotiated price (annual costs) of the assessed drug. A validation of the prices stated in module 3 and the G-BA resolution was conducted using Lauer-Taxe[®]. The negotiated price was determined by using the price published in Lauer-Taxe[®] at the end of the negotiation period (end of AMNOG procedure). For calculation of annual costs, the method of administration according to the G-BA decision was used. The criteria for price calculation (I-VI) described in the previous section were also applied to calculate the negotiated price.

2.4 Comparison of negotiated prices with ACT costs

We used the calculated annual costs to compare the negotiated prices with their corresponding most cost-efficient ACT. For this purpose, the most cost-efficient ACT per (sub)population for each included AMNOG procedure was identified. For benefit assessments that included only one population and corresponding ACT, we used the costs of the most cost-efficient ACT as the sole price ceiling for the analysis. If a benefit assessment included several subpopulations, a mixed price that considered firstly the most cost-efficient ACT per subpopulation was determined. Next these mixed prices were multiplied with the various subpopulation sizes as indicated in the G-BA resolution to derive the final mixed price. Since population sizes are often provided as ranges, the average size was used for calculation of the mixed price; this approach considers the minimum and maximum values accordingly. Subsequently, we compared these ACT costs with the negotiated price of the AMNOG-rated drug to determine whether the costs are similar, higher or lower than the costs of the most cost-efficient ACT. The difference between the most cost-efficient ACT and the negotiated price was determined both in absolute (EUR) and relative (percent) terms.

2.5 Comparison of negotiated prices regarding their deviation from the most cost-efficient ACT

Based on the comparison of the negotiated prices with their corresponding most cost-efficient ACT, we identified the proportion of AMNOG-rated drugs that achieved either a similar, higher or lower price than the ACT for the entire study period (2011–2020). For the negotiated price to be similar to the ACT costs, we allowed a $\pm 0.1\%$ deviation in annual costs. All deviations greater than this threshold were either categorized as procedures achieving greater or lower negotiated prices than the ACT annual costs. Additionally, we tested a potential change in distribution when allowing a $\pm 5\%$ deviation in a sensitivity analysis.

2.6 Potential budget impact for SHI (period 2011–2020)

To calculate the potential budget impact, we multiplied the delta of the negotiated price and the annual costs of the most cost-efficient ACT by the average population size, if existing, according

to the G-BA resolution. In case of multiple populations, we used the sum of the average population sizes. If the negotiated price exceeded the ACT costs, the result was categorized as a potential expenditure for SHI. If the negotiated price was lower than the ACT costs, the result of the multiplication was categorized as potential savings. Procedures for which the negotiated price was similar to the comparator costs were not considered for this part of the analysis. To arrive at the net potential expenditures or savings, we placed both variables in relation to each other to determine whether one outweighed the other for all identified AMNOG procedures during the entire study period. In addition, we conducted various sensitivity analysis. Firstly, we examined the influence of differing population sizes on our calculation of the budget impact. We used the 25th and 75th percentile to investigate whether, the averaged, large and small population sizes biased the overall sum. Secondly, we assessed the influence of equal indications (double counts) within our 33 procedures. If an indication occurred more than once, the next one was excluded from the analysis in chronological order of appearance. For further differentiation we investigated the impact of our average population size assumption for the overall time period. This was done for both thresholds 0.1% and 5%, by calculating the budget impact results for the minimum and maximum population size for procedures in which an interval was provided by G-BA. For further analysis, we determined the potential budget impact for AMNOG procedures showing only one comparator and several comparators separately.

2.7 Comparison of negotiated prices regarding their deviation from the most cost-efficient ACT before (2011–April 2017) and after (June 2017–2020) the AMVSG regulation

Based on a comparison of the negotiated prices with the annual costs of their corresponding most cost-efficient ACT, we identified the proportion of AMNOG-rated drugs that achieved either a similar, higher or lower price for the period before (2011–April 2017) and after (June 2017–2020) the effective date of the AMVSG regulation and matched the procedures accordingly. The end date of the AMNOG procedure was decisive for this allocation. Analogously to the analysis for the entire study period, the $\pm 0.1\%$ deviation and subsequent categorization of procedures was applied.

2.8 Potential budget impact for SHI before (2011–April 2017) and after (June 2017–2020) the AMVSG regulation

To calculate the potential budget impact before and after the AMVSG regulation, we matched the included procedures to either the first or second period and applied the same calculation method as described for the entire study period.

3. Results

3.1 Negotiated prices in relation to the annual costs of their most cost-efficient ACT (entire study period 2011–2020)

The total sample included 33 AMNOG procedures. The distribution of these procedures yielded the following results: During the entire study period (2011–2020), 54% of the drugs achieved a negotiated price higher than the annual costs of the most cost-efficient ACT, 3% of the drugs were identified as having a similar price and 42% of the drugs showed lower negotiated prices compared to their ACTs when considering the $\pm 0.1\%$ threshold, as shown in [Figure 2A](#). In nine of the 33 procedures, the ACT was included in a fixed reference price group (Supplement 1). For the 54% of drugs with a higher negotiated price, we found additional annual costs per procedure ranging from EUR 7 to EUR 36,842 (average: EUR 3764; median: EUR 281). The savings from procedures with a lower negotiated price compared to the ACT ranged from EUR 9 to EUR 206,100 per procedure (average: EUR -20,103; median: EUR -1148).

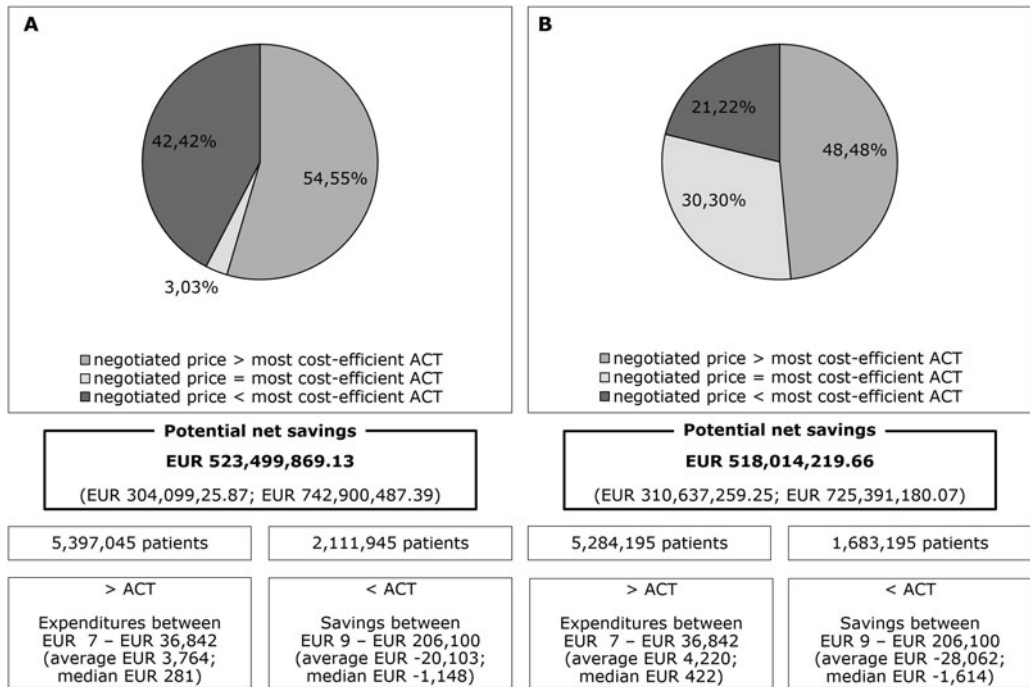


Figure 2. Deviation of the negotiated price from the most cost-efficient ACT (total time period 2011–2020) with minimum and maximum values of potential savings; (A) 0.1% threshold; (B) 5% threshold.

Subtracting the potential expenditures from the potential savings resulted in overall potential savings of around EUR 523.5 m. These potential overall savings vary from EUR 304 m to EUR 742.9 m considering the minimum and maximum potential amount of population sizes (Figure 2A). Additionally, the sensitivity analysis (5% threshold) in Figure 2B showed that the proportion of procedures resulting in drug prices below the annual costs of the most cost-efficient ACT has halved (21%). Absolute potential savings for SHI only decreased by approx. 1% (EUR 518 m) while 48% of procedures resulted in a higher drug price than ACT costs. These potential overall savings vary from EUR 310 m to EUR 725 m considering the minimum and maximum potential amount of population sizes (Figure 2B).

The sensitivity analysis looking at the 25th and 75th percentile showed that the 25th percentile (Figure 3A), with population sizes ranging from 240–11,250 patients for a total of 39,729 patients, resulted in over EUR 695 m in potential net savings. By contrast, the 75th percentile (Figure 3B) with a total of nearly 6.5 m patients yielded less than one third of the potential savings (EUR 202.5 m) of the 25th percentile. The result is further strengthened by the distribution of procedures whose negotiated prices are above or below the annual costs of the ACT. When looking at the 25th percentile, we identified four procedures for each category. Despite the balanced ratio, the potential savings outweighed the potential expenditures. Based on the 75th percentile, twice as many procedures achieved a negotiated price that was higher than the most cost-efficient ACT. However, when comparing the potential expenditures with the potential savings, the savings still outweighed the expenditures by EUR 202.5 m. Additionally, the procedures that were affected by the double count analysis are listed in Supplement 1 and the results of the analysis are presented in supplement 2. In total eight procedures, e.g., diabetes type 2 being removed three times, were deducted for the overall time frame (two within the first period and six in the second). However, the results underline the validity of our initial analysis, since for the

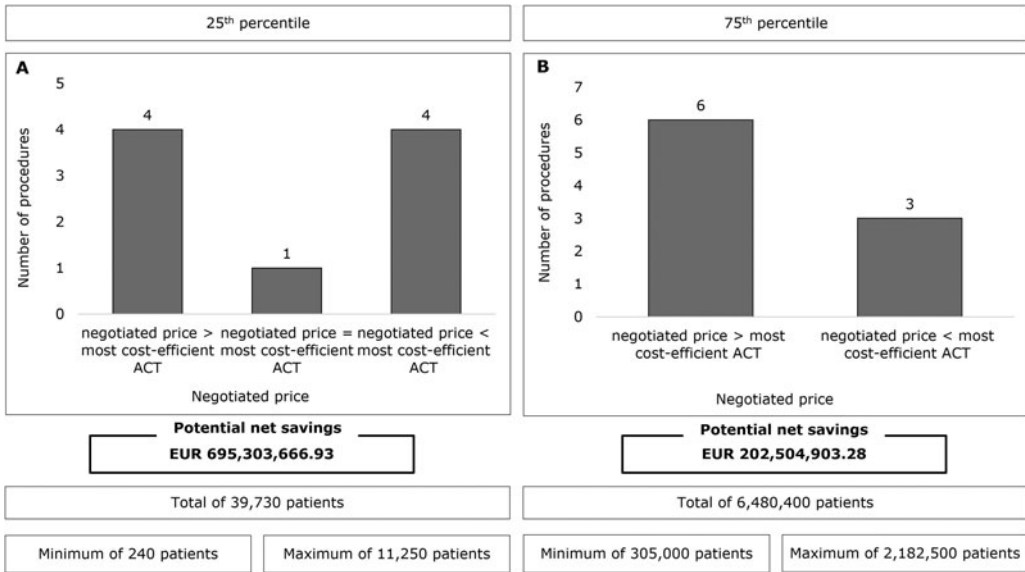


Figure 3. Deviations of the negotiated price from the most cost-efficient ACT depending on patient population size (A) for small patient populations using the 25th percentile; (B) for large patient populations using the 75th percentile.

25th as well as for the 75th percentile the potential savings only increase by this analysis (25th percentile + 5.1% and 75th percentile + 72.9%).

We conducted an additional analysis dividing our sample into two categories, the first including procedures with one comparator named by G-BA (Figure 4A), and the second category with procedures containing more than one comparator (Figure 4B). This approach was chosen to see whether there were any differences depending on the number of comparators. The sample of procedures with one ACT included a total of 10 AMNOG-rated drugs. In one procedure, the pharmaceutical company was able to achieve a higher negotiated price, whereas eight procedures ended up with a price below the single ACT. The resulting potential net savings in this first category totaled EUR 795.6 m. When analyzing the AMNOG procedures with more than one comparator, 17 of 23 procedures were able to achieve a higher negotiated price compared to the most cost-efficient ACT, whereas the prices of the remaining six drugs were negotiated below their corresponding ACT costs. Considering the potential expenditures and savings in this sample, we identified net expenditures for SHI of EUR 272.1 m. Despite the distribution of 17 vs. six procedures, the drugs with a negotiated price below the most cost-efficient ACT have a larger monetary impact when considering the potential expenditures in relation to the potential savings. To calculate the monetary impact, total potential additional expenditures (EUR 1.806 bn) and total potential savings (EUR 1.534 bn) resulting from the 23 procedures were calculated (EUR 3.340 bn in total savings plus expenditures). The next step was to determine the percentages of the potential savings and potential expenditures in relation to the above calculated total. This resulted in a distribution of 54% of the procedures with higher costs compared to the most cost-efficient ACT and 46% with a negotiated price below the most cost-efficient ACT. Dividing the 54% by the 17 procedures shows a monetary impact of 3.2% for each individual procedure. By contrast, dividing the 46% by the six procedures resulting in potential savings for SHI, each procedure has a monetary impact of 7.7%. Hence, the monetary impact of procedures with a negotiated price below the most cost-efficient ACT is twice as high as the impact of procedures with negotiated prices exceeding the ACT costs (7.7% vs. 3.2%).

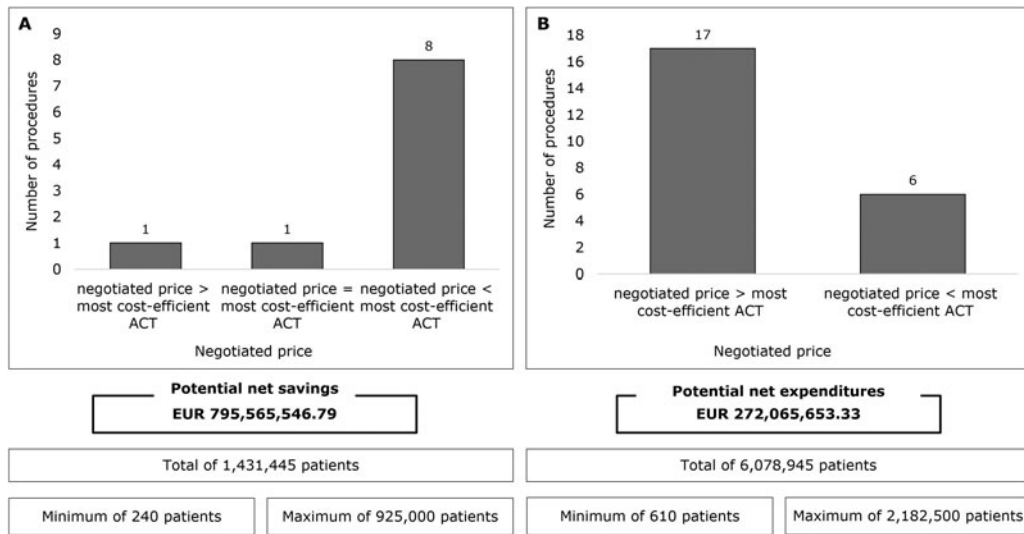


Figure 4. Deviation of the negotiated price from the most cost-efficient ACT for procedures with (A) one ACT and (B) with more than one ACT.

3.2 Negotiated prices in relation to the annual costs of their most cost-efficient ACT before (2011–April 2017) and after (June 2017–2020) the AMVSG regulation

Specifically, we aimed to identify whether the AMVSG regulation and accompanying price flexibility was leveraged in price negotiations. Of the 33 procedures, 18 relate to the first period and 15 to the second period. For the period before the AMVSG regulation (Figure 5A), 56% of procedures achieved a higher negotiated price compared to the most cost-efficient comparator, 6% were deemed similar and 39% showed a lower negotiated price than ACT costs. The procedures achieving a higher negotiated price led to potential expenditures (annual costs) of EUR 7 to EUR 5708 per procedure (average: EUR 1318; median: EUR 188). The total number of patients in these procedures is approx. 4.5 m according to the averages of the corresponding populations specified by G-BA. On the other hand, the procedures with a lower negotiated price than the annual costs of the ACT led to potential savings of EUR 9 to EUR 2565 per procedure (average: EUR –1142; median: EUR –1270). The total number of patients according to G-BA specifications for these procedures is around 1.6 m patients. When considering overall potential expenditures and savings relative to each other, potential savings outweighed expenditures by approx. EUR 461.4 m. This result is particularly interesting because only 26% of all patients included in all procedures prior to the AMVSG regulation are allocated to procedures with a lower negotiated price. This finding is further underlined by the median of potential expenditures and savings (EUR 188 vs. EUR –1270), illustrating the savings potential achieved by SHI before the AMVSG regulation. When looking at Figure 5B, which shows the period after the AMVSG regulation took effect, we see that the proportion of drugs that achieved a higher negotiated price than the annual costs of the most cost-efficient ACT is equal to the proportion that did so prior to the regulation. When comparing the pie charts, the only difference between the two periods is that, after the AMVSG regulation, no drug in our sample achieved a negotiated price similar to that of the most cost-efficient ACT. Moreover, the proportion of negotiated prices below the comparator costs increased from 38.89% to 43.75% of all drugs in our sample. A total of around 1.5 m patients according to G-BA numbers were included in the second period, which reflects 20% of patients during the entire study period (2011–2020). The 56.25% of drugs with negotiated prices above the most cost-efficient ACT resulted in potential expenditures per procedure ranging

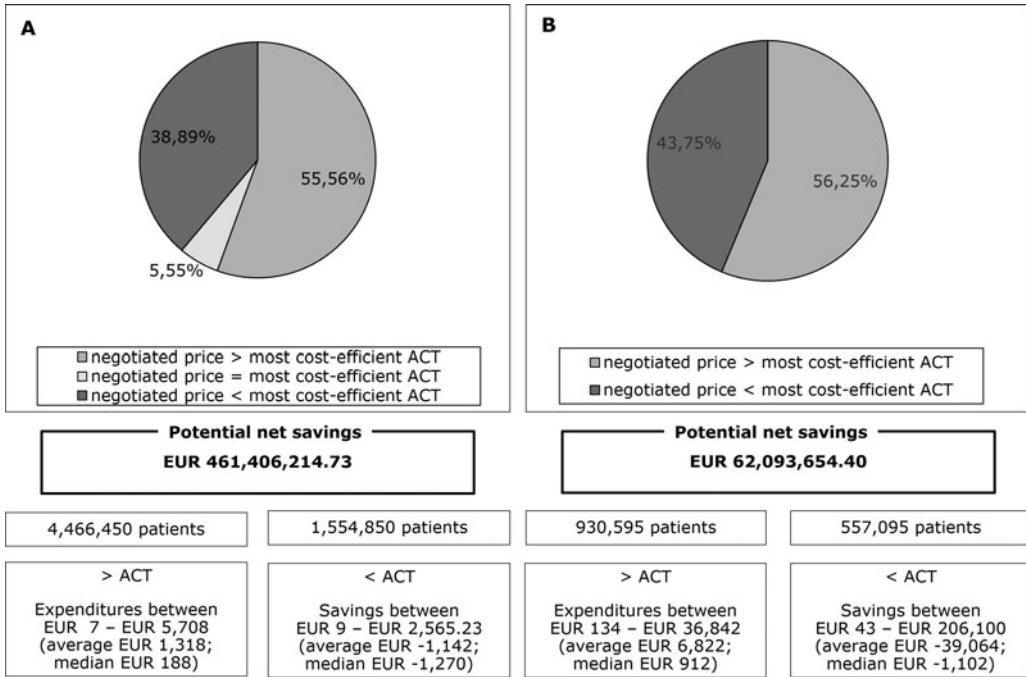


Figure 5. Deviation of the negotiated price from the most cost-efficient ACT before and after the AMVSG regulation (A) 2011–April 2017; (B) June 2017–2020.

from EUR 134 to EUR 36,842 (average: EUR 6822; median: EUR 912). For the 43.75% of drugs with prices below the ACT, we determined potential savings of EUR 43 to EUR 206,100 per procedure (average: EUR -39,064; median: EUR -1102). Although 63% of patients were allocated to procedures with potential expenditures, the potential savings for SHI after the AMVSG regulation exceed the potential expenditures, resulting in net savings of around EUR 62.1 m.

4. Discussion

The discussion about healthcare expenditures, including drug costs, is ubiquitous in health policy. Pharmaceutical costs are mostly presented unilaterally as gross costs without showing the rebates subsequently paid by the pharmaceutical industry due to various cost containment measures (Rodwin, 2021). The savings amount to EUR 72.3 bn between 2010 and 2020 (BASYS, 2022). One of the most important regulations for spending on innovative, patent-protected drugs in Germany was implemented in 2011 and is called AMNOG. The savings realized through AMNOG increased as the number of procedures grew from year to year. After ten years, the AMNOG legislation has generated savings accumulating to a total of EUR 14 bn for the health insurance funds. Savings of around EUR 6 bn were expected for 2021 alone (Wörmann *et al.*, 2021). Accordingly, every possible AMNOG reform is discussed controversial from the perspective of cost development. Lauenroth and Stargardt, calculated in their analysis for another time period (2011–2016) that pharmaceuticals with no additional benefit resulted in an average price premium of 9.1% (Lauenroth and Stargardt, 2017).

Due to the considerable impact of AMNOG reforms we analyzed in a first step, the price agreements of drugs with unproven additional benefit for the overall time period (2011–2020). It was surprising that around 55% of these drugs achieved a negotiated price above the ACT costs. However, the proportion of approx. 42% of drugs with unproven additional benefit that

ended up with a negotiated price below ACT costs is no less astonishing, since the legislator provided good arguments for sticking to the price of the most cost-efficient ACT in these cases. A publication from Hürer *et al.* (2021) stated that the expenditures on drugs show an annual growth rate of 3.5% (2010 vs. 2019), whereas other SHI healthcare expenditures grew annually by 4.2%. Thus, the share of drug costs relative to overall SHI healthcare expenditures during 10 years of AMNOG decreased from 18.9% to 17.8%. The AOK research institute showed that the costs of the patent-protected drug market almost doubled between 2010 and 2019 while the number of prescriptions dropped. Moreover, the report stated that the average costs of patent-protected drugs increased from EUR 2.85 per daily dose in 2010 to EUR 7.36 per daily dose in 2019 (Schröder *et al.*, 2020). Given the adversarial discussions about drug costs and AMNOG-related savings, we considered it important to analyze not only the mere distribution of procedures, but also the monetary impact of the drugs in these procedures that are priced above or below their most cost-efficient ACTs, as well as the relation of these procedures to each other. When looking at the potential budget impact of our overall sample of 33 procedures and the resulting total, we calculated potential net savings of EUR 523.5 m for the SHI. Given the fact that 55% of the 33 procedures achieved a higher price than their most cost-efficient ACT this was unexpected. However, this result illustrates that simply looking at the distribution is insufficient to adequately capture the pricing mechanisms of AMNOG for procedures deemed to have an unproven additional benefit. To verify our results on potential savings during the entire period, we conducted several further analyses. For instance, we used a 5% threshold for allocation of the procedures to the categories of costs below, similar and above the most cost-efficient ACT. Which paradoxically, halved procedures priced below the annual cost of the most cost efficient ACT (21%). However, potential savings for SHI only decreased by approx. 1% (EUR 518 m), with 48% of procedures still achieving a higher price than ACT costs. This underlines the bigger monetary budget impact of the procedures with a negotiated price below ACT costs and raises the question why several manufacturers negotiated prices far below the legislative price cap. It is worth mentioning that there are some cases in which companies entered the market already with lower list prices than their competitor. However, this remains an individual decision of the company, which is not publicly available. Hence it is not further discussed in our paper. In addition, the reimbursed price is usually negotiated according to a 'bottom-up approach' as a mark-up on top of the comparator costs (or, in absence of added benefit, at the level of the comparator costs), and the price level at launch is not a factor in this determination.

To supplement these findings, another sensitivity analysis was performed to assess whether large population sizes were responsible for great budget impacts. As shown in the results section, the 25th percentile (total of 39,729 patients), generated potential net savings of EUR 695 m, while the 75th percentile, (total of 6.5 m patients) generated EUR 202.5 m in potential net savings. These findings underline the fact that the great potential savings in our sample were not caused by an accumulation of small deviations from the most cost-efficient ACTs multiplied by huge patient populations set by G-BA. Unforeseen, however, was the fact that the GKV-SV apparently was able to negotiate huge negative deviations from the most cost-efficient ACT, specifically in indications with smaller population sizes. One might criticize the percentiles used. However, in medical statistics, percentile is a measure of the scattering of a statistical distribution sorted by the rank or size of the single values. As no common epidemiological classification or definition for small or large population sizes exists, using the 25th and 75th percentile was in our view the most accurate approach for this sensitivity analysis. Nonetheless, even when adjusting the sensitivity analysis, the results shown are so clear (25th percentile generates more than three times the savings of the 75th percentile) that such adjustments will not change the general finding we present.

An additional analysis was performed to better understand the possible influence of the number of comparators on the negotiated price. The results showed that procedures with only one comparator resulted in a negotiated price below that of the most cost-efficient ACT in eight

out of 10 cases (total potential net savings of EUR 795.6 m). This points out that in the case of one comparator the SHI is very likely to achieve a negotiated price below annual costs of the ATC. This is despite the fact that the legislator provides good arguments for setting the ACT costs as price anchors in procedures with unproven additional benefit.

However, this is in strong contrast to the procedures that include more than one comparator. In such cases, 17 of 23 procedures presented negotiated prices above those of the most cost-efficient ACT, leading to potential additional costs of EUR 272.1 m. For one, this leaves the impression that GKV-SV is much more flexible on prices during negotiations that include several comparators, given the fact that 74% of the drugs that did not show an additional benefit reached a higher price than their most cost-efficient ACT. This is also the subject of a critical discussion by Erdmann *et al.* (2021) that regularly, when there are multiple alternatives in the ACT, a debate arises about negotiated prices that are higher than the most cost-effective ACT. Nevertheless, this is the only outcome of our analysis that shows total potential additional expenditures. However, as shown in our results, this needs to be put into perspective, since the monetary impact of the six procedures with a negotiated price below that of the most cost-efficient ACT was twice as high as the impact of procedures with a negotiated price above ACT costs. In addition, for nine of the 33 procedures, the ACT was included in a fixed reference price group. These nine cases contain procedures with several subpopulations in which at least one ACT was included in a fixed reference price group. The impact of fixed reference price groups for an ACT on the presented results is not evident, as in the majority of cases a mixed price consisting of the most-efficient ACT per subpopulation was used for our calculations.

Several publications have stated that, as of implementation of the AMVSG regulation, a higher number of procedures that show no additional benefit achieved prices exceeding the ACT costs (Erdmann *et al.*, 2021; Haas *et al.*, 2021). Thus, the AMVSG regulation is often seen as a critical price mechanism that allows pharmaceutical companies to deviate from the ACT costs and to generalize the term ‘in justified cases’. Haas *et al.* (2021) recently stated that this fact undermines a basic principle of the AMNOG reform: no additional costs without additional benefit for patients. In the second step, we evaluated the effects of the AMVSG regulation on price negotiations between pharmaceutical companies and GKV-SV. Since the new regulation intended to increase the degree of flexibility by allowing deviations from the price cap of the most cost-efficient ACT in justified individual cases, we investigated resulting consequences. When comparing the periods before (18 procedures) and after (15 procedures) the AMVSG regulation, there were no significant changes in our dataset in terms of deviation from the most cost-efficient ACT. Rather, looking at the results, the proportions barely shift between the two periods (4.87% increase in drugs with negotiated prices below the prices of the most cost-efficient ACTs and a 0.69% increase in drugs with negotiated prices above the prices of the most cost-efficient ACTs). These minor increases, though, can be partly explained by a shift in procedures that are similar in cost to ACT costs. Before the AMVSG regulation, one procedure had a negotiated price similar to the most cost-efficient ACT and therefore couldn’t be allocated to either the above or below category when comparing drug and ACT prices. However, after the AMVSG regulation, all procedures resulted in prices either below or above ACT costs. When looking at this split, we identified savings of EUR 461.4 m for the period before and EUR 62.09 m for the period after implementation of the AMVSG regulation. The lower potential net savings after introduction of the legislation might be in part justified by the significantly smaller patient population size included in the second period (total of 6 m patients before and 1.4 m patients after AMVSG). Additionally, it is interesting that the sheer number of procedures with a negotiated price above the most cost-efficient ACT outweighs the number of procedures with a negotiated price below the most cost-efficient ACT both before and after the introduction of this legislation. Our results for the distribution of the procedures point in a similar direction.

Based on these results, we can conclude that the AMVSG regulation had no substantial effect on the price negotiations for the procedures included in our sample since the proportion barely

changed. However, the high proportion of procedures in which negotiated prices were lower than the prices of their most cost-efficient ACTs was surprisingly high (38.9% before and 43.7% after the AMVSG introduction). Surprising because the legislature had intended greater price flexibility when it amended the law. Our analysis does not allow us to conclusively determine whether different inclusion and exclusion criteria would have led to a different result. However, we consider our criteria to be robust, due to our specific exclusion criteria.

Since 2017, G-BA has used the official justification of the benefit assessment decision to indicate the value of a drug without proven additional benefit for health care by stating ‘therapy option relevant in individual cases’. This note might in theory introduce a supporting instrument for negotiating a price above the most cost-efficient ACT in the absence of an additional benefit. However, no official criteria and specifications state how this note should be taken into account during price negotiations. When considering the G-BA-specified option to define a drug as a ‘may represent a therapy option relevant in individual cases’, we identified one procedure [Ropeginterferon alfa-2b (Besremi®)] that falls in this category. In that case, the negotiated price was above the most cost-efficient ACT (approx. 718% /EUR 36,841). It is not clear whether there is a causal relationship between the definition as a ‘potential relevant therapeutic option’ and the deviation from the cost ceiling in the case we identified, or whether there are other reasons for the deviation. The influence of G-BA terminology on price negotiations cannot be conclusively assessed and would need further analysis to better understand the impact of this instrument.

In conclusion, our results, such as investigating the entire (2011–2020) and different periods (before and after AMVSG) or differing thresholds for these, changing the composition of our sample’s population or creating two different groups with varying comparators, lead mostly to potential net savings based on our calculation of the budget impact. When considering the mere distribution of 55% of the procedures achieving a higher negotiated price compared to ACT during the entire period (2011–2020), the impression arises that SHI must handle much additional cost for drugs without proven additional benefit. However, our analysis was able to show that limiting the view to the distribution of these procedures can present a distorted picture. Thus, it is crucial that the procedures identified are placed in context with their potential budget impact for the SHI. The results from the procedures we examined contradict the general perception of continuously rising drug costs (Schröder *et al.*, 2020; Haas *et al.*, 2021; Ludwig and Mühlbauer, 2021) and show that the German healthcare system might even generate savings -even during the time period with more price flexibility- when drugs without proven additional benefit are viewed holistically. Additionally, we would like to emphasize that since the introduction of the AMVSG, only a few drugs have been withdrawn from the market during or after price negotiations. The regulation thus helps to keep drugs on the market as necessary therapy alternatives.

These results are in view of the SHI Financial Stabilization Act of particular relevance. The legislation specifies, among other things, that for drugs without proven additional benefit, which have been evaluated against a patent-protected comparative therapy, a price must be negotiated that is at least 10% below the most cost-efficient comparative therapy annual costs. In these cases, the price flexibility introduced by the AMVSG is revoked and the affected drugs are priced less favorably than with the introduction of the AMNOG. Considering our results, the question can be raised if this law amendment was necessary since the SHI had in our analyzed procedures enough latitude over the last ten years to negotiate in relevant cases far below the most cost-efficient ACT.

4.1 Limitations

As our analysis did not consider medical guidelines, the comparators chosen in our dataset might not be the clinical standard. Furthermore, concrete insights in the negotiations between the corresponding pharmaceutical company and SHI could not be gained because such negotiations are

strictly confidential. For our analysis, only the numerical result of the negotiations is relevant. There may be good reasons for a negotiated price above or below comparator costs, but these are confidential and not publicly available and cannot be included in the analysis. Pharmaceutical companies, as well as SHI, might have logical individual reasons for deviations from the most cost-efficient ACT. Looking at the way we calculated the budget impact of our 33 procedures, one can argue that firstly, a 100% market penetration of all patients is unlikely and secondly that counting indications, if they arise more than once, distort the results. However, the approach we chose was tested in regard to adjusting to those two factors which in the end did not change the overall direction of our initial results. For further research, it would be interesting to analyze in more detail specific cases in which the deviation above or below the most cost-efficient ACT is greatest to better understand the approaches of the two stakeholders.

5. Conclusion

Price regulation is a well-established approach by policymakers seeking to address the challenges of rising healthcare expenditures under budgetary constraints. Accordingly, legislation specified that the annual therapy costs for drugs with unproven additional benefit must not exceed the costs of the most cost-efficient appropriate comparator therapy. Nevertheless, the legislator subsequently made these requirements more flexible in individual cases for reasons of supply policy to avoid potential market withdrawals. Our analysis shows for the first time, for a ten-year timespan and based on clear and transparent criteria, the results of negotiations and the financial significance to the SHI of drugs with unproven additional benefit. Surprisingly, the limits on cost are to a large extent lower than the most cost-efficient comparator therapy and result in significant potential overall net savings for the SHI. Even the price flexibility introduced by the legislator in individual cases in 2017 does not change the trend towards potential savings exceeding additional expenditures.

Even though not all procedures for drugs with unproven additional benefit were included in the analysis (e.g., additional benefit in one or more subgroups), we do not see that the AMVSG regulation is undermining the fundamental objective of the AMNOG, which is to avoid additional expenditures without increased benefit for patients. From our perspective, the important AMVSG regulation allows for the price flexibility in individual cases envisioned by the legislator in order to keep drugs with unproven additional benefit in the German healthcare system. The SHI Financial Stabilization Act removes this pricing flexibility in certain cases and represents a step backward from the perspective of therapy diversity.

Further research could aim for detailed insights into procedures with negotiated prices above or below the most cost-efficient ACT and further investigate aspects, such as market dynamics and peculiarities in specific indications, as well as the significance of specific ACTs for everyday care.

Supplementary material. The supplementary material for this article can be found at <https://doi.org/10.1017/S1744133123000117>

Financial support. Janssen-Cilag GmbH through authors' salaries and commissioned cooperation with EsFoMed GmbH. Janssen-Cilag GmbH played a role by providing the research question. Design, execution, analysis and interpretation of the data were performed by the authors.

Competing interest. Katrin Kleining, Jan Laufenberg, Philip Thrun, Dorothee Ehlert and Arne Bartol are employees of Janssen-Cilag GmbH, Neuss, Germany. Jürgen Wasem was in a paid commissioned cooperation with the company.

Ethical standards. Not applicable.

Consent. Not applicable.

Availability of data and material (data transparency). Analysis was conducted using commercially available databases. The raw data used are provided in the supplement.

Code availability (software application or custom code). Not applicable.

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