Does Biosimilar Bevacizumab Offer Affordable Treatment Options for Cancer Patients in the USA? A Budget Impact Analysis from US Commercial and Medicare Payer Perspectives

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Abstract

Background Bevacizumab remains the most widely used and most thoroughly characterized angiogenesis inhibitor for a range of advanced cancers. Bevacizumab-bvzr (Zirabev[®]), a biosimilar of bevacizumab, was recently approved by the US Food and Drug Administration (FDA), which provides a less costly option. This study aimed to evaluate the financial impact of introducing bevacizumab-bvzr from US commercial and Medicare payer perspectives.

Methods A Microsoft Excel-based budget impact model was developed over a 5-year time horizon. Target population was patients to be treated with bevacizumab for FDA-approved indications. Drug costs (2020 US\$) were based on average sales price and wholesale acquisition cost, accounting for payer-specific reimbursement models and provider settings. Drug dosing and duration were based on prescribing information and pivotal trial publications.

Results In a hypothetical 10-million-member health plan, 503 and 723 patients were estimated to be treated with bevacizumab in year 1 and year 5, respectively. Assuming an annual market shift of 1.7%, 3.6%, 6.7%, 9.4%, and 11.9% to bevacizumab-bvzr, an annual cost saving of \$313,363 (\$0.003 per member per month [PMPM]) was estimated for a commercial payer and \$92,880 (\$0.001 PMPM) for Medicare in year 1. Cumulative 5-year cost savings were \$7,030,924 (\$0.012 PMPM) for a commercial payer and \$4,059,257 (\$0.007 PMPM) for Medicare. More than half of the cost savings was attributed to patients with metastatic colorectal cancer.

Conclusions The introduction of biosimilar bevacizumab-bvzr was estimated to provide substantial cost savings for US payers, which would allow additional patients access to bevacizumab treatment.

Key Points for Decision Makers

The introduction of biosimilar bevacizumab-bvzr provides substantial cost savings for US payers due to significant efficiency savings in direct acquisition.

Biosimilars may allow the delivery of high-value care through expanded use of biologic treatment during episodes of cancer care.

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1 Introduction

Bevacizumab (Avastin[®]) is a recombinant humanized monoclonal IgG1 antibody and was the first anti-angiogenic oncology approved in the USA [1]. Bevacizumab binds to vascular endothelial growth factors (VEGFs), which prevents the interaction of VEGFs with endothelial cell receptors and blocks cell proliferation and the formation of new blood vessels. Bevacizumab was initially approved for the treatment of metastatic colorectal cancer (mCRC) in the USA in 2004 [2]. It is now indicated for a range of solid tumor indications including: first-line unresectable, locally advanced, recurrent, or metastatic non-squamous non-small-cell lung cancer (NSCLC) [3]; metastatic renal cell carcinoma (mRCC) [4]; recurrent glioblastoma (rGBM) [5]; persistent, recurrent, or metastatic cervical cancer (mCC) [6]; unresectable hepatocellular carcinoma [7]; first- and second-line metastatic colorectal cancer (mCRC) [8, 9]; and stage III or IV epithelial ovarian, fallopian tube, or primary

peritoneal cancer following initial surgical resection [10]. Despite more anti-angiogenic therapies becoming available in recent years [11, 12], bevacizumab remains the most widely used angiogenesis inhibitor [13]. When used in addition to standard-of-care chemotherapy, bevacizumab provides an effective therapeutic option in cancer patients [13].

However, biologic therapies are among the most expensive drugs, accounting for 40% of total US spending on prescription drugs despite only 2% of patients using biologics [14]. High development and treatment costs associated with biologics may limit patient access to these therapies. According to a physician survey conducted in the USA, Europe, and emerging markets, high out-of-pocket costs of bevacizumab are a barrier to prescribing bevacizumab and are a common reason physicians reduce the number of planned treatment cycles [15]. Previous studies that performed economic evaluations of bevacizumab have demonstrated a lack of cost-effectiveness in patients with mCRC in the USA, UK, Canada, Australia, and Israel [16–18], rGBM in Canada [19], mCC in the USA [20], and ovarian cancer in Canada and Belgium [21, 22], although the cost-effectiveness of bevacizumab in NSCLC was not conclusive according to a systematic review including ten countries [23].

Given the high cost of bevacizumab, which was among the top ten drug expenditures in the USA in 2018 for the Medicare Part B program [24], the introduction of biosimilars provides an opportunity for increased patient access and decreased healthcare expenditures across a number of oncologic indications. According to a RAND study, the introduction of biosimilars in the USA will result in substantial savings in the biologics market, potentially reducing direct spending on biologic drugs by \$54 billion from 2017 to 2026 [25].

A biosimilar is defined as a biologic product that is “highly similar to the reference product notwithstanding minor differences in clinically inactive components,” and one in which “there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product” [14]. Given the definition, biosimilars are approved through an abbreviated regulatory process, which focuses more on pharmaceutical and pharmacologic properties of the protein than safety and efficacy data [26].

Biosimilar bevacizumab-bvzr (Zirabev[®], Pfizer, Inc., NY, USA) has been approved by the US Food and Drug Administration (FDA) in June 2019 for all eligible indications (i.e., not covered by regulatory exclusivity) authorized for the reference product [27]. Bevacizumab-bvzr is the second-to-market biosimilar for bevacizumab in the USA, following bevacizumab-awwb (Mvasi[®], Amgen, Inc., CA, USA), which was approved by the US FDA in 2017 [28]. The biosimilarity of bevacizumab-bvzr to the reference product was supported by a double-blind, parallel-group study (ClinicalTrials.gov, NCT02364999) that compared the efficacy and

safety of biosimilar bevacizumab with that of the reference product, each with paclitaxel and carboplatin, in the first-line treatment of advanced non-squamous NSCLC [29]. There were no clinically meaningful differences in safety, pharmacokinetics, or immunogenicity across treatment groups [29].

In order to encourage lower-cost biosimilars in the USA, Medicare has introduced differential reimbursement for biosimilars. Specifically, provider-administered biologics are reimbursed at the product’s average sale price (ASP) plus 6% of the ASP. In contrast, a biosimilar is reimbursed at the biosimilar’s own ASP plus 6% of the originator biologic’s ASP [30]. Medicare biosimilar reimbursement may shift the incentive to lower-cost biosimilars among healthcare providers. In order to understand the potential savings if bevacizumab-bvzr is widely adopted in the USA, a budget impact model was developed to estimate the financial impact of introducing bevacizumab-bvzr to the formulary for the treatment of all FDA-approved indications from US commercial and Medicare payer perspectives.

2 Methodology

2.1 Model Overview

A budget impact model (BIM) was developed in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) to estimate the financial impact of introducing bevacizumab-bvzr to a payer’s formulary in the USA. A hypothetical 10-million-member health plan was assumed. The target population was defined as patients treated with bevacizumab for all FDA-approved indications, including first-line unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC, mRCC, rGBM, persistent, recurrent, or metastatic CC, and first-line and second-line mCRC.

The analysis was conducted from US commercial payer and Medicare perspectives separately. Patient cost exposure such as co-payment or co-insurance was not considered. The budget impact of bevacizumab-bvzr was estimated by comparing the total costs between two scenarios annually over a 5-year time horizon (Fig. 1). The first scenario reflected a formulary in which all the patients treated with bevacizumab are on either the reference product (Avastin[®], Genentech, CA, USA) or bevacizumab-awwb (Mvasi[™], Amgen, CA, USA), a bevacizumab biosimilar currently available in the US market, whereas the second scenario reflected a hypothetical new formulary where bevacizumab-bvzr was introduced. In the second scenario, a proportional market shift was assumed from the existing products to bevacizumab-bvzr in each year following biosimilar launch. The total drug costs for both scenarios were estimated as the sum of product of the number of eligible patients on each treatment and annual per-patient cost of specific medication. The budget

impact was estimated as the difference in total costs between the scenarios with and without bevacizumab-bvzr. Given the aim of the BIM was to compare annual cash flows, no discounting was applied [31]. Reporting of the study was guided by the consolidated health economic evaluation reporting standards (CHEERS) statement [32].

Costs associated with drug administration, adverse events (AEs), efficacy, and other healthcare resource utilization were assumed to be the same between bevacizumab biosimilars and reference product, and therefore non-drug costs were not included in the analysis. This assumption is consistent with the definition of biosimilar biologics and is supported by clinical trial data [29].

2.2 Target Population

The estimation of patients initiating treatment with bevacizumab for all FDA-approved indications was conducted

in two steps. First, the number of eligible patients in each year was estimated based on hypothetical health plan size, growth rate of plan population, and US-based epidemiology (Table 1). The incidence of each cancer indication and other disease burden data were obtained from the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review [33] and published literatures (referenced in Table 1), which were assumed to be the same for commercial payers and Medicare. The present analysis only included an incident population that was newly diagnosed in each model year. Treatment utilization rates of bevacizumab were applied to the number of eligible patients by indication, assuming that the utilization of bevacizumab would remain constant over time and that only the patients treated with bevacizumab reference product would switch to bevacizumab biosimilar. It was also assumed that all the patients initiating treatment with bevacizumab in a specific year started the treatment in the beginning of the year.

Fig. 1 Simplified model framework

Table 1 Epidemiology, treatment utilization of bevacizumab biologics, and number of patients initiating treatment with bevacizumab

Parameter	Value	Estimated population initiating treatment with bevacizumab				
		Year 1	Year 2	Year 3	Year 4	Year 5
Plan population in year 1	10,000,000					
Annual population growth rate [64]	0.6%	10,000,000	10,062,572	10,125,535	10,188,893	10,252,647
First-line unresectable, locally advanced, recurrent or metastatic non-squamous non-small-cell lung cancer						
Incidence, non-small-cell lung cancer (per 100,000) [33]	38.7	3871	3895	3920	3944	3969
Proportion with non-squamous disease [65]	73.7%	2854	2872	2890	2908	2926
Proportion with advanced disease [66]	58.8%	1679	1690	1700	1711	1721
Proportion receiving first-line treatment [67]	46.0%	772	777	782	787	792
Proportion treated with bevacizumab [68]	23.6%	182 ^a	183	185	186	187
Metastatic renal cell carcinoma						
Incidence, kidney cancer (per 100,000) [33]	15.7	1570	1580	1590	1600	1610
Proportion with renal cell carcinoma [65]	90.8%	1426	1435	1444	1453	1462
Proportion with metastatic disease [65]	13.3%	189	191	192	193	194
Proportion receiving first-line treatment [69]	85.1%	161	162	163	164	165
Proportion receiving second-line treatment among patients receiving first-line treatment [69]	62.0%	100	101	101	102	102
Proportion receiving third-line treatment among patients receiving second-line treatment [70]	47.0%	47	47	48	48	48
Proportion receiving fourth-line treatment among patients receiving third-line treatment [70]	32.8%	15	15	16	16	16
Proportion treated with bevacizumab ^b	1.0%	3 ^c	3	3	3	3
Recurrent glioblastoma						
Incidence, brain cancer (per 100,000) [33]	6.5	650	654	658	662	666
Proportion with glioblastoma [65]	51.5%	335	337	339	341	343
Proportion receiving first-line treatment [71]	49.9%	167	168	169	170	171
Proportion receiving second-line treatment among patients receiving first-line treatment [71]	32.6%	54	55	55	55	56
Proportion treated with bevacizumab [72]	36.0%	80 ^d	80	81	81	82
Persistent, recurrent, or metastatic cervical cancer						
Incidence, cervical cancer (per 100,000) [33]	6.7	668	672	676	681	685
Proportion with metastatic disease [33]	15.6%	104	105	106	106	107
Proportion with recurrent disease [73]	22.5%	150	151	152	153	154
Proportion receiving first-line treatment [74]	52.3%	133	134	135	136	137
Proportion receiving second-line treatment among patients receiving first-line treatment [74]	32.4%	43	44	44	44	44
Proportion treated with bevacizumab ^e	1.0%	2 ^f	2	2	2	2
First-line and second-line metastatic colorectal cancer						
Incidence, colorectal cancer (per 100,000) [33]	37.0	3700	3723	3746	3770	3793
Proportion with metastatic disease [75]	22.3%	825	830	835	841	846
Proportion receiving first-line treatment [76]	69.7%	575	579	583	586	590
Proportion receiving second-line treatment among patients receiving first-line treatment [76]	60.9%	350	352	354	357	359
Proportion treated with bevacizumab [77]	48.3%	447 ^g	450	453	456	458

^aEstimated as: 10,000,000 *38.7/100,000 *73.7% *58.8% *46.0% *23.6%^bEstimated as: As bevacizumab was not reported in any published real-world study for mRCC in the USA or UK [69, 70, 78, 79], indicating that bevacizumab was rarely used for mRCC, an uptake of 1% was assumed^cEstimated as: 10,000,000 * 15.7/100,000 *90.8% *13.3% *85.1% *(1+62.0% *(1+47.0% *(1 + 32.8%))) *1%^dEstimated as: 10,000,000 * 6.5/100,000 *51.5% *49.9% *(1+32.6%) *36.0%^eAs there was rarely any published real-world treatment pattern study in cervical cancer 15, an uptake of 1% was assumed^fEstimated as: 10,000,000 * 6.7/100,000 *(15.6%+22.5%) *52.3% *(1+32.4%) *1%^gEstimated as: 10,000,000 *37.0/100,000 *22.3% *69.7% *(1+60.9%) *48.3%

2.3 Treatment Duration

To account for treatment discontinuation due to disease progression, unacceptable toxicity, or death, the cumulative proportion of patients discontinuing treatment over time since treatment initiation was applied to the number of patients initiating treatment with bevacizumab in each year.

The cumulative proportion of patients discontinuing treatment was estimated based on the median treatment duration obtained from pivotal trial publications for bevacizumab reference product (Table 2), assuming that treatment discontinuation followed an exponential distribution (e.g., at a constant rate of treatment discontinuation) and that patients would discontinue treatment at mid-year (i.e., 0.5, 1.5, 2.5, 3.5, and 4.5 years since treatment initiation). The proportion of patients remaining on treatment was estimated as one minus the cumulative proportion of patients discontinuing treatment and then applied to both bevacizumab reference product and bevacizumab-bvzr, assuming that there was no difference in treatment discontinuation. The total number of eligible patients treated with bevacizumab in each year was estimated as the sum of the number of patients initiating treatment in the current year and the number of patients initiating treatment in previous year(s) but still remaining on treatment this year.

2.4 Treatment Distribution

Comparators to bevacizumab-bvzr in the present analysis were its reference biologic and biosimilar bevacizumab-awwb. In the scenario without bevacizumab-bvzr, it was assumed that all the patients on bevacizumab would be treated with either reference product or bevacizumab-awwb, using the projected treatment distributions from historical market research data [34]. In the scenario with

bevacizumab-bvzr, it was assumed that the uptake of bevacizumab-bvzr was proportionally taken from reference product and bevacizumab-awwb, with respect to the projected treatment distributions of these two drugs over years 1–5. Projected treatment distributions were assumed to be uniform across indications (Table 3).

2.5 Treatment Costs

The estimation of annual per-patient drug costs accounted for payer-specific reimbursement models and site of care (Table 4). Drug cost from a commercial payer perspective was estimated as a weighted average of costs of drugs administered in physician office (48%) and hospital outpatient setting (52%) [34]. Costs in physician offices was estimated using average sales price (ASP) with 10% cost recovery [35–38]. Costs in a hospital outpatient setting were typically a percentage of billed charges, as a proxy of which, wholesale acquisition cost (WAC) with 75% cost recovery was applied [35–37, 39]. The calculation of drug costs from a commercial payer perspective was the same between reference product and biosimilars.

Table 3 Projected treatment distribution over 5 years

Market scenario and treatment option	Treatment distribution (%)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Without bevacizumab-bvzr					
Bevacizumab	79.0	70.1	72.7	66.5	61.2
Bevacizumab-awwb	21.0	29.9	27.3	33.5	38.8
Bevacizumab-bvzr	0.0	0.0	0.0	0.0	0.0
With bevacizumab-bvzr					
Bevacizumab	77.6	67.6	67.8	60.2	53.9
Bevacizumab-awwb	20.7	28.8	25.5	30.4	34.2
Bevacizumab-bvzr	1.7	3.6	6.7	9.4	11.9

Table 2 Median treatment duration and proportion of patients remaining on treatment

Indication	Median treatment duration (month)	Patients remaining on treatment					
		Baseline (%)	After 0.5 year (%)	After 1.5 years (%)	After 2.5 years (%)	After 3.5 years (%)	After 4.5 years (%)
Non-small-cell-lung cancer [80]	4.9	100	43	8	1	0	0
Metastatic renal cell carcinoma [4]	9.7	100	65	27	12	5	2
Recurrent glioblastoma [5]	4.1 ^a	100	37	5	1	0	0
Cervical cancer [81]	4.8 ^b	100	42	8	1	0	0
Metastatic colorectal cancer [8, 9, 82]	4.6 ^c	100	40	7	1	0	0

^aEstimated based on observed duration of three 6-week treatment cycles

^bEstimated based on observed duration of seven 21-day treatment cycles

^cEstimated based on observed duration of ten 14-day treatment cycles and was applied to estimate the proportion of patients remaining on treatment

Drug cost from a Medicare perspective was estimated as a weighted average of costs in non-340B entities (63%) and 340B entities (37%) [34]. Reimbursement to non-340B entities for reference product was estimated as the ASP of reference product plus 6% of ASP of reference product, while reimbursement to non-340B entities for bevacizumab biosimilars was estimated as the ASP of bevacizumab biosimilars plus 6% of ASP of reference product, in line with CMS reimbursement policy for biosimilars [30]. Reimbursement to 340B entities for reference product was estimated as the ASP of reference product minus 22.5% of ASP of reference product [40]. However, reimbursement to 340B entities for bevacizumab biosimilars was estimated as the ASP of bevacizumab biosimilars plus 6% of ASP of reference product in the first 2 years of the model and estimated as the ASP of bevacizumab biosimilars minus 22.5% of ASP of bevacizumab biosimilars in years 3–5, assuming a 2-year duration of pass-through phase [41]. The ASPs and WACs of all products were obtained from Centers for Medicare and Medicaid Services [42] and RED BOOK [43], respectively. All costs were in 2020 US dollars.

Drug dosage was based on prescribing information (Table 5) [27, 44]. As bevacizumab reference product and biosimilars are dosed based on patient weights, average patient weights in each indication were estimated based on sex ratio from pivotal trial publications of the reference product and average weights for the general US population [45]. Costs of product wastage were included, given bevacizumab-bvzr is indicated as a single-dose vial [46].

2.6 Analysis

For both market scenarios with and without bevacizumab-bvzr, the total annual costs to the health plan in year 1 to year 5 were estimated as the sum of product of the number of eligible patients treated with specific medication in each year and the annual per-patient costs of specific medication.

The total budget impact was calculated as the difference in total costs between the scenarios with and without bevacizumab-bvzr for the entire target population in aggregate. In addition, budget impacts per member per year (PMPY), per member per month (PMPM), per patient per month (PPPM), and per patient per year (PPPY) were estimated. The PMPY budget impact was estimated by dividing the total budget impact to the health plan by the number of members in the plan. The PMPM budget impact was estimated by dividing the PMPY budget impact by 12 months. The PPPY budget impact was estimated by dividing the total budget impact to the health plan by the number of patients in the target population in the plan. The PPPM budget impact was estimated by dividing the PPPY budget impact by 12 months. In addition, additional number of patients treatable with bevacizumab-bvzr for a 1-year treatment course was estimated by dividing the total cost savings in specific year by the annual per-patient cost of bevacizumab-bvzr by indication.

Scenario analyses were conducted to assess the impact of key parameters on the results, including comparing market scenarios with and without bevacizumab biosimilars, change in bevacizumab-bvzr ASP, variations in projected uptake of

Table 4 Drug costs

Treatment	Cost inputs per 100 mg vial		Estimated costs per 100 mg vial by payer ^a		
	Average sales price [42]	Wholesale acquisition cost [42]	Medicare (year 1–2)	Medicare (year 3–5)	Commercial (year 1–5)
Bevacizumab	\$783.99	\$796.94	\$748	\$748	\$1,139
Bevacizumab-awwb	\$624.22	\$677.40	\$671	\$596	\$898
Bevacizumab-bvzr	\$631.80	\$613.40	\$679	\$603	\$909

^aPayer-specific reimbursement models and site of care were accounted for

Table 5 Drug dosage

Indication	Male (%)	Average weight (kg) ^a	Dosage (mg/kg)	Dose per admin (mg)	Admin frequency (days)	Admin per year
Non-small-cell-lung cancer [80]	54.4	83.1	15	1247	21	17.4
Metastatic renal cell carcinoma [4]	70.5	85.1	10	851	14	26.1
Recurrent glioblastoma [5]	60.6	83.9	10	839	14	26.1
Cervical cancer [81]	0.0	76.4	15	1146	21	17.4
Metastatic colorectal cancer [8, 9, 82]	60.4	83.9	7.5	629	14	26.1

^aAverage patient weights in each indication were estimated based on sex ratio from pivotal trial publications of the reference product and average weights (88.8 kg in males, 76.4 kg in females) for the general US population [45]

bevacizumab-bvzr and reimbursement markups, and time horizon.

3 Results

3.1 Base-Case Analysis

In a hypothetical 10-million-member US health plan, the numbers of patients to be treated with bevacizumab were estimated to be 503, 676, 709, 718, and 723 in year 1 through year 5, respectively (Table 6). The mCRC accounted for 62% of the total treated population, followed by NSCLC and recurrent glioblastoma, which accounted for 26% and 11% of the total treated population, respectively.

For a hypothetical 10-million-member commercial payer, bevacizumab-bvzr was associated with a total annual cost savings of \$313,363 (\$0.003 PMPM) in year 1, \$771,922 (\$0.006 PMPM) in year 2, \$1,564,205 (\$0.013 PMPM) in year 3, \$2,020,307 (\$0.017 PMPM) in year 4, and \$2,361,127 (\$0.019 PMPM) in year 5, resulting in a cumulative cost savings of \$7,030,924 (\$0.012 PMPM) over 5 years. The total annual costs savings would provide additional access to a 1-year treatment course of bevacizumab-bvzr for two patients, four patients, nine patients, 11 patients, and 13 patients in year 1 through year 5 (Table 6).

From a Medicare perspective, bevacizumab-bvzr resulted in a total annual cost savings of \$92,880 (\$0.001 PMPM) in year 1, \$226,412 (\$0.002 PMPM) in year 2, \$984,312 (\$0.008 PMPM) in year 3, \$1,270,889 (\$0.010 PMPM) in year 4, and \$1,484,765 (\$0.012 PMPM) in year 5, leading to a cumulative cost savings of \$4,059,257 (\$0.007 PMPM) over 5 years. The total annual costs savings would allow additional one patient, three patients, eight patients, 11 patients, and 12 patients in year 1 through year 5 to have access to a 1-year treatment course of bevacizumab-bvzr (Table 6).

3.2 Scenario Analyses

In the scenario analysis where a market scenario with bevacizumab biosimilars (including both bevacizumab-awwb and bevacizumab-bvzr) was compared to a market scenario with only the reference product, the cost savings were estimated to be \$0.093 PMPM (+675% relative to base case) for a commercial payer and \$0.050 PMPM (+614% relative to base case) for Medicare averaged across a 5-year time horizon (Table 7).

Assuming that the ASP of bevacizumab-bvzr decreased by 10%, it would result in an average cost saving of \$0.018 PMPM (+50% relative to base case) for a commercial payer and \$0.011 PMPM (+57% relative to base case) for Medicare. Decreasing bevacizumab-bvzr ASP by 20% would

further increase the average cost saving to \$0.025 PMPM (+108% relative to base case) for a commercial payer and to \$0.016 PMPM (+129% relative to base case) for Medicare. Doubling the annual uptake of bevacizumab-bvzr was associated with average cost savings of \$0.023 PMPM (+92% relative to base case) for a commercial payer and \$0.013 PMPM (+86% relative to base case) for Medicare, while decreasing the bevacizumab-bvzr uptake by half was associated with average cost savings of \$0.006 PMPM (−50% relative to base case) for a commercial payer and \$0.003 PMPM (−57% relative to base case) for Medicare. From a commercial payer perspective, increasing reimbursement markup relative to ASPs or WACs by 20% had limited effect on the budget impact, with average cost savings of \$0.012 PMPM (no change relative to base case). Decreasing the markups for ASPs or WACs by 20% was associated with slightly lower average cost savings of \$0.011 PMPM (−8% relative to base case) (Table 7).

4 Discussion

Our budget impact model has suggested that the introduction of bevacizumab-bvzr in the USA would lead to potential savings of \$313,363 for a 10-million-member commercial payer and \$92,880 for 10-million-member Medicare in the first year, assuming that 1.7% of the patients currently treated with the reference product or bevacizumab-awwb would switch to bevacizumab-bvzr. Over a 5-year time horizon, approximately \$7,030,924 and \$4,059,257 could be saved in total for a commercial payer and Medicare, respectively. These cost savings could be more substantial from a full Medicare plan level, which covers 62 million Medicare beneficiaries in the US [47]. The introduction of bevacizumab-bvzr could potentially lead to \$25 million savings over 5 years from a full Medicare plan level.

To our knowledge, the present study is the first budget impact analysis from a US payer perspective to incorporate all the latest Medicare Part B policies for biosimilar biologic products since 2016. These policies include establishment of unique codes for each biosimilar, a granted pass-through status for biosimilar, assigning a specific payment rate to each biosimilar product rather than a single blended payment rate, and implementation of differential reimbursement to biosimilars [30]. Our findings should be interpreted with caution, as the estimated cost savings depend on a variety of interrelated factors such as biosimilar price discount relative to the reference product, biosimilar uptake rate, and patient access to biosimilar.

The significant savings on drug spending when patients switch from reference product and bevacizumab-awwb to bevacizumab-bvzr observed in the present study are consistent with previous biosimilar literature. A budget impact

Table 6 Results from base-case analysis

	Medicare					Commercial payers				
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Bevacizumab biologics-treated patients, by indication										
Non-small-cell lung cancer	130	177	187	189	191	130	177	187	189	191
Metastatic renal cell carcinoma	3	4	5	5	5	3	4	5	5	5
Recurrent glioblastoma	54	71	74	75	75	54	71	74	75	75
Cervical cancer	1	2	2	2	2	1	2	2	2	2
Metastatic colorectal cancer	314	421	441	447	450	314	421	441	447	450
Total	503	676	709	718	723	503	676	709	718	723
Total annual costs in market without bevacizumab-bvzr										
By indication										
Non-small-cell lung cancer	\$21,536,848	\$29,034,369	\$29,818,146	\$29,844,500	\$29,728,223	\$32,014,919	\$42,709,376	\$45,281,589	\$45,295,065	\$45,095,629
Metastatic renal cell carcinoma	\$458,939	\$712,340	\$803,409	\$841,315	\$855,078	\$682,221	\$1,047,848	\$1,220,050	\$1,276,865	\$1,297,094
Recurrent glioblastoma	\$9,361,996	\$12,151,711	\$12,283,040	\$12,242,140	\$12,182,788	\$13,916,778	\$17,875,091	\$18,652,922	\$18,579,923	\$18,480,435
Cervical cancer	\$191,846	\$257,797	\$264,356	\$264,469	\$263,408	\$285,183	\$379,218	\$401,448	\$401,385	\$399,572
Metastatic colorectal cancer	\$41,991,010	\$55,812,554	\$56,952,777	\$56,897,650	\$56,650,188	\$62,420,406	\$82,099,919	\$86,488,014	\$86,353,690	\$85,934,362
Total	\$73,540,639	\$97,968,771	\$100,121,727	\$100,090,074	\$99,679,684	\$109,319,508	\$144,111,452	\$152,044,024	\$151,906,929	\$151,207,091
By treatment										
Bevacizumab	\$59,349,062	\$70,841,328	\$77,077,074	\$71,399,145	\$66,217,361	\$90,342,101	\$107,835,815	\$117,327,968	\$108,684,932	\$100,797,138
Bevacizumab-awwb	\$14,191,578	\$27,127,443	\$23,044,653	\$28,690,929	\$33,462,323	\$18,977,407	\$36,275,637	\$34,716,056	\$43,221,996	\$50,409,953
Bevacizumab-bvzr	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0	\$0
Total	\$73,540,639	\$97,968,771	\$100,121,727	\$100,090,074	\$99,679,684	\$109,319,508	\$144,111,452	\$152,044,024	\$151,906,929	\$151,207,091
Total annual costs in market with bevacizumab-bvzr										
By indication										
Non-small-cell lung cancer	\$21,509,648	\$28,967,269	\$29,524,999	\$29,465,551	\$29,285,410	\$31,923,149	\$42,480,607	\$44,815,740	\$44,692,657	\$44,391,452
Metastatic renal cell carcinoma	\$458,359	\$710,694	\$795,510	\$830,632	\$842,341	\$680,266	\$1,042,235	\$1,207,498	\$1,259,883	\$1,276,839
Recurrent glioblastoma	\$9,350,172	\$12,123,628	\$12,162,283	\$12,086,696	\$12,001,321	\$13,876,886	\$17,779,344	\$18,461,024	\$18,332,817	\$18,191,860
Cervical cancer	\$191,604	\$257,201	\$261,757	\$261,111	\$259,485	\$284,365	\$377,187	\$397,318	\$396,047	\$393,332
Metastatic colorectal cancer	\$41,937,977	\$55,683,567	\$56,392,865	\$56,175,195	\$55,806,363	\$62,241,478	\$81,660,156	\$85,598,239	\$85,205,218	\$84,592,480
Total	\$73,447,760	\$97,742,359	\$99,137,415	\$98,819,186	\$98,194,920	\$109,006,144	\$143,339,530	\$150,479,819	\$149,886,622	\$148,845,963
By treatment										
Bevacizumab	\$58,319,289	\$68,285,026	\$71,909,858	\$64,683,494	\$58,319,086	\$88,774,565	\$103,944,571	\$109,462,348	\$98,462,260	\$88,774,256
Bevacizumab-awwb	\$13,945,338	\$26,148,552	\$21,499,749	\$25,992,322	\$29,471,004	\$18,648,128	\$34,966,634	\$32,388,706	\$39,156,628	\$44,397,154
Bevacizumab-bvzr	\$1,183,132	\$3,308,781	\$5,727,808	\$8,143,370	\$10,404,830	\$1,583,452	\$4,428,325	\$8,628,765	\$12,267,735	\$15,674,553
Total	\$73,447,760	\$97,742,359	\$99,137,415	\$98,819,186	\$98,194,920	\$109,006,144	\$143,339,530	\$150,479,819	\$149,886,622	\$148,845,963

Table 6 (continued)

	Medicare					Commercial payers				
	Year 1	Year 2	Year 3	Year 4	Year 5	Year 1	Year 2	Year 3	Year 4	Year 5
Incremental annual budget impact										
Cost savings in total, by indication										
Non-small-cell lung cancer	\$27,200	\$67,100	\$293,147	\$378,949	\$442,813	\$91,770	\$228,770	\$465,850	\$602,408	\$704,177
Metastatic renal cell carcinoma	\$580	\$1,646	\$7,898	\$10,683	\$12,737	\$1,956	\$5,613	\$12,552	\$16,982	\$20,254
Recurrent glioblastoma	\$11,824	\$28,083	\$120,756	\$155,444	\$181,467	\$39,892	\$95,747	\$191,898	\$247,106	\$288,575
Cervical cancer	\$242	\$596	\$2,599	\$3,358	\$3,924	\$817	\$2,031	\$4,130	\$5,338	\$6,239
Metastatic colorectal cancer	\$53,033	\$128,987	\$559,912	\$722,455	\$843,825	\$178,928	\$439,762	\$889,775	\$1,148,472	\$1,341,881
Total	\$92,880	\$226,412	\$984,312	\$1,270,889	\$1,484,765	\$313,363	\$771,922	\$1,564,205	\$2,020,307	\$2,361,127
Cost savings in total, by treatment										
Bevacizumab	\$1,029,772	\$2,556,302	\$5,167,216	\$6,715,651	\$7,898,275	\$1,567,536	\$3,891,244	\$7,865,620	\$10,222,673	\$12,022,882
Bevacizumab-awwb	\$246,240	\$978,891	\$1,544,904	\$2,698,608	\$3,991,319	\$329,279	\$1,309,003	\$2,327,350	\$4,065,369	\$6,012,799
Bevacizumab-bvzr	-\$1,183,132	-\$3,308,781	-\$5,727,808	-\$8,143,370	-\$10,404,830	-\$1,583,452	-\$4,428,325	-\$8,628,765	-\$12,267,735	-\$15,674,553
Total	\$92,880	\$226,412	\$984,312	\$1,270,889	\$1,484,765	\$313,363	\$771,922	\$1,564,205	\$2,020,307	\$2,361,127
Cost savings PPPY	\$185	\$335	\$1,389	\$1,770	\$2,053	\$624	\$1,142	\$2,208	\$2,814	\$3,264
Cost savings PPM	\$15	\$28	\$116	\$148	\$171	\$52	\$95	\$184	\$235	\$272
Cost savings PMPY	\$0.009	\$0.023	\$0.097	\$0.125	\$0.145	\$0.031	\$0.077	\$0.154	\$0.198	\$0.230
Cost savings PMPM	\$0.001	\$0.002	\$0.008	\$0.010	\$0.012	\$0.003	\$0.006	\$0.013	\$0.017	\$0.019
Incremental cumulative cost savings over 5 years	\$92,880	\$319,292	\$1,303,604	\$2,574,493	\$4,059,257	\$313,363	\$1,085,286	\$2,649,491	\$4,669,797	\$7,030,924
Incremental cumulative cost savings PMPM over 5 years	\$0.001	\$0.001	\$0.004	\$0.005	\$0.007	\$0.003	\$0.005	\$0.007	\$0.010	\$0.012
Additional number of patients allowed for treatment	1	2	8	11	12	2	4	9	11	13

Table 7 Scenario analyses

Parameter	Base-case settings	Scenario-analysis settings	Cost savings per member per month averaged across a 5-year time horizon (% of changes from base case)		Additional patients treatable with bevacizumab-bvzr averaged across a 5-year time horizon (% of changes from base case)	
			Medicare	Commercial	Medicare	Commercial
Base-case analysis	–	–	\$0.007	\$0.012	7	8
Market scenarios for comparison	Market with bevacizumab-bvzr vs. market without bevacizumab-bvzr	Market with bevacizumab biosimilars vs. market without bevacizumab biosimilar ^a	\$0.05 (+ 614%)	\$0.093 (+ 675%)	50 (+ 614%)	62 (+ 675%)
Average sales price of bevacizumab-bvzr	\$631.8	10% decrease (\$568.6)	\$0.011 (+ 57%)	\$0.018 (+ 50%)	13 (+ 86%)	14 (+ 75%)
		20% decrease (\$505.4)	\$0.016 (+ 129%)	\$0.025 (+ 108%)	20 (+ 186%)	21 (+ 163%)
Uptake of bevacizumab-bvzr over years 1–5	1.7%, 3.6%, 6.7%, 9.4%, and 11.9%	100% increase (3.5%, 7.2%, 13.4%, 18.8% and 23.9%) ^b	\$0.013 (+ 86%)	\$0.023 (+ 92%)	13 (+ 86%)	15 (+ 88%)
		50% decrease (0.9%, 1.8%, 3.4%, 4.7% and 6.0%) ^b	\$0.003 (– 57%)	\$0.006 (– 50%)	3 (– 57%)	4 (– 50%)
Reimbursement markup for a commercial payer	10% relative to ASPs	20% increase in ASP markup (i.e., 12% markup)	Not applicable	\$0.012 (0%)	Not applicable	8 (0%)
		20% decrease in ASP markup (i.e., 8% markup)	Not applicable	\$0.011 (– 8%)	Not applicable	8 (0%)
	75% relative to WACs	20% increase in WAC markup (i.e., 90% markup)	Not applicable	\$0.012 (0%)	Not applicable	8 (0%)
		20% decrease in WAC markup (i.e., 60% markup)	Not applicable	\$0.011 (– 8%)	Not applicable	8 (0%)
Time horizon	5 years	1 year	\$0.001 (– 86%)	\$0.003 (– 75%)	1 (– 86%)	2 (– 75%)
		3 years	\$0.004 (– 43%)	\$0.007 (– 42%)	4 (– 43%)	5 (– 38%)

^aMarket share in the market with bevacizumab biosimilars was the same as that in the market with bevacizumab-bvzr in the base case. In the market without bevacizumab biosimilar, bevacizumab reference product accounted for 100% of the market share

^bIt was assumed that the market shift to bevacizumab-bvzr was proportionally taken from the bevacizumab reference product and bevacizumab-awwb relative to the market share of bevacizumab reference product and bevacizumab-awwb

analysis of switching to biosimilar Trastuzumab (CT-P6) for the treatment of breast cancer and gastric cancer in 28 European countries projected budget savings from a payer's perspective between €0.91 billion and €2.27 billion over a 5-year time horizon, which would allow an additional 3503–7078 patients to be treated with trastuzumab [48]. A study performed in Croatia that estimated the budgetary impact of introducing biosimilar trastuzumab for the treatment of breast cancer also indicated savings ranging from €0.26 million to €0.69 million in the first year after introduction [49]. Another analysis carried out in the EU that evaluated the budgetary impact of the introduction of rituximab biosimilar (CT-P10) in patients with rheumatology and cancer showed projected savings of €90.04 million in the first year, which could convert to treatment opportunities for 6.4% more patients [50]. Grewal et al. conducted a US

case analysis of cost savings for a filgrastim biosimilar. They estimated 5-year cost savings of \$256 million, of which 18% were from reduced patient out-of-pocket costs, 34% were savings for commercial payers, and 48% were savings for Medicare [51].

The net budget impact was sensitive to market uptake rates and the price discount applied to biosimilars. In the filgrastim-sndz (Zarxio) case, which was the first biosimilar launched in the USA, a 30% decrease in overall drug spending on any filgrastim products was seen in the Medicare Part B program following a sharply increased utilization and gradually decreased ASP of the biosimilar, filgrastim-sndz [52]. It was reported that by March 2018, approximately 3 years after its launch, filgrastim-sndz accounted for 47% of filgrastim use among commercially insured and 42% among Medicare Advantage beneficiaries [53]. The price difference

between filgrastim-sndz and its originator was more than 30% [53].

However, several features of the current US healthcare system may hamper biosimilar uptake. First of all, policies on biosimilar reimbursement and insurer coverage can have a strong influence on the potential savings that biosimilars can bring. For biosimilars that are covered under medical benefit and reimbursed using the “buy-and-bill” method, the current reimbursement model set up by commercial payers may disincentivize providers from adopting lower-cost biosimilars. In order to avoid disincentivizing biosimilars in Medicare, CMS reimburses providers at the biosimilar’s ASP plus a markup of 6% of the reference ASP, which equalizes the cost recovery of biosimilars to reference products [30]. However, in 2019, among 17 of the largest US commercial health plans, only 14% granted biosimilars preferred coverage, 33% nonpreferred coverage, and 53% on-par coverage [54]. A lack of preferred coverage among commercial health plans may also explain the slow uptake. Second, oncologists and pharmacists in the USA have inventory management, regulatory, and administrative considerations for biosimilar substitutions [55], such as pharmacovigilance requirements, education, tracking, and product characteristics (e.g., labeling, package, storage and supply chain) [55]. Most states, for example, require that pharmacists notify prescribers and patients of interchangeable biosimilar substitutions [56]. However, notification requirements may compromise the role of pharmacists in driving biosimilar adoption. A survey of 781 members of the Academy of Managed Care Pharmacy and the Hematology/Oncology Pharmacy Association has shown that the biosimilar post-dispense notification requirements may impact willingness of some pharmacists to substitute [57]. FDA guidance on pharmacy-level substitution of reference biologics with biosimilars may help to overcome biosimilar adoption challenges in the USA [58]. In terms of treating physicians, key considerations include (1) how adverse events should be tracked or reported; (2) how they should document if switching occurs over the planned course of treatment; and (3) how to evaluate the financial burden of patients with different health plans that may have different patient cost sharing strategies for biosimilar versus reference products [59]. Hence, there is a crucial need for treating physicians to have a better understanding of biosimilars in order to make informed decisions. Lastly, biosimilars are also facing legal actions, patents, and exclusivity, for which many solutions have been proposed [60].

Also, substantial skepticism among physicians and other key stakeholders relating to the efficacy and safety of biosimilars remains. A survey of a national sample of New Zealand medical specialists has indicated that physicians held generally positive attitudes towards biosimilars, but were less confident in biosimilar indication extrapolation

or switching [61]. In a survey of 300 managed-care and specialty pharmacy professionals, the strategy rated most likely to overcome barriers to biosimilar adaptation was prescriber education about evidence from switching studies [58]. Aside from prescribers, patient education will likely accelerate biosimilar’s integration into clinical practice. In an international survey of 3,198 patients, only 6% of the participants had a basic awareness of biosimilars while the majority did not know what biosimilar medicines were [62]. Patients who were aware of biosimilars were more willing to switch [62]. Hence, patients must be educated to understand the definition of biosimilars and the regulatory process that leads to approval of biosimilar. Particularly, it should be emphasized that clinical equivalence is established through a series of preclinical and clinical trial data. Most importantly, stakeholders should be aware of the potential savings and increased access that biosimilars can bring to biological therapies.

4.1 Limitations

Our study had several limitations. First, the major cost driver between biosimilar and reference product was the difference in ASP or other drug pricing benchmarks alone [63]. However, we did not take into account costs associated with education, formulary management, and additional laboratory tests/procedures. Second, the reimbursement of medical products for commercial payers, a percentage of billed charges was assumed in the present analysis. However, it is worth noting that each commercial payer has their own formulary decisions/coverage for biosimilars. Our results may under- or overestimate the cost savings on an individual plan level. Third, the use of bevacizumab treatment is likely changing given the introduction of innovative targeted therapies and immune-oncology drugs. Fluctuations in the use of bevacizumab treatment will affect our projected savings. Fourth, the epidemiology inputs used to estimate target population were assumed to be the same for commercial payers and Medicare. However, it is acknowledged that the distribution of demographics could vary between a commercially insured population and a Medicare population. Future studies with claims data from specific payers are needed to improve the accuracy of the estimated cost savings. Fifth, given the trial data did not report range of treatment duration, additional scenario analysis may be required with varying treatment durations to assess its impact on the results. Finally, as more bevacizumab biosimilar products enter the US market, the competition may accelerate price decreases for both reference product and biosimilars, which may result in even greater savings. However, the timing of entry and magnitude of price decrease is uncertain.

5 Conclusion

Our budget impact analysis suggested a substantial cost savings from the introduction of the biosimilar bevacizumab-bvzr, primarily driven by the lower cost of bevacizumab-bvzr relative to its reference product, from a US payer perspective. The exact cost-saving estimates may vary depending on a variety of factors such as rebates, biosimilar uptake and price discount relative to the reference product.

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