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ORIGINAL RESEARCH ARTICLE

A Budget Impact and Cost Per Additional Responder Analysis for Baricitinib for the Treatment of Moderate-to-Severe Rheumatoid Arthritis in Patients with an Inadequate Response to Tumor Necrosis Factor Inhibitors in the USA

Elizabeth Wehler[1] · Natalie Boytsov[2] · Claudia Nicolay[3] · Oscar Herrera-Restrepo[4] · Stacey Kowal[4]

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Abstract

Background/Objective Baricitinib is a selective and reversible Janus kinase (JAK) inhibitor indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response to one or more tumor necrosis factor inhibitors (TNFis) and has been shown to improve multiple clinical and patient-reported outcomes. However, it is unclear what the budgetary impact would be for US commercial payers to add baricitinib to their formulary and how the efficacy of baricitinib compares to other disease-modifying antirheumatic drugs (DMARDs) with a similar indication.

Methods A budget impact model (BIM) was developed for a hypothetical population of 1 million plan members that compared a world without and with baricitinib. A retrospective observational study was carried out to estimate market utilization of advanced therapies. Number needed to treat (NNT) and cost per additional responder were calculated for American College of Rheumatology (ACR) 20%/50%/70% improvement criteria (ACR20/50/70) response outcomes combining cost estimates from the BIM and efficacy values from a network meta-analysis (NMA). The model included costs related to drug acquisition and monitoring costs.

Results Adding baricitinib would save a commercial payer $US169,742 for second-line therapy and $US135,471 for third-line therapy over a 2-year time horizon (all costs correspond to 2019 US dollars). Cost savings were driven by baricitinib drawing market share away from more expensive comparators. The NMA, based on nine studies, found no statistically significant differences in the median treatment difference between baricitinib and comparators except for versus a conventional synthetic DMARD (csDMARD), and thus NNT versus a csDMARD was similar. The cost per additional responder for baricitinib in patients with inadequate response to a TNFi was substantially lower than all other treatments for all three ACR response criteria at 12 weeks (ACR20: $US129,672; ACR50: $US237,732; ACR70: $US475,464), and among the lowest at 24 weeks (ACR20: $US167,811; ACR50: $US259,344; ACR70: $US570,557).

Conclusions Baricitinib, compared to other DMARDs, was a less expensive option (− $US0.01 incremental cost per member per month in second- and third-line therapy over a 2-year time horizon) with comparable efficacy in patients with inadequate response to TNFi. Adding baricitinib to formulary would likely be cost saving for US payers and expands treatment options for these patients.

1 Introduction

Rheumatoid arthritis (RA) is a systemic and chronic inflammatory disease of unclear etiology [1]. It leads to a progressive and destructive polyarthritis and is characterized by chronic pain and joint destruction that usually progress from distal to more proximal joints [1]. RA affects approximately 1.3 million people in the USA [2].

In the last decade, management of RA patients has shifted from controlling symptoms to preventing and controlling

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✉ Elizabeth Wehler
beth.wehler@iqvia.com

Extended author information available on the last page of the article

Key Points for Decision Makers

Baricitinib is a less expensive treatment option for rheumatoid arthritis (RA) patients who have had an inadequate response to one or more tumor necrosis factor inhibitors and shows similar efficacy to other treatment options.

The cost per additional responder was lowest for baricitinib at 12 weeks and among the lowest at 24 weeks.

Use of baricitinib could lower RA treatment costs from a healthcare payer perspective and provides an additional treatment option for patients.

damage [3]. With the availability of biologic disease-modifying antirheumatic drugs (bDMARDs), which includes tumor necrosis factor (TNF) inhibitors (TNFis) and non-TNFis, and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), which includes Janus kinase (JAK) inhibitors, treatment guidelines recommend a 'treat-to-target' approach in which the goals of treatment are to target remission or low disease activity and maintain remission [4]. Recommendations suggest patients begin with disease-modifying antirheumatic drug (DMARD) monotherapy, and, should disease activity remain moderate or high, switch to combination traditional DMARDs, or add a TNFi, non-TNF biologic, or tofacitinib [4]. This approach has been shown to lead to better health outcomes and quality of life [3].

Despite the availability of various treatment options and evidence supporting early and aggressive treatment, there are still significant challenges in the current management of patients with RA [4, 5]. For example, many patients have an inadequate response (IR) to their treatment, which can include lack of efficacy and/or treatment intolerance [4, 6]. Barriers to optimizing treatment exist for both patients and physicians, which can delay the use of new treatment options and thus increase the risk of irreversible joint damage. For inadequate responders, dose escalation of TNFis provides minimal clinical benefit and may increase the risk of adverse events (AEs) [7]. Furthermore, when an incomplete response to TNFis occurs, cycling through treatments of the same mechanism of action has been shown to result in diminished treatment response [8–11].

The economic consequences resulting from an IR to treatment are substantial, with several studies reporting that patients who have an IR generate approximately twice the total healthcare costs on average than those who do achieve remission or low disease activity [12–15]. Additionally, dosing escalation for biologics are associated with higher total annualized healthcare expenditures [16–18] and switching to another therapy with a different mechanism of action is likely more cost effective than switching from one TNFi to another TNFi [19].

Baricitinib is an oral selective and reversible JAK inhibitor (categorized as a tsDMARD) indicated for the treatment of adult patients with moderately to severely active RA who have had an IR to one or more TNFis [20]. Baricitinib has been shown to be effective in RA patients who have had an IR to one or more TNFis, other bDMARDs, or both [21], with improvement in multiple clinical measures and patient-reported outcomes and a rapid onset of action as early as 1 week from baseline compared with placebo [6, 22, 23]. The introduction of baricitinib in the US market broadens the availability of RA treatment choices for TNFi-IR patients, thereby potentially alleviating the burdens already described. However, it is unclear what the budgetary impact would be for US payers to add baricitinib within the context of current market dynamics. Nor is it clear what the comparative effectiveness of baricitinib is relative to treatments with a similar indication.

This study provides results from a budget impact model (BIM) that forecasts the fiscal implications of adding baricitinib to a formulary that already includes several treatment options available in the US (i.e., subcutaneous biologics [etanercept, adalimumab, abatacept, golimumab, tocilizumab, certolizumab pegol, and sarilumab] and JAK inhibitors [tofacitinib]). Comparative effectiveness was determined using number needed to treat (NNT) and cost per additional responder, which leveraged treatment costs from the BIM and American College of Rheumatology (ACR) 20%/50%/70% improvement criteria (ACR20/50/70) response outcomes reported from a network meta-analysis (NMA).

2 Methods

2.1 Estimating the Budgetary Consequences of Adding Baricitinib

A BIM was developed to estimate the budgetary consequences of the use of baricitinib for the treatment of TNFi-IR patients from the perspective of a US healthcare commercial payer. The model used a comparative cost determination framework where costs were calculated based on a world without and with baricitinib following modeling best practices [24]. The model was developed using Microsoft Office Excel® (Microsoft Corp., Redmond, WA, USA) to estimate the current evidence-based US costs of treating adult patients with moderately to severely active RA who have had an IR to one or more TNFis, as well as to understand the value of baricitinib in RA.

2.1.1 Target Population

To quantify the target population eligible for baricitinib each year, epidemiologic and claims-based studies were leveraged. The model started with a hypothetical population of 1 million plan members, of which 774,000 (77.4%) were estimated as adults based on 2017 US Census estimates [25]. An annual RA prevalence of 0.53% [2] and incidence of 0.04% [26] were applied to arrive at 4420 RA patients in year 1 and 4737 in year 2. It was assumed that 88.35% of patients were treated with DMARDs [27], and 19.17% of them were treated with TNFis [28]. The model also considered that 47.5% had an IR (ESM Online Resource Table 3) [29].

2.1.2 Market Utilization

A retrospective observational study using data from the Truven Health MarketScan Research data warehouse was conducted to assess market share of advanced therapies in RA by line of therapy, including TNFis (adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab), non-TNFis (abatacept, rituximab, sarilumab, tocilizumab, and anakinra), and JAK inhibitors (tofacitinib). The line of therapy was determined by evaluating the number of advanced therapies prior to the index therapy during a 6-year history. Data retrieval focused on the period from 1 January 2017 to 31 December 2017. Patients included in the analysis were selected based on criteria shown in Fig. 1. After applying the inclusion/exclusion criteria, 20,384 patients were included in the analysis. See Electronic Supplementary Material (ESM) Online Resource Table 1 for patient characteristics of the final sample.

Utilization data stratified by line of therapy were used in the BIM to explore budgetary implications of treatments either by second-line after a conventional synthetic DMARD (csDMARD) (after TNFi use) or third-line after a csDMARD (after TNFi and use of another advanced therapy). Table 1 shows the market utilization data that were used in the BIM. The output from the claims-based study was reweighted to only include the comparators of interest.

To calculate future market utilization, it was assumed that baricitinib would take market shares equi-proportionally from all included market comparators. The market uptake of baricitinib was forecasted by the manufacturer anchored to the market share of tofacitinib at launch (i.e., not current uptake), the other comparator in its class. In addition to the market utilization retrieved from the claims-based study, the BIM also allowed methotrexate to be used as combination therapy. By default, the model assumed that 65% of patients on non-csDMARDs regimens used methotrexate while the remaining 35% received monotherapy [30, 31]. Additionally, the BIM assumed that 88.8% of methotrexate users (used in combination with primary therapy) received methotrexate orally with the remainder receiving intravenous methotrexate. This value was derived from claims data and provided by the manufacturer.

2.1.3 Cost and Resource Use

The model calculated the total annual cost per patient by summing costs related to drug acquisition and monitoring costs (Table 2). All costs correspond to 2019 US dollars. The model assumed all administration was self-administered (subcutaneous or oral treatments) and therefore no administration costs were applied [32–40]. Drug acquisition costs for all treatments were calculated based on drug dosing and unit costs (2019 Wholesale Acquisition Cost) data from Medispan Price Rx [41]. In the base case, rebates were assumed to be zero and patient cost sharing and dispensing fees were not included. Dosing was based on product prescribing information (PI) and accounted for loading doses or altered dosing patterns when patients first initiate therapy as well as dose escalation based on published literature (ESM Online Resource Table 2). Dose escalation was assumed to occur 6 months after treatment initiation and patients were assumed to continue at the escalated dose for the duration of the model [36, 42–45].

Per the ACR RA guidelines and product PIs, patients on RA treatment require safety monitoring, which can be broken into four time periods: baseline, < 3 months, 3–6 months, and 6–12 months. For each timeframe, and for each treatment, a set of required monitoring resources were itemized and unit costs applied. Resource use in the 6- to 12-month range was assumed to apply for the duration of the model. Given limited data availability for the commercial perspective, physician fees and laboratory fees were based on national payment rates per the Centers for Medicare Services (CMS) physician fee schedule and the CMS laboratory fee schedule [46, 47]. A summary of inputs used in the BIM is provided in the ESM Online Resource Tables 3 and 4.

AEs were not included in the model for several reasons. First, AEs have not been found to be significant model drivers in previous RA health technology assessments and have sometimes been excluded given the assumption that there is no difference in the safety profiles of bDMARDs [48]. Second, a previously published BIM in RA excluded AEs due to heterogeneity in AE reporting [49]. Finally, even if AEs were included, the RA-BEACON trial results show that the impact would be low [6].

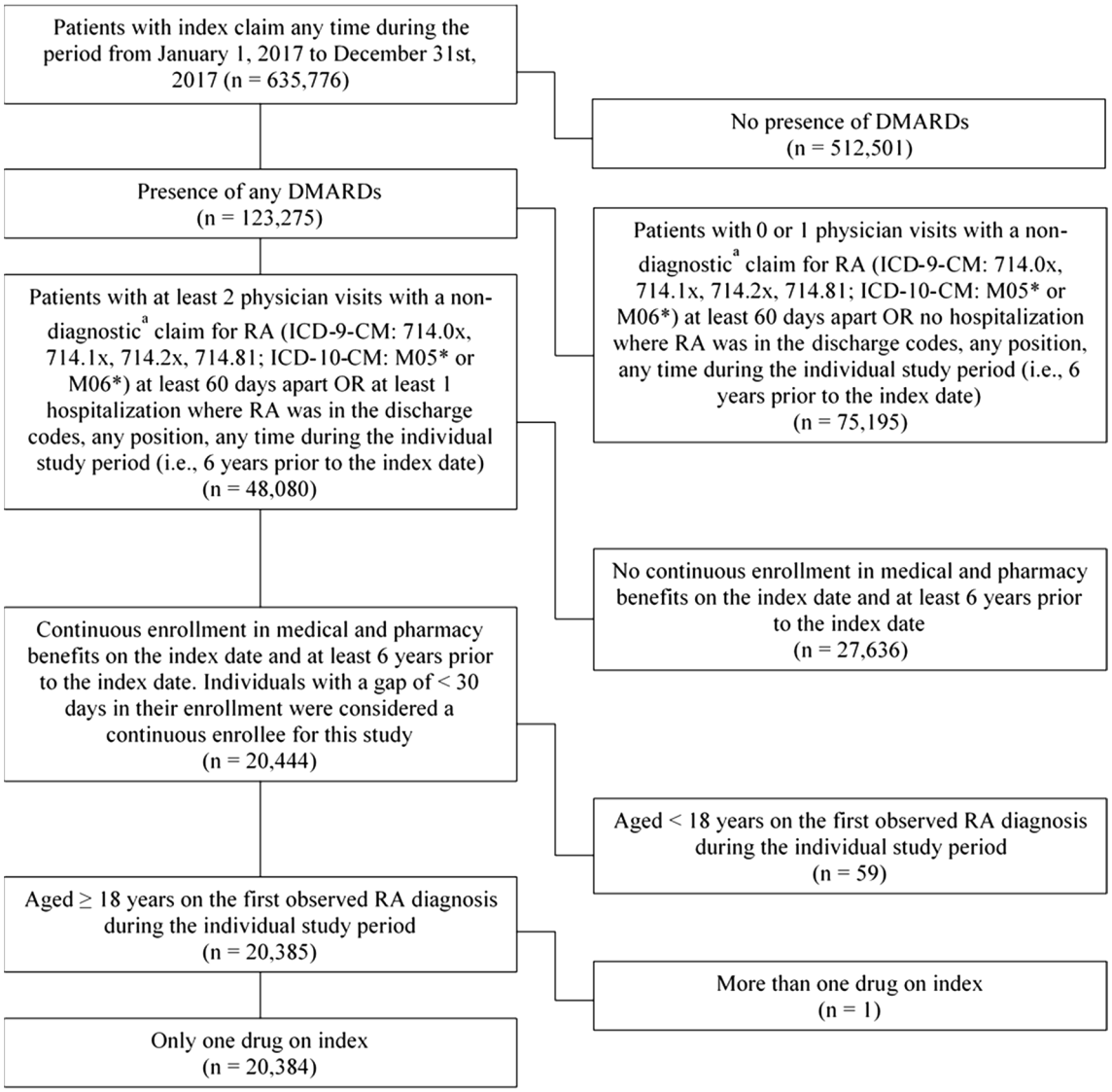


Fig. 1 Claims-based study criteria. [a]Non-diagnostic is a claim that is not for a diagnostic test (laboratory, radiology). *DMARDs* disease-modifying antirheumatic drugs, *ICD-9-CM* International Classification of Diseases, Ninth Revision, Clinical Modification, *ICD-10-CM* International Classification of Diseases, Tenth Revision, Clinical Modification, *RA* rheumatoid arthritis. Asterisk represents any subsequent codes under the particular major code heading

2.2 Response Rates for Number Needed to Treat (NNT) and Cost per Additional Responder: Systematic Literature Review and Network Meta-Analysis

ACR20/50/70 response rates were derived from a systematic literature review (SLR) and NMA. The SLR and NMA aimed to identify and synthesize clinical effectiveness evidence of treatments for the moderate-to-severe TNFi-IR RA patients from randomized controlled trials published between 1999 and December 2017. While the SLR and NMA included a full spectrum of treatments, the NNT and cost per additional responder calculations presented here include only subcutaneous or oral treatments relevant to the USA. Furthermore, safety endpoints were not included as part of the NMA, as most studies allowed the use of rescue therapy for the control arm if a certain treatment response was not observed. In general, safety endpoints are only

Table 1 Estimated market share data from the claims-based study

Treatment option[a]	Second line (%)	Third line (%)
Abatacept	15.5	24.1
Adalimumab	26.7	8.9
Certolizumab pegol	5.4	7.7
Etanercept	21.5	7.9
Golimumab	7.3	9.2
Sarilumab	0.0	0.0
Tocilizumab	8.7	16.6
Tofacitinib	14.9	25.6
Total	100.0	100.0

csDMARD conventional synthetic disease-modifying antirheumatic drug, *TNFi* tumor necrosis factor inhibitor

[a]Utilization data stratified by line of therapy were used in the budget impact model to explore budgetary implications of treatments either by second line after csDMARD (after TNFi use) or third line after csDMARD (after TNFi and use of another advanced therapy)

reported for the whole duration of the study and not at intermediate endpoints, such as week 12. As a result, reporting of, for example, discontinuation and AEs are confounded with the occurrence of rescue therapy. The details of the SLR can be found in ESM Online Resources Tables 5, 6, and Fig. 1. In summary, a total of 10,008 citations were identified after removing duplicates and were screened for inclusion, of which 322 studies were included in the SLR. These 322 studies consisted of a mix of RA populations including csDMARD-naive, csDMARD including methotrexate IR (MTX-IR), MTX-IR, and TNFi-IR patients. Of these, only nine studies included the TNFi-IR population and met the inclusion criteria for the NMA (Table 3) [6, 50–76]. The quality assessment of studies was performed to standards recommended by the National Institute for Health and Care Excellence (NICE) and the Centre for Reviews and Dissemination [77, 78].

The NMA estimated between-treatment differences in ACR20/50/70 response (median difference, 95% credible interval [Cr-Int]). A Bayesian mixed-treatment comparison using a simultaneous model consisting of baseline and treatment effects was conducted as described in the NICE Decision Support Unit (DSU) [79]. Fixed- and random-effect models were fitted. However, random-effect models were unstable and did not converge, and therefore fixed-effects models were chosen as the primary approach. Extensive sensitivity analyses were pre-planned. Given the limited number of studies, only independent baseline models and frequentist models could be performed. The main analyses are presented for the 12- and 24-week timepoints as the median difference in ACR20, ACR50 and ACR70 response rates, and only consider the 2 mg dose of baricitinib, which is the dose approved in the USA. For the NNT and cost per additional responder calculations, results from the probit simultaneous fixed-effects models were used. See Table 4 for a description of the baseline characteristics of the studies included in the NMA and ESM Online Resource Fig. 2 for further details on the NMA results.

2.2.1 NNT and Cost per Additional Responder

NNT and cost per additional responder were calculated for the ACR20/50/70 response at 12 and 24 weeks. The ACR criteria measure response to treatment, defined by both improvement in the number of tender and number of swollen joints, and improvement in three of the following five criteria: patient's global assessment, physician's global assessment, functional ability measure, visual analog pain scale, and erythrocyte sedimentation rate or C-reactive protein [80, 81]. A response of ACR20/50/70 corresponds to a percentage improvement between two timepoints. The treatments in the NNT and cost per additional responder calculations focused only on those products that compete directly with

Table 2 Total annual costs by treatment per patient

Treatment option	Annual costs per patient ($US; 2019 values)					
	Treatment[a]		Monitoring		Total	
	Year 1	Year 2	Year 1	Year 2	Year 1	Year 2
Abatacept	57,256	57,256	229	94	57,485	57,349
Adalimumab	72,768	72,768	260	128	73,027	72,896
Baricitinib	28,110	28,110	240	94	28,350	28,204
Certolizumab pegol	65,242	56,587	292	128	65,534	56,715
Etanercept	72,767	72,767	260	128	73,027	72,895
Golimumab	62,848	62,848	260	128	63,107	62,976
Sarilumab	86,735	86,735	255	123	86,990	86,859
Tocilizumab	26,918	27,902	255	123	27,173	28,026
Tofacitinib	58,579	58,579	240	94	58,818	58,672

[a]The annual costs presented here assume 88.8% methotrexate use in combination with the primary therapy based on manufacturer data from a claims analysis

Table 3 Studies included in the NMA: inclusion criteria and disease severity

Study	Inclusion criteria	Details of disease severity/activity
ATTAIN [51, 52]	Met the ACR criteria for RA. Were at least 18 years of age. Had had RA for at least 1 year. Had an IR to anti-TNF-α therapy with ETN, IFX, or both at the approved dose after at least 3 months of treatment	Moderate to severe RA: ≥ 10 swollen joints and ≥ 12 tender joints
BREVACTA [53, 54]	≥ 18 years of age with RA for ≥ 6 months. Swollen joint count ≥ 6. Tender joint count ≥ 8. Radiographic evidence of ≥ 1 joint(s) with a definite erosion attributable to RA at screening. A CRP level ≥ 10 mg/L, and/or ESR ≥ 28 mm/h at screening. An IR to ≥ 1 DMARDs that, in up to 20% of patients, could include ≥ 1 anti-TNF agents. Patients must have received ≥ 1 traditional DMARD(s) at a stable dose for ≥ 8 weeks prior to baseline. Prior to randomization, patients had to have discontinued ETN for ≥ 2 weeks; IFX, CZP, GOL, ABA, or ADA for ≥ 8 weeks, and ANA for ≥ 1 week. Concomitant oral glucocorticoids and NSAIDs were permitted if patients had a stable dose regimen ≥ 4 weeks prior to baseline	Moderate to severe: SJC ≥ 6 (66-joint count), TJC ≥ 8 (68-joint count), radiographic evidence of ≥ 1 joint(s) with a definite erosion attributable to RA, and a CRP level ≥ 10 mg/L and/or ESR ≥ 28 mm/h
GO-AFTER [55]	Aged ≥ 18 years. Had been diagnosed with active RA according to the criteria of the ACR at least 3 months before screening. Patients must have been treated with at least 1 dose of a TNF-α inhibitor, the last dose of which must have been given at least 8 or 12 weeks before the first dose of the study drug. Previous treatment with the TNF-α inhibitor could have been discontinued for any reason. Investigators were asked to categorize the reasons for discontinuation as lack of effectiveness, intolerance, or other. A text box was available for the investigator to specify if other was selected: inconvenience and accessibility issues were the most common entries in the text box	Active RA: persistent disease activity with ≥ 4 swollen and 4 tender joints
ORAL STEP [56, 57]	Aged ≥ 18 years with active moderate-to-severe RA based on ACR. Previous IR or intolerance to ≥ 1 approved TNF inhibitor. Have taken oral or parenteral MTX continuously for ≥ 4 months before the first study dose and be on a stable dose of 7.5–25 mg/week for ≥ 6 weeks before the first study dose	Established, moderate-to-severe RA and active disease. Active disease was defined as ≥ 6 tender or painful joints (of 68-joint count) and ≥ 6 swollen joints (of 66-joint count) and either ESR (Westergren method) > 28 mm/h or CRP of > 66–67 nmol/L (7 mg/L)
RA-BEACON [6, 58–61]	Inadequate response or intolerance to ≥ 1 prior TNF inhibitor, ≥ 28 days since last bDMARD; 6 months for rituximab, stable background cDMARD, ≥ 6/68 tender joints, ≥ 6/66 swollen joints, hsCRP ≥ 3 mg/L, stable doses of conventional synthetic DMARDs, NSAIDs, analgesics, or glucocorticoids (≤ 10 mg of prednisone or the equivalent per day)	Moderate-to-severe RA defined as TJC and SJC ≥ 6 and hsCRP ≥ 3.6 mg/L
RADIATE [62–64]	≥ 18 years with moderate-to-severe active RA for and ≥ 6 months, SJC ≥ 6, TJC ≥ 8, and CRP > 1.0 mg/dL or ESR > 28 mm/h at baseline with failure to respond or intolerance to ≥ 1 TNF antagonist(s) within the past year. Patients had to be treated with MTX for ≥ 12 weeks before baseline (stable dose ≥ 8 weeks)	Moderate-to-severe active RA for ≥ 6 months, SJC ≥ 6, TJC ≥ 8, and CRP > 1.0 mg/dL or ESR > 28 mm/h

Table 3 (continued)

Study	Inclusion criteria	Details of disease severity/activity
REALISTIC [65, 66]	≥ 18 years, with adult-onset RA as defined by the 1987 ACR criteria for at least 3 months and showed an unsatisfactory response or intolerance to at least one DMARD (MTX, LEF, SSZ, chloroquine or HCQ, AZA, and/or gold). Subjects had active disease as defined by at least 5 tender and ≥ 4 swollen joints (28-joint count) and either CRP ≥ 10 mg/L or ESR ≥ 28 mm/h (Westergren method) at screening. ETN and ANA should have been discontinued at least 1 month before study entry, and other biologic RA therapies within 2 months of study entry	Active RA defined by ≥ 5 tender and ≥ 4 swollen joints (28-joint count) and either CRP ≥ 10 mg/L or ESR ≥ 28 mm/h (Westergren method) at screening
REFLEX [67–69]	Adult patients with RA for at least 6 months, according to the ACR 1987 revised criteria, and had active disease, which was defined as ≥ 8 swollen joints (of 66 joints assessed) and ≥ 8 tender joints (of 68 joints assessed), a CRP level ≥ 1.5 mg/dL or an ESR ≥ 28 mm/h, and radiographic evidence of at least 1 joint with a definite erosion attributable to RA, as determined by a central reading site (a centralized organization independent of the sponsors that provided blinded radiographic assessments). Eligible patients had to be taking MTX (10–25 mg/week) for at least 12 weeks prior to screening, with the last 4 weeks at a stable dosage	Active RA defined as ≥ 8 swollen joints (of 66) and ≥ 8 tender joints (of 68), CRP level ≥ 1.5 mg/dL or ESR ≥ 28 mm/h, radiographic evidence of ≥ 1 joint with a definite erosion attributable to RA, as determined by a central reading site
TARGET [50, 70–76]	Adults with active, moderate-to-severe RA (SJC ≥ 6/66, TJC ≥ 8/68, hsCRP ≥ 8 mg/L), disease duration ≥ 6 months, inadequate response or intolerance to ≥ 1 TNF inhibitors, and continuous treatment with standard doses of 1 or a combination of background cDMARD(s)	Active, moderate-to-severe RA, defined as SJC ≥ 6/66, TJC ≥ 8/68, and hsCRP ≥ 8 mg/L

ABA abatacept, *ADA* adalimumab, *ACR* American College of Rheumatology, *ANA* anakinra, *ATTAIN* Abatacept Trial in Treatment of Anti-TNF INadequate responders, *AZA* azathioprine, *bDMARD* biologic disease-modifying antirheumatic drug, *cDMARD* conventional disease-modifying antirheumatic drug, *CRP* C-reactive protein, *CZP* certolizumab pegol, *DMARD* disease-modifying antirheumatic drug, *ESR* erythrocyte sedimentation rate, *ETN* etanercept, *GO-AFTER* GOlimumab After Former antitumour necrosis factor α Therapy Evaluated in Rheumatoid arthritis, *GOL* golimumab, *HCQ* hydroxychloroquine, *hsCRP* high-sensitivity C-reactive protein, *IFX* infliximab, *IR* inadequate response, *LEF* leflunomide, *MTX* methotrexate, *NSAID* non-steroidal anti-inflammatory drug, *ORAL Oral Rheumatoid Arthritis triaL, RA* rheumatoid arthritis, *RADIATE* RheumAtoiD ArthrItis study in Anti-TNF failurEs, *REALISTIC* RA EvALuation In Subjects receiving TNF Inhibitor Certolizumab pegol, *SJC* swollen joint count, *SSZ* sulfasalazine, *TJC* tender joint count, *TNF* tumor necrosis factor

baricitinib and are listed in Table 5. Note that for some comparators only either 12- or 24- week trial endpoints were available for the NMA.

The NNT was calculated as the inverse of the difference in response rate between each treatment and csDMARD at 12 and 24 weeks (i.e., 1/[Intervention − csDMARD]). Cost per additional responder was calculated as the first-year cost of each treatment, as derived from the BIM, multiplied by the NNT versus csDMARD. The first-year costs assumed all patients on each treatment were also taking methotrexate to match the clinical data used in the NMA.

2.3 BIM Base-Case and Sensitivity Analyses

The BIM considered two base-case scenarios as derived from the claims-based study market utilization: Base Case 1—market share for second-line therapy after csDMARD; and Base Case 2—market share for third-line therapy after a csDMARD. Since baricitinib can be used for patients who have an IR to one or more TNFis, it can be used across multiple lines of downstream treatment. For each scenario, the model calculated total costs, cost per member per month (PMPM), cost per member per year, cost per patient per month, and cost per patient per year over a 2-year time horizon.

A one-way sensitivity analysis was conducted for all parameters, including inputs for market adoption, epidemiology, dose escalation, and administration. These variables were varied by 20% iteratively. In addition, a scenario with updated 2018 Early View MarketScan data for populating market shares was considered.

All analyses were from the US commercial healthcare payer perspective.

3 Results

3.1 Budget Impact Analysis Results: Base Case

Based on the population cascade estimates, 356 patients were eligible for baricitinib in year 1 and 381 patients were eligible in year 2, an increase of 25 due to the inclusion of incident patients in year 2. Given the projected market share of baricitinib (0.2% in year 1, 1.1% in year 2), the number of baricitinib-treated patients in each year was relatively low, with one and four patients in a hypothetical 1 million-member plan, respectively. The addition of baricitinib for the treatment of moderate-to-severe RA for patients with an IR to TNFi therapy would be cost saving to the commercial payer (net budget impact: − $US169,742 [− 0.37%] for second-line therapy after a csDMARD and − $US135,471 [− 0.33%] for third-line therapy after a csDMARD; Table 6). The cost saving result in both the second-line and third-line was driven by baricitinib drawing market shares away from more expensive comparators. Third-line market shares produced slightly lower cost savings than second-line market shares as patients were assumed to have higher use of inexpensive therapies with less use of products such as adalimumab and etanercept. Nonetheless, both scenario results showed that shifting to a less expensive therapy option (baricitinib) produced cost savings.

3.2 NNT and Cost per Additional Responder

The NMA found that there were no statistically significant differences in ACR response median treatment differences between baricitinib and the other comparators included in this analysis at weeks 12 and 24 except for versus csDMARD (see Fig. 2).

Table 5 presents the NNT versus csDMARD and cost per additional responder per treatment. The NNT was lowest overall for ACR20 than for ACR50 and ACR70, which reflects the declining response rate with an increasing threshold for response. At 12 weeks, the NNT did not differ considerably within each response criteria, ranging from 3.9 to 5.3 for ACR20, 6.3 to 10.0 for ACR50, and 12.5 to 20.0 for ACR70. Similarly, at 24 weeks the NNT did not differ considerably for ACR20 (range of 3.3–5.9) and ACR50 (range of 4.8–9.1), although for ACR70 there was a wider range of NNT values (9.1–20.0). Given that the median treatment difference was not statistically significantly different for baricitinib versus other comparators (except for a csDMARD), NNT point estimates within each response criteria should be interpreted cautiously. Use of the 95% Cr-Ints in scenarios to test model sensitivity produced similar trends.

At 12 weeks, the cost per additional responder for baricitinib was substantially lower than for all other treatments for all ACR response criteria. At 24 weeks, tocilizumab had the lowest cost per additional responder followed by baricitinib for ACR20 and ACR50. For ACR70 at 24 weeks, tocilizumab and abatacept had the lowest cost per additional responder followed by baricitinib. Tocilizumab and baricitinib produced the low costs per additional responder due to their relatively low price.

3.3 Sensitivity Analysis

Sensitivity analyses revealed that the most influential variables across the results were epidemiological inputs including plan size, percentage adults (target population), percentage treated with DMARDs, percentage treated with first TNFi, and the percentage of patients with TNFi-IR (see Fig. 3 in the ESM Online Resource). However, the model results

Table 4 Studies included in the network meta-analysis: baseline characteristics

Study	Treatment (number randomized)	Naïve	bDMARD naïve	Males (%)	Age (years) [mean (SD)]	RF positive [*n*/*N* (%)]	CDAI [mean (SD)]	SDAI [mean (SD)]	ACR [mean (SD)]	DAS [mean (SD)]
ATTAIN [51, 52]	ABA 10 mg/kg (*n* = 256)	No	No	22.9	53.40 (12.40)	73.3	NR	NR	NR	DAS-28 ESR = 6.50 (0.90)
	PBO (*n* = 133)	No	No	20.3	52.70 (11.30)	72.9	NR	NR	NR	DAS-28 ESR = 6.50 (0.80)
BREVACTA[a] [53, 54]	TCZ 162 mg Q2 W (*n* = 437)	No	Mixed	14.2	52.10 (11.45)	349/432 (80.80)	NR	NR	NR	DAS-28 ESR = 6.70 (0.92)
	PBO (*n* = 219)	No	Mixed	17.4	52.00 (11.71)	178/218 (81.70)	NR	NR	NR	DAS-28 ESR = 6.60 (0.94)
GO-AFTER[b] [55]	GOL 50 mg Q4 W (*n* = 153)	Unclear	No	26	Median = 55.00 (12.59)	108/149 (72.00)	NR	NR	NR	Median DAS-28 = 6.30 (1.19)
	PBO (*n* = 155)	Unclear	No	15	Median = 54.00 (13.33)	110/151 (73.00)	NR	NR	NR	Median DAS-28 = 6.30 (1.19)
ORAL STEP[c] [56, 57]	TOFA 5 mg BID (*n* = 133)	No	No	15.04	55.40 (11.50)	80/132 (60.61)	NR	NR	NR	DAS-28 ESR = 6.50 (1.10) DAS-28 CRP = 5.40 (1.00)
	TOFA 10 mg BID (*n* = 134)	No	No	13.43	55.10 (11.30)	83/134 (61.94)	NR	NR	NR	DAS-28 ESR = 6.40 (0.90) DAS-28 CRP = 5.30 (0.90)
	MTX QW (*n* = 132)	No	No	19.7	54.40 (11.30)	86/131 (65.65)	NR	NR	NR	DAS-28 ESR = 6.40 (1.10) DAS-28 CRP = 5.40 (1.00)
RA-BEACON [6, 58–61]	BARI 2 mg QD (*n* = 174)	No	No	21.3	55.10 (11.10)	128/174 (73.90)	42.62 (13.08)	44.62 (13.75)	NR	DAS-28 ESR = 6.70 (0.98) DAS-28 CRP = 5.89 (0.94)
	BARI 4 mg QD (*n* = 177)	No	No	15.8	55.90 (11.30)	128/177 (72.30)	40.30 (13.65)	42.28 (14.40)	NR	DAS-28 ESR = 6.58 (1.06) DAS-28 CRP = 5.87 (1.00)
	PBO (*n* = 176)	No	No	17.6	56.00 (10.70)	130/176 (73.90)	40.62 (12.85)	42.65 (13.75)	NR	DAS-28 ESR = 6.59 (0.93) DAS-28 CRP = 5.89 (0.94)

Table 4 (continued)

Study	Treatment (number randomized)	Naïve	bDMARD naïve	Males (%)	Age (years) [mean (SD)]	RF positive [*n*/*N* (%)]	CDAI [mean (SD)]	SDAI [mean (SD)]	ACR [mean (SD)]	DAS [mean (SD)]
RADIATE [62–64]	TCZ 8 mg/kg + MTX (*n* = 175)	No	No	16	53.90 (12.70)	134/170 (79.00)	NR	NR	NR	DAS-28 = 6.79 (0.93)
	MTX 10–25 mg QW (*n* = 160)	No	No	21	53.40 (13.30)	119/158 (75.00)	NR	NR	NR	DAS-28 = 6.80 (1.06)
REALISTIC[d] [65, 66]	CZP 400–200 mg QOW (*n* = 851)	No	Unclear	22.4	55.40 (12.40)	555/851 (73.90)	NR	NR	NR	DAS-28 ESR = 6.40 (0.90) DAS-28 CRP = 5.70 (0.90)
	MTX QW (*n* = 212)	No	Unclear	20.3	53.90 (12.70)	137/212 (76.50)	NR	NR	NR	DAS-28 ESR = 6.40 (0.90) DAS-28 CRP = 5.70 (0.90)
REFLEX [67–69]	MTX 10–25 mg QW (*n* = 209)	No	No	19	52.80 (12.60)	165/209 (79.00)	NR	NR	NR	DAS-28 = 6.80 (1.00)
	RTX 1000 mg + MTX (*n* = 311)	No	No	19	52.20 (12.20)	242/308 (79.00)	NR	NR	NR	DAS-28 = 6.90 (1.00)
TARGET [50, 70–76]	SARI 150 mg QOW (*n* = 181)	No	No	21.5	54.00 (11.70)	135/181 (74.60)	NR	NR	NR	DAS-28 CRP = 6.10 (0.90)
	SARI 200 mg QOW (*n* = 184)	No	No	17.9	52.90 (12.90)	132/184 (72.90)	NR	NR	NR	DAS-28 CRP = 6.30 (1.00)
	PBO + cDMARDs (*n* = 181)	No	No	14.9	51.90 (12.40)	142/181 (78.90)	NR	NR	NR	DAS-28 CRP = 6.20 (0.90)

ABA abatacept, *ACR* American College of Rheumatology, *ATTAIN* Abatacept Trial in Treatment of Anti-TNF INadequate responders, *BARI* baricitinib, *bDMARD* biologic disease-modifying antirheumatic drug, *BID* twice daily, *CDAI* Clinical Disease Activity Index, *cDMARD* conventional disease-modifying antirheumatic drug, *CRP* C-reactive protein, *CZP* certolizumab pegol, *DAS* Disease Activity Score, *DAS-28* Disease Activity Score in 28 joints, *ESR* erythrocyte sedimentation rate, *GO-AFTER* GOlimumab After Former antitumour necrosis factor α Therapy Evaluated in Rheumatoid arthritis, *GOL* golimumab, *MTX* methotrexate, *n* number, *N* total number, *NR* not reported, *ORAL* Oral Rheumatoid Arthritis triaL, *PBO* placebo, *Q2 W* every 2 weeks, *Q4 W* every 4 weeks, *QD* once daily, *QOW* every other week, *QW* weekly, *RADIATE* RheumAtoiD ArthrItis study in Anti-TNF failurEs, *REALISTIC* RA EvALuation In Subjects receiving TNF Inhibitor Certolizumab pegol, *RF* rheumatoid factor, *RTX* rituximab, *SARI* sarilumab, *SD* standard deviation, *SDAI* Simplified Disease Activity Index, *TCZ* tocilizumab, *TNFi-IR* tumor necrosis factor inhibitor inadequate response, *TOFA* tofacitinib

[a]Only results from the subgroup of BREVACTA patients that were TNFi-IR are used in the analysis

[b]Approximately 30% of patients did not have concomitant cDMARD

[c]Results at week 24 were excluded from the analysis due to a disconnect in the network. This was because of the PBO patients all switching to active drug at/after 12 weeks. This leaves only the two TOFA arms, which are then disconnected from the network

[d]Only results from the subgroup of REALISTIC patients that were TNFi-IR are used in the analysis

Table 5 Number needed to treat and cost ($US; 2019 values) per additional responder

Treatment option	Annual cost ($US)[a]	12 weeks			24 weeks		
		Response rate (%)[b]	NNT vs. csDMARD	Cost per additional responder ($US)	Response rate (%)[b]	NNT vs. csDMARD	Cost per additional responder ($US)
ACR20							
Abatacept	57,663	49.0	3.85	221,782	49.0	3.45	198,839
Adalimumab	73,205	NR	N/A	N/A	NR	N/A	N/A
Baricitinib	28,528	45.0	4.55	129,672	37.0	5.88	167,811
Certolizumab pegol	65,711	42.0	5.26	345,849	NR	N/A	N/A
Etanercept	73,205	NR	N/A	N/A	NR	N/A	N/A
Golimumab	63,285	43.0	5.00	316,426	41.0	4.76	301,358
Sarilumab	87,168	49.0	3.85	335,262	44.0	4.17	363,200
Tocilizumab	27,350	NR	N/A	N/A	50.0	3.33	91,168
Tofacitinib	58,996	46.0	4.35	256,506	NR	N/A	N/A
csDMARD	N/A	23.0	N/A	N/A	20.0	N/A	N/A
ACR50							
Abatacept	57,663	24.0	6.25	360,395	27.0	5.00	288,316
Adalimumab	73,205	NR	N/A	N/A	NR	N/A	N/A
Baricitinib	28,528	20.0	8.33	237,732	18.0	9.09	259,344
Certolizumab pegol	65,711	18.0	10.00	657,114	NR	N/A	N/A
Etanercept	73,205	NR	N/A	N/A	NR	N/A	N/A
Golimumab	63,285	19.0	9.09	575,319	20.0	7.69	486,809
Sarilumab	87,168	24.0	6.25	544,800	23.0	6.25	544,800
Tocilizumab	27,350	NR	N/A	N/A	28.0	4.76	130,240
Tofacitinib	58,996	21.0	7.69	453,818	NR	N/A	N/A
csDMARD	N/A	8.0	N/A	N/A	7.0	N/A	N/A
ACR70							
Abatacept	57,663	10.0	12.50	720,790	13.0	9.09	524,211
Adalimumab	73,205	NR	N/A	N/A	NR	N/A	N/A
Baricitinib	28,528	8.0	16.67	475,464	7.0	20.00	570,557
Certolizumab pegol	65,711	7.0	20.00	1,314,228	NR	N/A	N/A
Etanercept	73,205	NR	N/A	N/A	NR	N/A	N/A
Golimumab	63,285	7.0	20.00	1,265,703	9.0	14.29	904,073
Sarilumab	87,168	10.0	12.50	1,089,601	10.0	12.50	1,089,601
Tocilizumab	27,350	NR	N/A	N/A	13.0	9.09	248,641
Tofacitinib	58,996	9.0	14.29	842,805	NR	N/A	N/A
csDMARD	N/A	2.0	N/A	N/A	2.0	N/A	N/A

ACR American College of Rheumatology, *ACR20/50/70* American College of Rheumatology 20%/50%/70% improvement criteria, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *N/A* not applicable, *NMA* network meta-analysis, *NNT* number needed to treat, *NR* not reported

[a]The annual costs presented here assume 100% methotrexate use in combination with the primary therapy

[b]Median ACR response rate estimated from the NMA (simultaneous fixed-effects, probit model)

remained robust across all one-way sensitivity analyses, as total cost and incremental PMPM values remained negative (cost saving). When considering updated 2018 real-world market shares, results trends remained similar.

4 Discussion

The results of this study illustrate that baricitinib is a cost-saving treatment option for US payers. The efficacy of baricitinib was comparable to other subcutaneous biologics (abatacept, golimumab, tocilizumab, certolizumab pegol, and sarilumab) and tofacitinib (JAK inhibitor) and is less

Table 6 Budget impact model results

Model result	Base Case 1: second-line after csDMARD ($US)			Base Case 2: third-line after csDMARD		
	Year 1	Year 2	Year 1–2	Year 1	Year 2	Year 1–2
Overall cost to plan	− 24,688	− 145,053	− 169,742	− 19,718	− 115,753	− 135,471
PMPM	0.00	− 0.01	− 0.01	0.00	− 0.01	− 0.01
PMPY	− 0.02	− 0.15	− 0.08	− 0.02	− 0.12	− 0.07
PPPM	− 6	− 32	− 19	− 5	− 25	− 15
PPPY	− 69	− 380	− 230	− 55	− 304	− 184

All costs correspond to 2019 US dollars

csDMARD conventional synthetic disease-modifying antirheumatic drug, *PMPM* per member per month, *PMPY* per member per year, *PPPM* per patient per month, *PPPY* per patient per year

expensive. Given comparable response rates across TNFis, JAKs, and non-TNFis, NNT values versus csDMARD were also similar across treatments. Baricitinib had the lowest cost per additional responder across all three ACR criteria at 12 weeks due to its comparable efficacy and low relative cost. At 24 weeks, baricitinib was second to tocilizumab for ACR20 and ACR50, and third to tocilizumab and abatacept for ACR70. Efficacy differences between baricitinib and tocilizumab are likely explained by differences in the underlying study populations and should be interpreted with caution. Tocilizumab reported a better response rate than baricitinib, although this may be due to differences in the study population. The patient population in the baricitinib trial had a longer duration of disease (14 years vs. 11.1 years for tocilizumab), higher proportion on prior non-TNFi (40% vs. 0% for tocilizumab), and a higher proportion on more than three biologics than the other trials included in the NMA (29% vs. value not reported for tocilizumab) [6, 53].

The NMA results are consistent with prior NMAs conducted in the TNFi-IR population, published before the availability of baricitinib, in that they also showed comparable efficacy across bDMARDs and tocilizumab [82–84]. A more recent NMA that included baricitinib 4 mg (the approved dose in the European Union [85]), which was conducted as part of a technology appraisal guidance by NICE [48], also drew similar conclusions about comparable efficacy [86]. In that NMA, tocilizumab plus csDMARDs also showed better response rates than all other treatments (using the European League Against Rheumatism [EULAR] response criteria), although clinical experts highlighted that the tocilizumab trial had different characteristics than the trials for the other treatments and deemed tocilizumab to have similar efficacy to other bDMARDs [48].

Two prior BIMs related to the TNFi-IR population were published before the availability of baricitinib. The first BIM estimated the 5-year budget impact of sarilumab to US healthcare commercial payers by considering a patient population with moderate-to-severe RA and IR to csDMARDs or TNFis [49]. Overall, the analysis found that sarilumab was cost saving with a lower treatment cost and consistent dosing. The analysis highlighted the need for lower cost options in RA and the importance of considering claims-based analyses to understand real-world trends. While the second BIM was not directly comparable to the one presented here given differences in structure and purpose, the results are still relevant and insightful. In 2018, Claxton et al. [87] (an update of Claxton et al. [88]) investigated the economic impact of treatment cycling with DMARDs versus using a JAK inhibitor (tofacitinib) directly following methotrexate, or after methotrexate and one or two previous TNFis. The authors report that tofacitinib directly following methotrexate was associated with the lowest total 2-year costs, PMPM costs, and costs per ACR20/50 responder versus adalimumab and etanercept. Their study supports the notion that switching to another therapy with a different mechanism of action is potentially more cost saving than switching from one TNFi to another TNFi.

This study had several limitations that should be considered when interpreting the results. First, for the BIM, there was a lack of data on the number of patients who were csDMARD IRs among treated patients with moderate-to-severe RA. This value was derived from a retrospective analysis of the Corrona Rheumatoid Arthritis Disease Registry and was calculated as those with worsening or sustained moderate to high disease activity among those who initiated TNFis in the index period. This value was included in a one-way sensitivity analysis and did not impact trends. Second, current market share data are based on an analysis using commercial claims data, which tends to under-represent the 65 + population and may not fully represent the csDMARD-IR population. Although the Truven Health MarketScan Research data are a limited sample, they do cover the entire US population, allowing for greater generalizability to the USA as opposed to using site-specific or regional data. Third, the BIM calculated drug acquisition costs based on assumptions on dosing and dose escalation. While dose escalation occurs on a per-patient basis, the model sought to capture these changes on overall costs over time using the best available

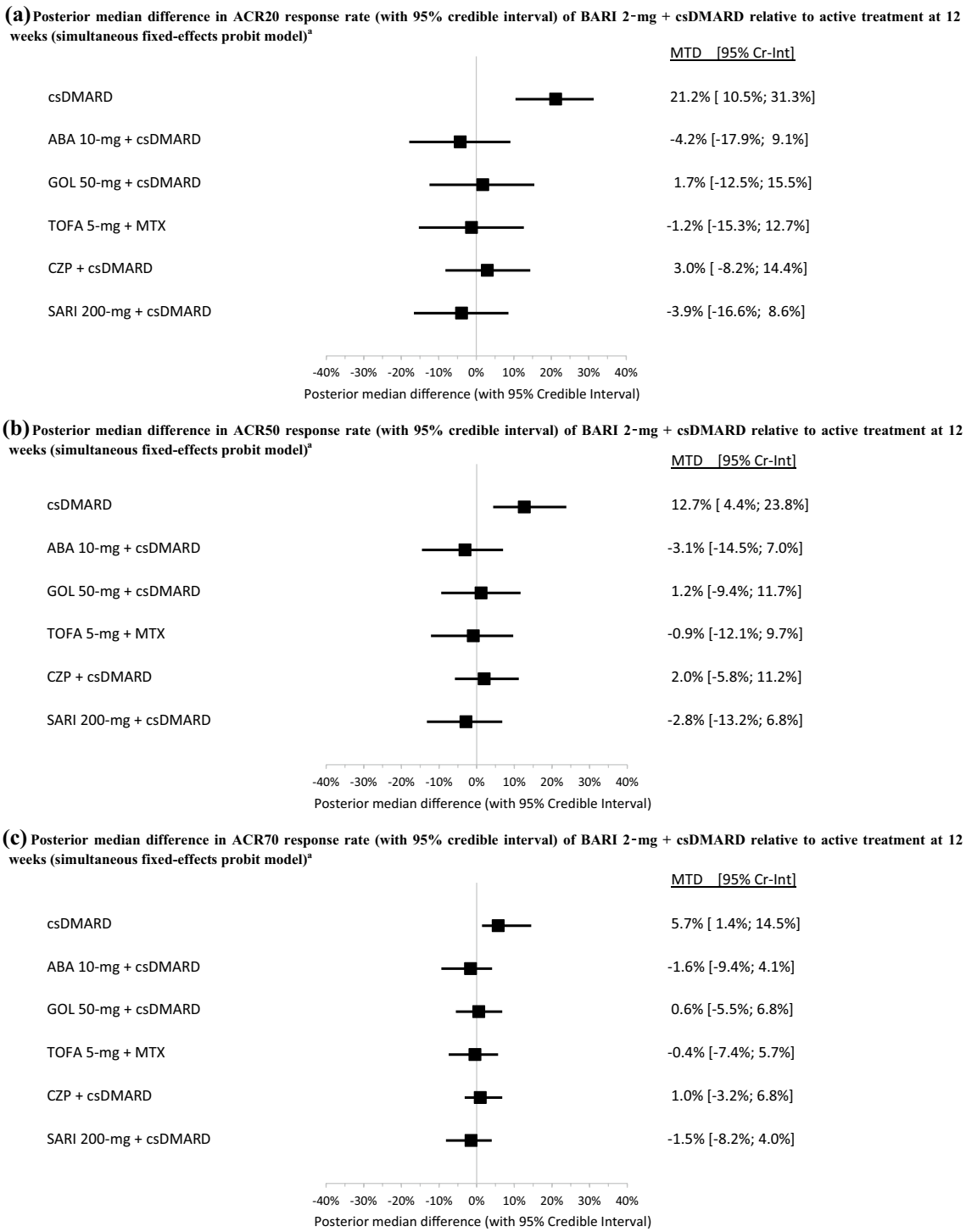
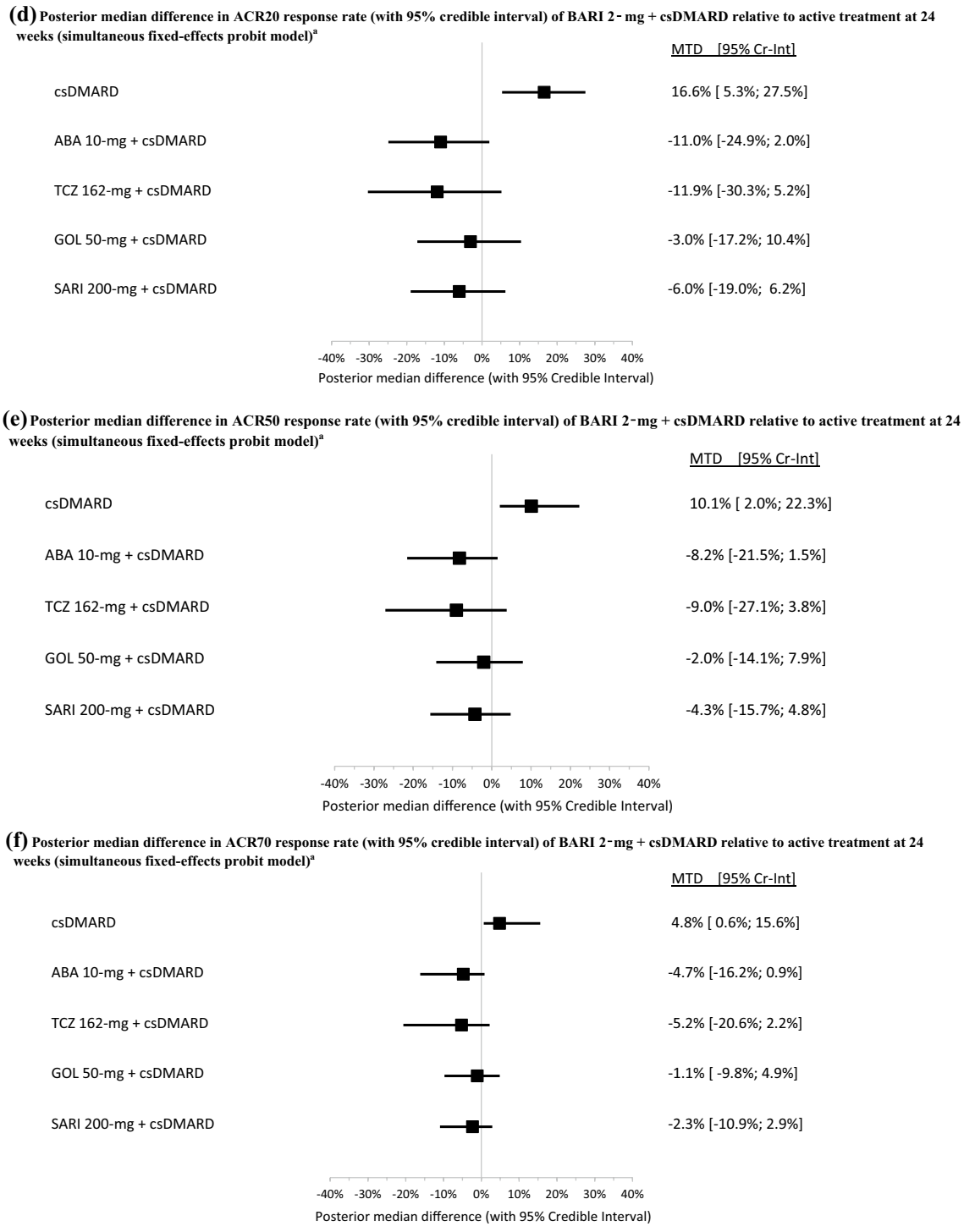


Fig. 2 ACR forest plots. **a** Posterior median difference in ACR20 (**a**), ACR50 (**b**), and ACR70 (**c**) response rate (with 95% cr-Int) of BARI 2 mg + csDMARD relative to active treatment at 12 weeks (simultaneous fixed-effects probit model) and Posterior median difference in ACR20 (**d**), ACR50 (**e**), and ACR70 (**f**) response rate (with 95% cr-Int) of BARI 2 mg + csDMARD relative to active treatment at 24 weeks (simultaneous fixed-effects probit model). Differences > 0 are in favor of BARI 2 mg + csDMARD, with the graph quantifying the median difference in ACR response in % for BARI 2 mg + csDMARD relative to each comparator. *ABA* abatacept, *ACR* American College of Rheumatology, *ACR20/50/70* American College of Rheumatology 20%/50%/70% improvement criteria, *BARI* baricitinib, *Cr-Int* credible interval, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *CZP* certolizumab pegol, *GOL* golimumab, *MTD* median treatment difference, *TCZ* tocilizumab, *TOFA* tofacitinib, *SARI* sarilumab



[a]Differences >0 are in favor of BARI 2-mg + csDMARD, with the graph quantifying the median difference in ACR response in % for BARI 2-mg + csDMARD relative to each comparator.

ABA: abatacept; ACR: American College of Rheumatology; BARI: baricitinib; csDMARD: conventional synthetic disease-modifying antirheumatic drug; Cr-Int: credible interval; CZP: certolizumab pegol; GOL: golimumab; MTD: median treatment difference; TCZ: tocilizumab; TNFi: tumor necrosis factor inhibitor; TOFA: tofacitinib; SARI: sarilumab

Fig. 2 (continued)

evidence from the literature. Finally, for the NMA, cross-study heterogeneity and the small number of studies on clinical performance limit the ability to draw clear conclusions. Testing the effect of heterogeneity and for overall robustness though planned sensitivity analyses was not feasible due to the sparseness of the data.

5 Conclusion

Baricitinib, compared with tsDMARDs and bDMARDs in the TNFi-IR population in this analysis, is a less expensive option with similar efficacy. Adding baricitinib to a formulary would likely be cost saving for US payers and expands treatment options for adult patients with moderately to severely active RA who have had an IR to one or more TNFis.

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Compliance with Ethical Standards

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Conflict of interest Elizabeth Wehler, Oscar Herrera-Restrepo, and Stacey Kowal are employees of IQVIA who were hired by Eli Lilly and Company to conduct the analysis. Natalie Boytsov and Claudia Nicolay are employees and shareholders of Eli Lilly and Company.

Author contributions EW, SK, and NB developed the budget impact model along with number needed to treat and cost per responder calculations. CN developed the systematic literature review and network meta-analysis. OH-R collected data, performed computations, and consolidated results. All authors discussed the results and contributed to the final manuscript writing and revisions.

Data availability The datasets generated and/or analyzed during the current study are not publicly available as they contain proprietary data but are available from the corresponding author on reasonable request.

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Affiliations

Elizabeth Wehler[1] · Natalie Boytsov[2] · Claudia Nicolay[3] · Oscar Herrera-Restrepo[4] · Stacey Kowal[4]

1 IQVIA, 1 IMS Drive, Plymouth Meeting, PA 19462, USA

2 Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, USA

3 Lilly Deutschland GmbH, Bad Homburg, Germany

4 IQVIA, 3110 Fairview Park Drive, Falls Church, VA 22042, USA