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ORIGINAL RESEARCH

The Cost-Effectiveness of Anti-IL17 Biologic Therapies for Moderate-to-Severe Plaque Psoriasis Treatment in Italy and Germany: A Sequential Treatment Analysis

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Objective: The objective of this study was to optimise the cost-effectiveness of different anti-IL17 treatment sequences used in the treatment of moderate-to-severe plaque psoriasis in Italy and Germany over a five-year time horizon.

Methods: We adjusted a previously published treatment sequence model for biologic drugs used in psoriasis treatment to an Italian and German setting, respectively. The model included all anti-IL17 biologics currently available in the treatment of moderate-to-severe plaque psoriasis in the markets of scope (secukinumab, ixekizumab, brodalumab and bimekizumab). Real-world discontinuation rates were used to model switches between the four anti-IL17 biologics included in the study. The treatment costs were based on label dosing recommendations for each drug, including induction and maintenance therapy, and the manufacturer prices of each drug in Italy and Germany, respectively. We used long-term Psoriasis Area and Severity Index 100 (PASI100) measures to inform the model on the efficacy for each treatment. The cost-effectiveness in the analysis was evaluated based on the cost per PASI100-responder.

Results: We found that the most cost-effective treatment sequence was achieved by using brodalumab as first-line treatment, bimekizumab as second-line treatment, ixekizumab as third-line treatment and secukinumab as fourth-line treatment in both Italy and Germany, which resulted in a total cost per responder of €128,200 and €138,212, respectively, over a five-year period. Several scenario analyses were also conducted and ensured that the results were robust to changes in key input parameters.

Conclusion: Our study showed that using brodalumab as a first-line therapy to treat moderate-to-severe psoriasis in both Italy and Germany leads to the most cost-effective treatment sequence, when compared to all possible combinations of anti-IL17s over a five-year time horizon. In addition, we found that treatment discontinuation and switching are important factors when assessing the cost-effectiveness of biologic therapies.

Keywords: cost-per-responder, psoriasis vulgaris, treatment sequences, interleukin-17

Introduction

Plaque psoriasis is a chronic, autoimmune skin condition that affects approximately 2% of the population in Italy and Germany.[1,2] It is characterised by the rapid turnover of skin cells, leading to the formation of red, scaly plaques on the skin. These plaques can be itchy, painful, and often have a negative impact on the patient's quality of life.[3] While there is currently no cure for plaque psoriasis, a variety of treatment options are available to manage the symptoms and improve quality of life for those living with the condition.[3–6]

The pathogenesis of plaque psoriasis is characterised by sustained inflammation that promotes uncontrolled proliferation of keratinocytes in the epidermis. This process is mediated by a dysregulated secretion of cytokines, including interleukin 17 (IL-17), interleukin 23 (IL-23), and tumour necrosis factor (TNF), which play pivotal role in the inflammatory cascade, ultimately leading to the sustained inflammation observed in plaque psoriasis.[3]

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One class of treatments that has gained increasing attention in recent years is biologic drugs.[7–9] These are genetically engineered proteins that target specific immune pathways involved in the development of psoriasis.[10] Biologics have been shown to be highly effective in reducing the severity of psoriasis symptoms and are often used in the treatment of patients with moderate-to-severe psoriasis.[7,11] Often, the Psoriasis Area Severity Index (PASI) is used to assess disease severity and treatment response rates (eg, PASI100 response is defined by a 100% improvement from the baseline PASI score). Especially, the biologics targeting IL-17 and IL-23 have been proven highly effective in suppressing the psoriatic symptoms and seem to be superior in achieving a PASI response compared to biologics targeting interleukin 12/23 (IL-12/23) and TNF.[12–15]

However, the use of biologic drugs is not without its challenges. The typical treatment pattern for patients treated with biologics involves loss of treatment response over time or potential unwanted side effects experienced by some patients.[4,9,16] Thus, switching to different treatment options is usually necessary to continue managing the condition effectively. This can be particularly challenging for patients with moderate-to-severe plaque psoriasis, who may require a biologic treatment in order to achieve good disease control.[4,6,17,18] Treatment with biologics is associated with a significant economic burden, especially during the first year due to the higher dosage and treatment frequency required during the induction phase compared to maintenance therapy.[4,19]

In recent years, a number of new biologic drugs have been introduced, including bimekizumab targeting IL-17.[5,20] Patients with plaque psoriasis can switch between different drug classes, however, patients also sequence within classes (eg, within anti-IL17s). With the recent addition of bimekizumab, there is currently a lack of evidence on the optimal treatment sequence within the anti-IL17 class in the management of moderate-to-severe plaque psoriasis. Given the cost of biologic drugs, it is important to consider the cost-effectiveness of different treatment options.[11,12,17] This is an important consideration, as the choice of treatment sequence can have a significant impact on the overall cost of treatment, as well as the likelihood of achieving good disease control.[17]

The objective of this study was to assess the cost-effectiveness of different anti-IL17 treatment sequences (secukinumab, ixekizumab, brodalumab and bimekizumab) used in the treatment of moderate-to-severe plaque psoriasis in Italy and Germany over a five-year time horizon. We aimed to provide guidance on the most cost-effective approach to managing moderate-to-severe plaque psoriasis in an Italian and German setting by focusing on the current landscape of anti-IL17s that was recently expanded by a new treatment option, bimekizumab.

Methods

Treatment Sequence Model

To evaluate the cost-effectiveness of different anti-IL17 treatment sequences of biologics used in psoriasis, we adapted a treatment sequence model which had previously been developed and published by Egeberg et al[17] to an Italian and German payer perspective.

The model simulated the progression of treatment for patients with moderate-to-severe plaque psoriasis. Patients would enter the model in a state of first-line biologic treatment. After each model cycle, covering four weeks of treatment, patients could either discontinue their treatment and switch to the next treatment in the sequence or they could stay on their initial treatment. The probability of a patient transitioning to a different treatment was determined by the rate of discontinuation for each of the biologic drugs included in the analysis. In addition, patients were only allowed to make one treatment switch in each cycle. Figure 1 illustrates the patient flow in the model.

The model simulated the treatment of moderate-to-severe plaque psoriasis using up to four different biological therapies over a five-year period. As a result, patients who had reached the fourth-line treatment were assumed to remain on this treatment for the remainder of the time horizon.

While simulating the use of different biologic therapies, the model also accumulated the costs associated with each treatment. This allowed for the comparison of different treatment sequences in terms of costs. When considering the cost-effectiveness of a treatment, it is important to consider not only the cost, but also the efficacy of the drugs, as this varies between different treatment options. Thus, each biologic treatment was associated with a response rate for patients who achieve a certain level of improvement in their psoriasis symptoms after treatment. In the model, we accounted for

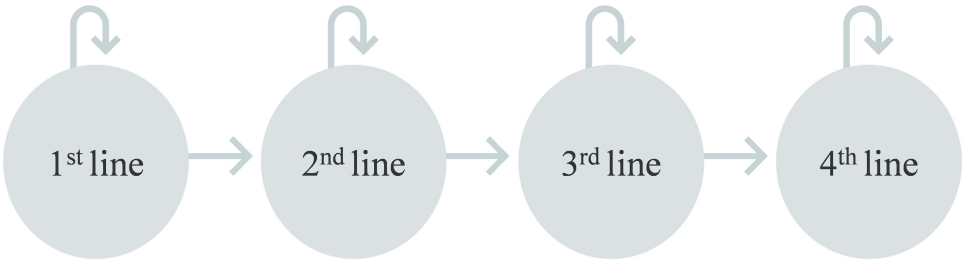

Figure 1 Patient flow in the model.
Notes: The figure illustrates the patient flow in the model. Patients can either remain on their current treatment or move to the next-in-line treatment. Patients who reach fourth-line treatment cannot switch and will remain on this treatment for the remainder of the time horizon.

treatment efficacy by dividing the accumulated cost for each treatment in the sequence by the corresponding treatment efficacy (defined by improvement in PASI score from baseline) for each drug. Thus, the cost-effectiveness in the analysis was evaluated based on the cost per patient achieving response in the treatment sequence. In this analysis, the following four anti-IL17 biologics were included: secukinumab, ixekizumab, brodalumab and bimekizumab. We calculated the cost-effectiveness of all possible treatment sequence combinations of anti-IL17s and ranked them according to cost-effectiveness; from most cost-effective to least cost-effective sequence.

Model Inputs

Treatment Efficacy

We used long-term efficacy measure (48–56 weeks of treatment), defined by PASI100 (complete clearance of psoriasis), to evaluate cost-effectiveness in the primary analysis. The PASI100 response rate of the included anti-IL17s was based on a network meta-analysis (NMA) published by Armstrong et al,[21] which was identified through a systematic literature review (SLR) focusing on treatment efficacy of anti-IL17s and other biologic treatments.[22]

To assess the robustness of the analysis, we performed a scenario analysis where we changed the responder definition to PASI90 (48–56 weeks of treatment) instead of PASI100. The efficacy measures for PASI90 were also based on the NMA published by Armstrong et al[21] and are presented in Table 1.

Discontinuation and Treatment Switching

Drug survival is a key indicator of therapeutic effectiveness, as it reflects both clinical outcomes and patient adherence to treatment, tolerability and the occurrence of adverse events that may lead to treatment discontinuation.[16] In this treatment sequence model, it was assumed that patients would gradually discontinue their current biologic therapy and switch to the next treatment in the sequence to reflect the real-world treatment pattern of patients treated with biologics.

In the analysis, the risk of discontinuation was based on 12-month real-world discontinuation rates for secukinumab, ixekizumab and brodalumab from Torres et al.[16] The primary cause of discontinuation in Torres et al was ineffectiveness

Table 1 Efficacy of Biologics

Drug	Long-Term Response Rate (48–56 Weeks)	
	PASI90	PASI100
Secukinumab	66.2%	41.3%
Ixekizumab	72.0%	47.8%
Brodalumab	78.6%	56.1%
Bimekizumab	79.4%	57.3%

Notes: The response rates are based on estimates by Armstrong et al.[21] The response rates correspond to the share of patients achieving PASI90 or PASI100 at weeks 48–56 of treatment.

of the treatment while safety issues, patients' decision to discontinue and other non-specified causes also contributed to treatment discontinuation.[16] As the discontinuation rates from Torres et al was based on real-world data, development of psoriasis arthritis or other psoriasis related secondary illnesses that may affect treatment adherence or discontinuation rates were indirectly accounted for as patients with poor treatment response would discontinue treatment.

The average discontinuation rate for these drugs (secukinumab, ixekizumab, and brodalumab) was applied to bimekizumab, as real-world evidence on drug survival for this drug is currently very limited due to its recent launch. The per-cycle discontinuation rate for each therapy is presented in Table 2.

In the base case analysis, the discontinuation rate for bimekizumab was assumed to be the same as the average discontinuation rate for secukinumab, ixekizumab, and brodalumab. To assess the significance of this assumption, we conducted two scenario analyses on the discontinuation rate of bimekizumab using ±20% of the base case value.

The effects of biological treatments may not be immediately apparent and are typically evaluated after the initial 12–16 weeks of therapy. This initial period is referred to as the induction phase. In the analysis, the length of the induction phase for each treatment was determined based on recommendations in the Summaries of Product Characteristics (SmPC) for the different therapies.[23–26] It was assumed that during the induction phase, patients would remain on their treatment regardless of clinical response, as the effects of the treatment may not yet be fully achieved. The share of patients discontinuing treatment after the induction phase was estimated based on the accumulated risk of discontinuation in the period between treatment initiation and the induction treatment evaluation. This meant that discontinuation was higher in the cycle following the induction treatment evaluation than in the subsequent cycles. The time of treatment evaluation is presented in Table 2.

Treatment Dosing

The dosing for each drug included in the analysis was based on recommendations in the SmPCs.[23–26] To accurately model the course of treatment, both the induction phase and the maintenance phase of the treatments were included in the model (Table 3). In the analysis, we assumed that all patients underwent a new induction treatment phase, every time they switched to a new treatment. In addition to this, we assumed that patients who switched treatment did not have a wash-out period, meaning that patient commenced the subsequent treatment immediately after discontinuation of their previous treatment.

In clinical practice, dose adjustment is frequent and sometimes occurs due to suboptimal treatment.[27,28] We performed a scenario analysis to assess the significance of including real-world evidence on dose adjustment from Egeberg et al[27] and Torres et al.[18] In Egeberg et al, the average weighted dosage for secukinumab was reported to be 8% above the recommended SmPC level.[24,27] As Egeberg et al did not investigate dose adjustment for the remaining three anti-IL-17s, we used the finding from Torres et al[18] to estimate a dose adjustment factor for these drugs. Torres et al[18] found that the proportion of patients being dose adjusted was 7.4% for secukinumab, 6.4% for ixekizumab and 2.4% for brodalumab. The dose adjustment factor for secukinumab (8%) and the relative proportion of patients being dose adjusted between secukinumab and the remaining anti-IL17s was then multiplied to estimate a dose adjustment factor for each drug.

Table 2 Discontinuation Rates and Evaluation Periods

Drug	Annual Treatment Discontinuation	Per-Cycle Treatment Discontinuation	Discontinuation at Treatment Evaluation	Evaluation Time (Cycle)*
Secukinumab	14.45%	1.19%	4.68%	4
Ixekizumab	13.31%	1.09%	4.29%	4
Brodalumab	11.00%	0.89%	3.51%	4
Bimekizumab	12.92%	1.06%	4.16%	4

Notes: Discontinuation rates were based on Torres et al,[16] except for bimekizumab, which was based on the average values of all other anti-IL17s. *Cycle length is four weeks.

Table 3 Dosing and Drug Costs

Drug	Dosing	Vial Size (mg)	Pack Size (No. of Vials)	Pack Price(€) *		Drug Cost per Year (€)			
				Italy	Germany	Italy		Germany	
						First Year	Subsequent Years	First Year	Subsequent Years
Secukinumab	Induction (weeks 0–4): 300 mg every week Maintenance: 300 mg monthly (every 4 weeks)	150	2	948	1250	15,162	12,319	19,998	16,249
Ixekizumab	Induction: • Week 0: 160 mg • Weeks 2–12: 80 mg every 2 weeks Maintenance: 80 mg every 4 weeks	80	2	2025**	2138	16,355	12,507	18,177	13,900
Brodalumab	Induction (weeks 0–2): 210 mg every week Maintenance: 210 mg every 2 weeks	210	2	1105**	1114	14,175	13,650	15,039	14,482
Bimekizumab	Induction (week 0–16): 320 mg every 4 weeks Maintenance: 320 mg every 8 weeks	160	2	2166	2423	19,494	12,996	21,810	14,540

Notes: Dosing is based on the SmPC for each drug. Drug cost is based on the pack with the lowest cost per milligram to minimise the cost of each treatment. *Manufacturer prices were used in the analysis. **According to a national cashback agreement in Italy a 5% discount was applied to price of ixekizumab and brodalumab in the Italian base case analysis, resulting in a price per pack of €1924 and €1050, respectively.

Bimekizumab was not included in either Egeberg et al[27] or Torres et al,[18] and thus, we used the average value from secukinumab, ixekizumab and brodalumab to estimate a dose adjustment factor. The dose adjustment factors applied in the scenario analysis were 8% for secukinumab, 6.9% for ixekizumab, 2.2% for brodalumab, and 5.7% for bimekizumab.

Treatment Pricing

The cost of each treatment was based on the pharmaceutical manufacturer prices in Italy and Germany extracted on 5 October 2022 and 15 March 2023, respectively.[29,30] The drug costs were based on the pack with the lowest cost per milligram to minimise the cost of each treatment. We did not include costs related to administration, monitoring or adverse events, as these costs previously have been deemed miniscule compared to the drug costs.[31]

In Italy, a cashback agreement on ixekizumab and brodalumab is put in place, meaning that the Italian healthcare system receives a 5% discount on these drugs.[32] In the base case analysis, we accounted for this by adjusting the price of these two drugs by −5%. To assess the significance of including a 5% discount in the price level of ixekizumab and brodalumab in Italy, we performed a scenario analysis where the costs were based solely on the pharmaceutical manufacturer prices without the mandatory cashback. As the cashback agreement only applies in Italy, this scenario analysis was not conducted for Germany.

Results

Primary Analysis

In this analysis, we calculated the cost-effectiveness of all possible treatment sequence combinations of anti-IL17s and ranked them according to cost-effectiveness; from most cost-effective to least cost-effective sequence in Italy and Germany (Table 4 and 5). Given the four treatments included in the analysis, a total of 24 (4 factorial) different

Table 4 Cost per Responder of All Treatment Sequence Combinations with Anti-IL17 in the Base Case Analysis (Italy) (€)

Rank	1st Line	2nd Line	3rd Line	4th Line	Cost 1st Line	Cost 2nd Line	Cost 3rd Line	Cost 4th Line	Total Cost
1	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	93,716	27,086	6158	1239	128,200
2	Brodalumab	Bimekizumab	Secukinumab	Ixekizumab	93,716	27,086	6666	1223	128,691
3	Brodalumab	Ixekizumab	Bimekizumab	Secukinumab	93,716	28,308	6031	1239	129,294
4	Brodalumab	Ixekizumab	Secukinumab	Bimekizumab	93,716	28,308	6823	1194	130,041
5	Brodalumab	Secukinumab	Bimekizumab	Ixekizumab	93,716	30,767	6482	1223	132,188
6	Brodalumab	Secukinumab	Ixekizumab	Bimekizumab	93,716	30,767	6775	1194	132,452
7	Bimekizumab	Brodalumab	Ixekizumab	Secukinumab	98,177	28,107	6158	1239	133,681
8	Bimekizumab	Brodalumab	Secukinumab	Ixekizumab	98,177	28,107	6666	1223	134,173
9	Bimekizumab	Ixekizumab	Brodalumab	Secukinumab	98,177	32,524	6000	1239	137,940
10	Ixekizumab	Brodalumab	Bimekizumab	Secukinumab	102,266	28,730	6031	1239	138,266
11	Ixekizumab	Brodalumab	Secukinumab	Bimekizumab	102,266	28,730	6823	1194	139,013
12	Bimekizumab	Ixekizumab	Secukinumab	Brodalumab	98,177	32,524	7910	1144	139,755
13	Bimekizumab	Secukinumab	Brodalumab	Ixekizumab	98,177	35,354	6453	1223	141,206
14	Ixekizumab	Bimekizumab	Brodalumab	Secukinumab	102,266	31,800	6000	1239	141,305
15	Bimekizumab	Secukinumab	Ixekizumab	Brodalumab	98,177	35,354	7853	1144	142,528
16	Ixekizumab	Bimekizumab	Secukinumab	Brodalumab	102,266	31,800	7910	1144	143,121
17	Ixekizumab	Secukinumab	Brodalumab	Bimekizumab	102,266	36,128	6605	1194	146,193
18	Ixekizumab	Secukinumab	Bimekizumab	Brodalumab	102,266	36,128	7690	1144	147,228
19	Secukinumab	Brodalumab	Bimekizumab	Ixekizumab	111,308	30,751	6482	1223	149,764
20	Secukinumab	Brodalumab	Ixekizumab	Bimekizumab	111,308	30,751	6775	1194	150,027
21	Secukinumab	Bimekizumab	Brodalumab	Ixekizumab	111,308	34,003	6453	1223	152,987
22	Secukinumab	Bimekizumab	Ixekizumab	Brodalumab	111,308	34,003	7853	1144	154,308
23	Secukinumab	Ixekizumab	Brodalumab	Bimekizumab	111,308	35,537	6605	1194	154,644
24	Secukinumab	Ixekizumab	Bimekizumab	Brodalumab	111,308	35,537	7690	1144	155,680

Table 5 Cost per Responder of All Treatment Sequence Combinations with Anti-IL17 in the Base Case Analysis (Germany) (€)

Rank	1st Line	2nd Line	3rd Line	4th Line	Cost 1st Line	Cost 2nd Line	Cost 3rd Line	Cost 4th Line	Total Cost
1	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	99,428	30,305	6844	1634	138,212
2	Brodalumab	Ixekizumab	Bimekizumab	Secukinumab	99,428	31,462	6747	1634	139,272
3	Brodalumab	Bimekizumab	Secukinumab	Ixekizumab	99,428	30,305	8793	1359	139,885
4	Brodalumab	Ixekizumab	Secukinumab	Bimekizumab	99,428	31,462	8999	1336	141,225
5	Bimekizumab	Brodalumab	Ixekizumab	Secukinumab	109,842	29,820	6844	1634	148,141
6	Brodalumab	Secukinumab	Bimekizumab	Ixekizumab	99,428	40,581	7252	1359	148,621
7	Brodalumab	Secukinumab	Ixekizumab	Bimekizumab	99,428	40,581	7529	1336	148,875
8	Bimekizumab	Brodalumab	Secukinumab	Ixekizumab	109,842	29,820	8793	1359	149,814
9	Ixekizumab	Brodalumab	Bimekizumab	Secukinumab	113,658	30,481	6747	1634	152,520
10	Bimekizumab	Ixekizumab	Brodalumab	Secukinumab	109,842	36,147	6365	1634	153,989
11	Ixekizumab	Brodalumab	Secukinumab	Bimekizumab	113,658	30,481	8999	1336	154,474
12	Ixekizumab	Bimekizumab	Brodalumab	Secukinumab	113,658	35,579	6365	1634	157,236
13	Bimekizumab	Ixekizumab	Secukinumab	Brodalumab	109,842	36,147	10,433	1214	157,637
14	Ixekizumab	Bimekizumab	Secukinumab	Brodalumab	113,658	35,579	10,433	1214	160,884
15	Bimekizumab	Secukinumab	Brodalumab	Ixekizumab	109,842	46,632	6846	1359	164,679
16	Bimekizumab	Secukinumab	Ixekizumab	Brodalumab	109,842	46,632	8727	1214	166,415
17	Ixekizumab	Secukinumab	Brodalumab	Bimekizumab	113,658	47,652	7008	1336	169,653
18	Ixekizumab	Secukinumab	Bimekizumab	Brodalumab	113,658	47,652	8603	1214	171,128
19	Secukinumab	Brodalumab	Bimekizumab	Ixekizumab	146,814	32,625	7252	1359	188,051

(*Continued*)

Table 5 (Continued).

Rank	1st Line	2nd Line	3rd Line	4th Line	Cost 1st Line	Cost 2nd Line	Cost 3rd Line	Cost 4th Line	Total Cost
20	Secukinumab	Brodalumab	Ixekizumab	Bimekizumab	146,814	32,625	7529	1336	188,304
21	Secukinumab	Bimekizumab	Brodalumab	Ixekizumab	146,814	38,044	6846	1359	193,063
22	Secukinumab	Ixekizumab	Brodalumab	Bimekizumab	146,814	39,496	7008	1336	194,653
23	Secukinumab	Bimekizumab	Ixekizumab	Brodalumab	146,814	38,044	8727	1214	194,799
24	Secukinumab	Ixekizumab	Bimekizumab	Brodalumab	146,814	39,496	8603	1214	196,128

treatment sequences were evaluated in each country. The most cost-effective treatment sequence for patients with moderate-to-severe plaque psoriasis among the four anti-IL17s was brodalumab, bimekizumab, ixekizumab, and secukinumab (BRO-BIM-IXE-SEC) in both Italy and Germany, resulting in a cost per responder of €128,200 and €138,212, respectively, over a five-year period.

The analysis showed that all six sequence combinations in Italy where brodalumab was the first-line treatment were more cost-effective compared to all remaining sequences where brodalumab was not the first-line treatment. The first sequence where brodalumab was not the first-line treatment was BIM-BRO-IXE-SEC (ranked as no. 7) and had a cost per responder of €133,681, 4% higher compared to the most cost-effective sequence.

The results for Germany also indicated that using brodalumab as the first-line treatment would result in the lowest cost per responder, as the four most cost-effective treatment sequences had brodalumab as first-line treatment. The fifth most cost-effective sequence was BIM-BRO-IXE-SEC, had a cost per responder of €148,141, 7% higher compared to the most cost-effective sequence, and was the first sequence where brodalumab was not the first-line treatment.

The analysis also suggested that drug survival plays an important role in the cost-effectiveness of each sequence. Drug survival was particularly relevant in terms of the increased costs associated with a treatment switching due to patients receiving induction therapy when starting a new treatment. This is indicated by Table 3, where the cost in the first year of treatment is compared to the subsequent years of therapy. The table shows that there are higher costs associated with first year of treatment compared to the subsequent years. As such, a high drug survival rate means that a higher percentage of patients will continue treatment with the same drug, which leads to fewer patients needing to switch to a different therapy. This reduces the cost of treatment by reducing the number of patients who need induction therapy, which is more costly compared to maintenance therapy. This was shown by the simulation of BRO-BIM-IXE-SEC (ranked as no.1 in both Italy and Germany), where the aggregated treatment distribution after five years of treatment was brodalumab 56%, bimekizumab 31%, ixekizumab 10%, and secukinumab 3% (Figure 2). In comparison, the simulation of BIM-BRO-IXE-SEC (ranked as no. 7 in Italy and 4 in Germany) showed that the aggregated treatment distribution after five years of treatment was bimekizumab 51%, brodalumab 37%, ixekizumab 10%, and secukinumab 3% (Figure 3). Fewer patients discontinuing from brodalumab compared to bimekizumab contributed to reducing the costs of BRO-BIM-IXE-SEC compared to BIM-BRO-IXE-SEC.

In Italy, we found that the first year of treatment with brodalumab was associated with an added cost of €525, corresponding to a 4% increase compared to the subsequent years (Table 3). In contrast, the added cost for the first year of treatment with bimekizumab was €6498, corresponding to a 50% increase compared to future years. Bimekizumab had a slightly higher response rate compared to brodalumab (57.3% vs 56.1%) and a 5% lower annual cost for maintenance treatment (€12,996 vs €13,650). Despite this, sequences with bimekizumab as a first-line treatment remained less cost-effective compared to sequences with brodalumab as a first-line treatment due to the induction costs of bimekizumab being 36% higher compared to brodalumab (€19,494 vs €14,175).

In Germany, the added cost of the first year of treatment with brodalumab was €557, corresponding to a 4% increase compared to the subsequent years, while the added cost for bimekizumab was €7270, corresponding to a 50% increase compared to future years. As in Italy, this contributed to sequences with bimekizumab as a first-line treatment being less

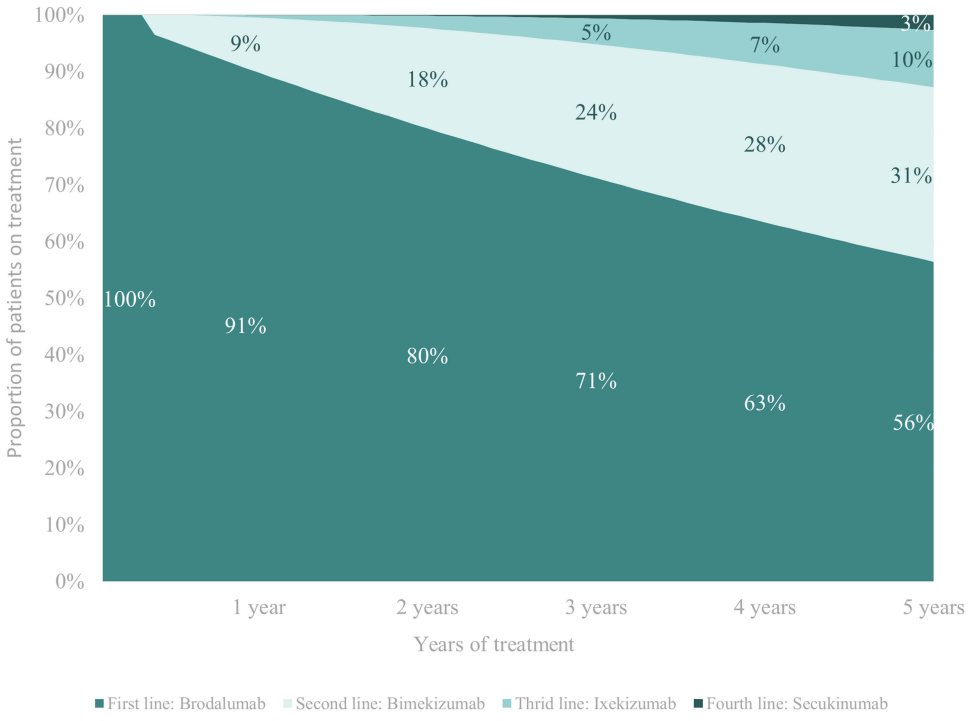

Figure 2 Treatment distribution for patients treated with BRO-BIM-IXE-SEC.
Notes: Data labels present the proportion of patients on each treatment in years 1–5. Data labels were only presented when the proportion were greater than 2%.

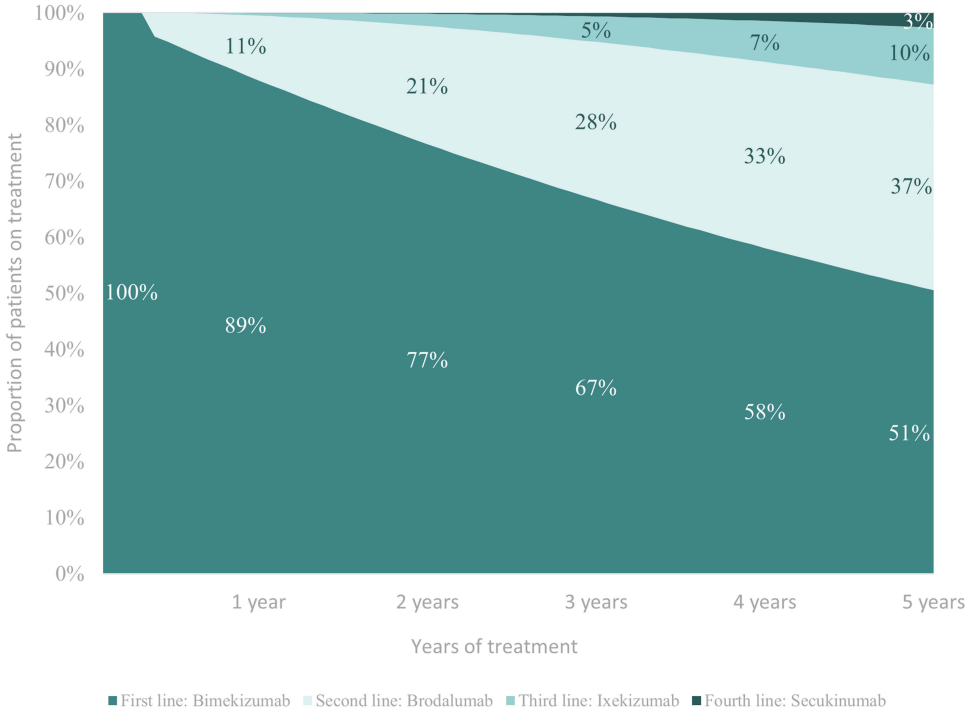

Figure 3 Treatment distribution for patients treated with BIM-BRO-IXE-SEC.
Notes: Data labels present the proportion of patients on each treatment in years 1–5. Data labels were only presented when the proportion were greater than 2%.

cost-effective compared to sequences with brodalumab as a first-line treatment. In addition, the treatment costs of bimekizumab were 45% higher compared to brodalumab in the first year of treatment (€21,810 vs €15,039), while it was 0.4% higher in the subsequent years (€14,540 vs €14,482).

Scenario Analyses

To assess the robustness of the analysis, we performed a series of scenario analyses where alternative inputs were used for key parameters in the model. The parameters included in the scenario analyses included altering the definition of a responder, adjusting the dosage of each drug according to real-world evidence estimates, altering the discontinuation rate of bimekizumab and applying a different price level to the treatments. The scenario analyses performed in this study are presented in Table 6.

Changing the responder definition in the analysis to patients achieving PASI90 by weeks 48–56 instead of PASI100 implied that the cost of treatments became more significant, as a larger proportion of patients were responders. The most cost-effective treatment sequences when applying PASI90 as response definition were BRO-BIM-SEC-IXE in Italy and BRO-IXE-BIM-SEC in Germany. Thus, no changes were observed when considering the optimal first-line treatment, while minor changes were observed when considering the second-, third- and fourth-line treatments. In Italy, ixekizumab and secukinumab had switched places, while bimekizumab and ixekizumab had switched places in Germany. As indicated by row 1 in Table 6, the total cost per responder was significantly lower when using PASI90 compared to PASI100 in both Italy and Germany, as more patients were considered responders in this analysis.

In the scenario analysis where dose adjustment was included, a slight increase in the total cost per responder was observed due to increased drug usage. No changes to the optimal sequence order were observed in either Italy or Germany when compared to the base case. Thus, the inclusion of dose adjustment had a marginal effect of the results of the analysis (Table 6).

As the discontinuation rate for bimekizumab was estimated based on the average drug survival of brodalumab, ixekizumab and secukinumab, we undertook two sensitivity analyses on the discontinuation rate of bimekizumab. We changed the per-cycle discontinuation rate of bimekizumab by ±20% to 1.27% and 0.85% per cycle (base case was 1.06%). This was performed to assess whether the results were driven by the estimated drug survival rate of bimekizumab. As indicated by row 3 and 4 in Table 6, these analyses did not change the results significantly and did not change the overall conclusion.

We also performed a scenario analysis on the Italian drug price for ixekizumab and brodalumab where the 5% discount was not included. As expected, this increased the total cost per responder for all treatment sequences; however, no changes to the optimal sequence order were observed in Italy when compared to the base case (Table 6).

Discussion

This study was the first to compare the cost-effectiveness of all possible sequences of all available anti-IL17s (secukinumab, ixekizumab, brodalumab and bimekizumab) for the treatment of moderate-to-severe plaque psoriasis in Italy and Germany. We found that a treatment sequence with brodalumab as first-line treatment and bimekizumab as second-line treatment was the most cost-effective in both countries. Several scenario analyses were also conducted and ensured that the results were robust to changes in key input parameters.

Relatively few studies have assessed the cost-effectiveness of different biologic treatment sequences for patients with moderate-to-severe plaque psoriasis. Egeberg et al[17] investigated the sequential cost-effectiveness of seven different biologic treatments in Spain (certolizumab, ustekinumab, brodalumab, secukinumab, ixekizumab, guselkumab, and risankizumab) and found that treatment sequences starting with brodalumab as first-line therapy were the most cost-effective. Among the anti-IL17s, Egeberg et al also found that, while sequences starting with brodalumab were most cost-effective, sequences starting with ixekizumab and secukinumab, respectively, gradually became less cost-effective.[17] Thus, these findings are in line with the results of the present study. Another study by Di Matteo et al[33] investigated the sequential cost-effectiveness of brodalumab, risankizumab and secukinumab as second-line therapy after treatment with adalimumab in Italy. The study found that brodalumab was a more cost-effective treatment compared to both risankizumab and secukinumab as second-line treatment, thus also suggesting that brodalumab should be used prior to secukinumab in the treatment sequence order.[33]

An advantage of using a treatment sequence model when evaluating cost-effectiveness is that drug survival can be incorporated in the analysis; traditional pair-wise cost-effectiveness models do not allow this. Thus, we were able to

Table 6 Scenario Analyses

Scenario Analyses	Italy					Germany				
	1st Line	2nd Line	3rd Line	4th Line	Total Cost	1st Line	2nd Line	3rd Line	4th Line	Total Cost
Base case	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	128,200	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	138,212
PASI90 used to define response	Brodalumab	Bimekizumab	Secukinumab	Ixekizumab	94,970	Brodalumab	Ixekizumab	Bimekizumab	Secukinumab	97,742
Treatment dosages adjusted according to real-world evidence estimations	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	131,852	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	142,200
Discontinuation of bimekizumab 20% higher	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	128,459	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	138,537
Discontinuation of bimekizumab 20% lower	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	127,920	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	137,862
No cashback on brodalumab and ixekizumab in Italy	Brodalumab	Bimekizumab	Ixekizumab	Secukinumab	133,456	-	-	-	-	-

Notes: The table presents the most cost-effective treatment sequence for each scenario analysis. The "total cost" column represents the combined cost per responder for all four treatments in each sequence.

mimic the nature of psoriasis treatment progression over time and to include the added costs associated with a switch. We found that both parameters were important for the cost-effectiveness and that these should not be disregarded when evaluating cost-effectiveness of biologics used in moderate-to-severe plaque psoriasis.

A limitation of the model was that patients could not switch beyond a fourth-line treatment and thus, remained on this treatment for the remainder of the time horizon. It was observed that only few patients (2.6–3.4% depending on the sequence) would transition to the fourth-line treatment during a five-year time horizon, thus, suggesting that this assumption has a minimal impact on the results of the model when using a five-year time horizon. Egeberg et al also found that only a small number of patients reached the fourth treatment over a five-year period, suggesting that four lines of treatment were sufficient in this time frame.[17] In addition, the drug survival reported by Torres et al[16] also indicate that a time horizon shorter than five years would result in insufficient time to model the transition of patients from a first-line to a fourth-line treatment. Therefore, this cost-effectiveness analysis required a longer time horizon compared to traditional cost per responder analyses, which does not include treatment switching.

We used real-world evidence from Torres et al[16] to estimate the drug survival of secukinumab, ixekizumab and brodalumab. In the absence of real-world drug survival of bimekizumab, due to its recent launch in Europe, we made an assumption that drug survival was an average of the drugs in the anti-IL17 class. This was an inherent limitation of the study; however, the sensitivity analyses performed on the discontinuation rate of bimekizumab showed that the base case result were robust to changes in this parameter.

Dose adjustment of biologics is relatively common and often results in patients receiving higher or more frequent treatment dosages.[28] It may be an expression of suboptimal treatment and have implications for the cost of treatment. As a result, the treatment costs in the present study may have been underestimated across all four treatments. In a multi-centric, multi-country cohort study in the EU, Torres et al[18] reported that dose adjustment was performed for 7.4% of patients treated with secukinumab, 6.4% of patients treated with ixekizumab, and 2.4% for brodalumab. These findings may suggest that the costs of brodalumab might, however, have been underestimated to a minor degree compared to secukinumab and ixekizumab. This could have disfavoured brodalumab in the present analysis, despite it being the optimal first-line treatment.

To investigate the impact of including dose adjustment to the analysis, we performed a scenario analysis where the SmPC treatment dosages were adjusted according to Egeberg et al[27] and Torres et al.[18] We found that this parameter had a minor impact on the cost-effectiveness of the included drugs. Nonetheless, it is essential to acknowledge that adjusting the dosages could potentially affect the overall expenses for payers, as the overall drug costs increase. In addition, it must be noted that this scenario analysis was affected by several limitations in data availability and that more data is warranted to confirm the effects of dose adjustment in real life. As such, this scenario analysis must be interpreted with caution with the main limitation being that the dose adjustment factor for bimekizumab was estimated based on the average value of the remaining anti-IL17s. In addition to this, there may also be safety implications, as well as potential effects on efficacy which are important aspects in relation to dose adjustment. Ideally, these factors should be considered when modelling the cost-effectiveness of biologics used in the treatment of plaque psoriasis; however, more studies are required to inform of these parameters.[28]

We used the 48–56-week PASI100 response rate from Armstrong et al[21] to define a responder. As such, we indirectly assumed that this response rate applied throughout the five-year time horizon, regardless of the duration patients had been on a given treatment. As the response rate of biologics tend to increase during the first year of treatment, this may have overestimated the response rate for patients staying on a treatment for less than a year.[21] On the contrary, patients may lose response after being on the same treatment for several years.[16] This was observed by Torres et al, who found that 11% of patients on secukinumab, 6% of patients on ixekizumab and 3% of patients on brodalumab had discontinued treatment due to loss of treatment response between month 12 and month 24 of treatment.[16] However, as the model took into account discontinuation, this issue mainly applied to patients discontinuing treatment before completing one year of therapy.

Another potential limitation of modelling long-term cost-effectiveness was that treatment costs were kept constant throughout time horizon. In reality, changes in drug prices are likely to occur over a five-year period due to new entries in

the market and biosimilar competition. Thus, the results of our study may change if the competitive landscape of biologics are altered.

Conclusion

To optimise cost-effectiveness of anti-IL17s used in the treatment of moderate-to-severe plaque psoriasis in Italy and Germany, our results show that of all possible treatment sequences combinations with all anti-IL17s, brodalumab should be used as first-line treatment and bimekizumab should be used as second-line treatment. Over a five-year period, the most cost-effective treatment sequence was (1) brodalumab, (2) bimekizumab, (3) ixekizumab and (4) secukinumab in both Italy and Germany, resulting in the lowest cost per responder out of 24 possible sequence combinations.

Using a sequential treatment model, we optimised the cost-effectiveness of anti-IL17 biologic treatments used in moderate-to-severe plaque psoriasis. Besides efficacy and treatment costs, we found that accounting for drug survival and the added costs associated with treatment switching is important when evaluating cost-effectiveness. This research will be of particular relevance to patients, healthcare providers, and payers, as it will provide valuable insights to guide the selection of treatment options for managing moderate-to-severe plaque psoriasis in an Italian and German setting.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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