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ORIGINAL RESEARCH



## Assessing the value contribution of bimekizumab for the treatment of moderate-to-severe psoriasis using a multidisciplinary reflective multi-criteria decision analysis

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### ABSTRACT

**Background:** Multi-criteria decision analysis (MCDA) was proposed to surmount arbitrary clinical decisions in the field of biological therapies for psoriatic patients. At the same time, MCDA may further highlight the potential of bimekizumab for the treatment of moderate-to-severe psoriasis, compared to placebo, adalimumab, ustekinumab, secukinumab, and even ixekizumab and risankizumab.

**Research design and methods:** The EVIDEM framework was adapted to reflect relevant criteria for the assessment. Estimated values were obtained by means of an additive linear model combining weights and scores assigned by a multidisciplinary committee of 12 experts. Consistency and replicability were evaluated through an alternative weighting method and a re-test.

**Results:** Bimekizumab was assessed by the committee as an intervention with a positive value contribution for the treatment of moderate-to-severe psoriasis in comparison to any of the alternatives. The drug provides a substantial therapeutic benefits and improves the health results reported by the patients, as it combines a higher level of clearance, rapidity, and persistence with a similar safety and tolerability profile.

**Conclusions:** Under a methodology with increasing use in the health field, bimekizumab was evaluated as a drug with a high added value for the treatment of moderate-to-severe psoriasis when compared to six different alternatives.

### ARTICLE HISTORY

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### KEYWORDS

Psoriasis; moderate-to-severe; biologics; multi-criteria decision analysis; MCDA; bimekizumab

## 1. Introduction

The popularity of biological treatments for moderate-to-severe plaque psoriasis has increased over the last decades, resultant of their associated clinical benefits and safety profile. However, given the bounded resources available in healthcare budgets, allocation decisions play a critical role in determining the most appropriate alternatives to be employed. Cost-effectiveness analyses are progressively developing into the most prominent tools used in funding decisions, in general and also in dermatology [1].

Notwithstanding, this methodology has been criticized for many reasons, such as the inadequacy on capturing the social value and an implicit judgment of other aspects outside the range of efficacy, safety, and cost, generating heterogeneity in

coverage decisions across settings for the same treatment or indication. Although those could be explained by different budget constraints and priorities, an increased comprehension of the rationale used in the decision-making process could enhance the validity and acceptability of such determinations [2].

The multi-criteria decision analysis (MCDA) framework, which is being used to an increased extent in healthcare decision making, yields ways of solving those hurdles, as it consists of a structured, multi-dimensional, transparent, and systematic approach, incorporating a vast set of criteria and their individual value contribution to the decision or allocation problem. As a result, it can be particularly useful as a complement to the standard economic evaluations in the assessment of drugs [3].

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 Supplemental data for this article can be accessed [here](#)

Psoriasis is a chronic, systemic, inflammatory condition, characterized by a variable clinical course, usually chronic, with periods of relapse and remission of unpredictable duration [4]. It affects approximately 41 million people globally, out of which, 1.1 million in Spain [5]. Plaque psoriasis is the most common form of psoriasis, responsible for 90% of the cases [6]. It manifests not only through the skin as visible plaques, pain, and itching, but also more widely, resulting in increased mortality, productivity losses, emotional and quality of life deterioration and risk of comorbidities, such as metabolic syndrome, obesity, and psoriatic arthritis compared to the general population, adversities, which are amplified according to psoriasis severity [4]. Moderate-to-severe psoriasis accounts for about one-third of patients with plaque psoriasis in Spain [7].

The use of biologic treatments for the management of moderate-to-severe psoriasis is swiftly growing, and may account for roughly 20% of systemic treatments [8]. There is an extensive breadth of biologics therapies approved by the European Medicines Agency (EMA), entailing tumor necrosis factor (TNF) inhibitors (infliximab, etanercept, adalimumab, and certolizumab pegol), and different interleukin (IL) inhibitors, targeting IL12/23 (ustekinumab), IL-17A (secukinumab, ixekizumab), IL-17 receptor (brodalumab), and IL-23p19 (guselkumab, tildrakizumab, and risankizumab) [9].

Regardless of this extensive number of alternatives, people suffering from moderate-to-severe psoriasis still face multiple unmet needs. From an efficacy perspective, there is no cure for the disease, 40%–60% of patients do not obtain complete or almost complete skin clearance (Psoriasis Area and Severity Index [PASI]100 or PASI90 in clinical trials, PASI <2 in clinical practice), whilst for the half who achieve absolute clearance, it takes from 3 to 8 months after the start of treatment. Moreover, 50% of the patients discontinue their treatment with biologicals before the fifth year due to lack of efficacy [10–14]. In addition, the need for biologic switch is increasing significantly, given failure related mainly to efficacy and safety issues, which generates additional costs and potential health risks, since persistent inflammation may trigger or worsen several cardiac, respiratory, and metabolic comorbidities [15,16]. Switching or combination of therapies, rather than persisting on a treatment that has primarily or secondarily failed, may improve outcomes [17,18]. In this sense, development of predictive models capable of estimating the probability of non-responses based on clinical features or endotypes may be of paramount clinical and pharmaco-economic importance [19,20].

From a broader angle, other necessities can be highlighted, namely: treatment adequacy, patient's satisfaction, ability to reduce emotional distress, route and frequency of administration of drugs, heterogeneity in access and the imperative to (re)define treatment goals beyond skin manifestations [8,21].

Bimekizumab (Bimzelx®, UCB Pharma S.A., Brussels, Belgium), an humanized IgG1/κ monoclonal antibody, is the first drug designed to selectively and directly inhibit both IL-17A and IL-17F cytokines, and has been authorized

by EMA for the treatment of moderate-to-severe plaque psoriasis in August 2021 [22].

The main objective of this study was to apply a multi-criteria decision analysis (MCDA) to assess the value of bimekizumab (BKZ) for the treatment of moderate-to-severe psoriasis, using placebo (PBO), adalimumab (ADA), ustekinumab (UST), secukinumab (SEC), ixekizumab (IXE) and risankizumab (RIS) as comparators.

## 2. Methods

### 2.1. Expert panel design and conduct of the study

The study was carried out through a multidisciplinary expert committee (MEC) of 12 individuals, with a balanced geographical representation from six autonomous regions. The participants were nationally recognized by their broad experience in the management of moderate-to-severe psoriasis and decision-making in Spain, who had participated as authors and coauthors in national and international publications. The number of experts included was in line with previous MCDA exercises undertaken in Spain [23,24]. The constitution of the MEC with these characteristics was done in order to factor in a wide-ranging volume of perspectives in the assessment of the value contribution of bimekizumab versus placebo and five biological drugs. Moreover, another selection criterion was the absence of any conflict of interest.

The MEC was composed by three dermatologists from three reference university hospitals in Spain (two from Catalonia [Germans Trias i Pujol University Hospital and Hospital de la Santa Creu i Sant Pau] and one from Madrid [La Paz University Hospital]; one nurse (from a referral hospital in Madrid, University Hospital Gregorio Marañón); one psychologist specialized in psoriasis (Hospital de la Santa Creu i Sant Pau); two patients (representatives of the National Patient Association for Psoriasis, 'Acción Psoriasis'); two healthcare managers (one hospital manager from a referral hospital in Valencia, west region of Spain [Hospital Doctor Peset], one regional healthcare manager in the area of Galicia, north region of Spain); one hospital pharmacist (from a reference hospital in the Balearic Islands [University Hospital Son Espases]); one health economist (Department of Pharmacology and Clinical Therapeutics, Biomedical Research Institute of Málaga [IBIMA]); and one representative of the political sphere (Andalusian Public Health School, former General Secretary of Health and healthcare vocal at the Parliament).

The rationale used for the selection of the comparators combined the inclusion of at least one drug for each mechanism of action and recommendations based upon the practical experience of the members of the MEC.

Two online meetings were held with the MEC. In the first one (June 2021), experts received training on the MCDA methodology, based on a pre-read document sent prior to the meeting. Additionally, they agreed on adapting the EVIDEM (Evidence and Value: Impact on DEcision Making) framework (10<sup>th</sup> edition), a widely used and flexible methodology [25], to the context of psoriasis (Table 1). Finally, the MEC assigned weights to each of the fifteen criteria, by distributing 100 points amongst them, that revealed their

**Table 1.** MCDA framework for the evaluation of drugs in moderate-to-severe psoriasis.

Domains/criteria	Type	Adaptations made on the EVIDEM framework (10th edition)
Need for the intervention	Absolute	<i>One criterion was disaggregated:</i> The criterion effectiveness was disaggregated into three (level, rapidity and persistence of clearance), to capture relevant features in the assessment of drugs for moderate-to-severe psoriasis.
Disease severity	Absolute	
Size of affected population	Absolute	
Unmet needs	Absolute	
Outcomes of the intervention		
Level of clearance	Relative	<i>One criterion was added:</i> The criterion consistency of the effect was added, in order to capture outcomes from the use of the drugs in patients with psoriasis in specific locations (i.e. scalp, palmoplantar, etc.) and psoriatic arthritis.
Rapidity of clearance	Relative	
Persistence of clearance	Relative	
Safety/tolerability	Relative	
Patient reported outcomes	Relative	
Type of benefit of the intervention		<i>One criterion was excluded:</i> The criterion type of preventive benefit was excluded, as the drugs being assessed in this MCDA are focused on the treatment of the disease, and not on its prevention.
Type of therapeutic benefit	Absolute	
Consistency of the effect	Relative	
Economic consequences of the intervention		
Cost of intervention	Relative	
Impact on other direct costs	Relative	
Impact on indirect costs	Relative	
Knowledge about the intervention		
Quality of evidence	Absolute	
Expert consensus/clinical practice guidelines	Relative	

*Absolute criterion:* does not contemplate comparisons between interventions. Scores range from 0 to 5, with 0 being the lowest value and 5, the highest.  
*Relative criterion:* it is used when comparing bimekizumab with placebo or another drug. Scores range from -5 (bimekizumab is much worse than the comparator) to 5 (bimekizumab is much better than the comparator)

individual relative importance – the greater the points assigned, the higher the importance of the criterion.

Prior to the second meeting, the experts scored (online) each criterion and intervention individually, based on the evidence matrices provided and their individual experience and perception. Some of the criteria are defined by EVIDEM as absolute (with scores ranging from 0 to 5, as no comparison between interventions are made) and some as relative (scores from -5 to 5, as they compare different interventions: a score of 5 means that bimekizumab is much better than the comparator in the criterion analyzed, whilst a score of -5, that bimekizumab is much worse than the comparator and 0, that there are no differences between bimekizumab and the alternative drug evaluated).

In the second meeting (September 2021), scores and value estimates were presented and debated amongst members of the MEC, with the objective to gather qualitative information around the rationale applied in their assessment. One week after that the MEC members were asked to assign (online) weights and scores again, as well as use an alternative weighting method, based on a nonhierarchical 5-point direct rating scale (1 = lowest relative importance, 5 = highest relative importance). The re-test weights and scores as well as the alternative weighting method generated new value estimates,

which were used to check consistency and validity of the MCDA.

## 2.2. Literature review and evidence matrix

A comprehensive review of the literature was conducted to collect the available evidence regarding the fifteen criteria and each drug included in this MCDA. The information was assembled in seven evidence matrices and one summary document (**supplementary file 1**), which were reviewed and validated by the clinicians from the MEC. The search was performed using major biomedical databases, such as PubMed and Medline, clinical trial registries, clinical practice guidelines, official European and Spanish healthcare evaluation bodies webpages, namely European Medicines Agency (EMA), Spanish Medicines and Healthcare Products Agency (AEMPS), and Spanish regional and hospital evaluations, as well as gray literature. No date or language restrictions were applied.

## 2.3. Data analysis

An overall estimated value (ranging from -1 to 1) was obtained for each comparison, through an additive linear model of all individual criteria value contributions, which were calculated as the product of normalized weights and scores:

$$V = \sum_{x=1}^n V_x = \sum_{x=1}^n \left( \frac{W_x}{\sum W_n} S_x \right)$$

where V is the total estimated value, V<sub>x</sub> the value contribution of the criterion x, W<sub>x</sub> the weighting of the criterion x,  $\sum W_n$  the sum of all weights, and S<sub>x</sub> the normalized score for each criterion (S<sub>x</sub> = score/5). A value estimation greater than 0 means that bimekizumab has a positive value contribution in relation to its comparator, whilst a value, which is lower than 0 represents a negative value contribution from the evaluated drug against the alternative. A more detailed explanation of how each parameter is evaluated is described in a previously published methodological guideline [26].

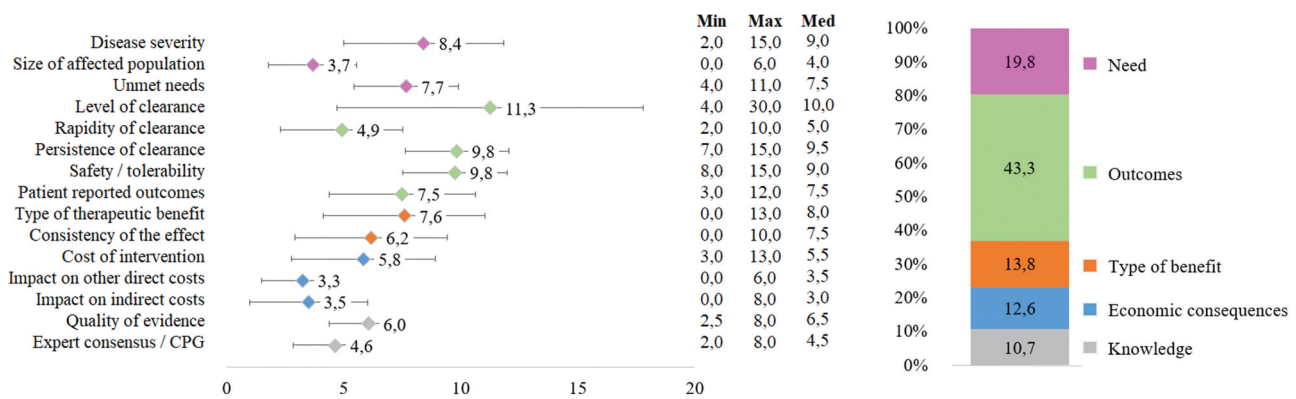
The degree of agreement between the responses made at the two timepoints (test and re-test) was evaluated through the intra-rater correlation coefficients (ICC 3,1) using STATA® version 14 (STATA Corp., LP, College Station, TX, USA).

## 3. Results

### 3.1. Weights: relative importance of each criterion

The experts distributed 100 points between the 15 different criteria of the MCDA framework, disclosing their appreciation on the relative importance of each individual attribute when appraising any drug for the treatment of moderate-to-severe psoriasis. The analysis of the results by domain suggests that the parameters, which are usually assessed by economic evaluations (outcomes and costs) were given a relative importance of 55.9% over the total, whilst the other (need, type of benefit and knowledge about the intervention) represented





**Figure 1.** Relative importance of each individual criterion in the assessment of drugs for the treatment of moderate-to-severe psoriasis (mean, min, max and median weights and standard deviations). The 100-points distribution method was applied, by which the experts assigned a weight to each criterion, provided its aggregation resulted in 100. CPG: clinical practice guidelines.

a slightly lower, but still highly significant, share of the total (44.3%) (Figure 1).

Individually, the three most relevant criteria were level of clearance ( $11.3 \pm 6.6$ ), persistence of clearance and safety/tolerability ( $9.8 \pm 2.2$  each), which were considered to be between two and three times more important than the three least significant ones: impact on other direct costs ( $3.3 \pm 1.8$ ), impact on indirect costs ( $3.5 \pm 2.5$ ) and size of the affected population ( $3.7 \pm 1.9$ ). Variability in responses was low (SD: 1.7–3.4), except for the criterion level of clearance (SD: 6.6) which can be explained by one extreme case in the managers' subgroup (30/100, being responsible for 54% of this deviation).

For healthcare professionals (dermatologists, nurse, and psychologist,  $n = 5$ ) and managers (healthcare managers, hospital pharmacist, health economist, and politician,  $n = 5$ ), the three most and least important criteria coincided with the global results. In contrast, for the patients ( $n = 2$ ), unmet needs and consistency of the effect were two out of the three features considered as with upmost significance, while level of clearance and safety/tolerability occupied the seventh and eighth positions in order of importance for this subgroup (**supplementary file 2**).

### 3.2. Scores based on evidence and insights from the MEC

The fifteen criteria included in this MCDA and rated by the MEC are summarized in **Table 2 and Supplementary file 2**. The overall average score ( $n = 12$ ) for the 'disease severity' criterion was  $3.8 \pm 0.5$  out of 5.0 (median: 4.0), reflecting the fact that moderate-to-severe psoriasis is considered a severe disease by the experts as, despite not being a life-threatening disease, it has a high impact on patients' quality of life, work environment and emotional (psychological and psychiatric) spheres.

The 'size of affected population' is the only criterion in the EVIDEM framework that has a pre-specified scoring scale [25], and the overall average score for this criterion ( $3.0 \pm 0.4$  out of 5.0 [median: 3.0]) showed a consensus in relation to the prevalence of moderate-to-severe psoriasis in Spain (0.6% of the population).

Moreover, in the opinion of the MEC, moderate-to-severe psoriasis is a disease with considerable 'unmet needs,' given the overall average score of  $3.5 \pm 0.9$  out of 5.0 (median: 4.0) attributed to this criterion. Experts considered that the unmet needs are not only clinical, but also related to other aspects, such as psychological support and access to therapies.

'Level of clearance' received overall mean scores ranging from  $4.8 \pm 0.4$  (median: 5.0) for BKZ vs. PBO to  $2.1 \pm 1.0$  (median: 2.0) for BKZ vs. IXE. A score of 5.0 means that bimekizumab achieves a much higher level of clearance than the comparator. The experts agreed with the resulting ratings, adding that, for all efficacy criteria, they would have expected an absolute consensus of a 5.0 score in the comparison between BKZ and PBO.

Additionally, the scores for 'rapidity of clearance' were consistent with the evidence analyzed [27–32] (ranging from  $4.8 \pm 0.6$  [median: 5.0] for BKZ vs. PBO to  $2.1 \pm 0.8$  [median: 2.0] for BKZ vs. IXE. A score of 5.0 means that bimekizumab is much quicker than the comparator in achieving the expected results), reflecting that the IL-17 (BKZ IL-17A/F, SEC IL-17A, and IXE IL-17A) are the drugs, which provide the fastest onset of action.

'Persistence of clearance' (which means the durability of the clearance achieved) was considered by the MEC as a criterion, which would need more long-term results and data to allow for a full assessment of its effect after the first year. Nevertheless, they were able to provide ratings based on the available evidence related to the persistence of clearance at 1 year, resulting in aggregated scores ranging from  $4.8 \pm 0.6$  (median: 5.0) for BKZ vs. PBO to  $2.2 \pm 1.6$  (median: 3.0) for BKZ vs. RIS. A score of 5.0 means that the effects produced by bimekizumab are much more persistent over time than the ones produced by the comparator.

The criterion 'safety and tolerability' received scores between  $1.7 \pm 1.6$  (median: 2.0) for BKZ vs. ADA, and  $-0.3 \pm 2.6$  (median:  $-1.0$ ) for BKZ vs. PBO. A score of +5.0 means that bimekizumab is much safer than the comparator, and  $-5.0$ , less safe. The experts commented that bimekizumab, overall, has a similar safety/tolerability profile compared to most of the comparators and that, some of the low scores assigned to this drug could be explained by the adverse event related to candidiasis, although they highlighted that this is

**Table 2.** Scores assigned per criterion, and main comments from the multidisciplinary experts committee or observation of subgroup results.

Criterion	Scores (box-and-whisker plot) *	Comments
<b>Need for the intervention</b> Disease severity		<ul style="list-style-type: none"> <li>Moderate-to-severe psoriasis was considered as a severe disease.</li> <li>This high score is due to the consideration of moderate-to-severe psoriasis as a whole, as there are many differences between moderate and severe psoriasis.</li> <li>It has a high impact on patients' quality of life, work environment, and emotional (psychological and psychiatric) spheres.</li> <li>It is not a life-threatening disease. Other skin diseases, such as melanoma, are more serious.</li> <li>Median scores for all subgroups were 4.0.</li> </ul>
Size of affected population		<ul style="list-style-type: none"> <li>There was a consensus (10 out of 12 experts scored 3.0) around the prevalence of psoriasis: 2,3% of the total population in Spain has psoriasis, and 0,6% has moderate-to-severe psoriasis.</li> <li>The difficulty lies in quantifying patients with moderate-to-severe psoriasis who require biologic treatments and those who can be treated with conventional systemic drugs.</li> <li>One of the experts commented that the estimated figure for the population with moderate-to-severe psoriasis in Spain (0,6% of the population) may be underestimated, arguing that, due to economic criteria, such as avoiding or delaying the entry into higher-cost treatments, some patients may be diagnosed as having mild-to-moderate psoriasis.</li> <li>Median scores for all subgroups were 3.0.</li> </ul>
Unmet needs		<ul style="list-style-type: none"> <li>Experts considered that moderate-to-severe psoriasis is a disease with considerable unmet needs.</li> <li>Lower scores were assigned by those who considered only the clinical unmet needs, as the existing therapeutic arsenal provides very effective treatments.</li> <li>Higher scores considered other needs, such as psychological support and access to therapies.</li> <li>Healthcare professionals considered the unmet needs to be lower (median: 3.0), in comparison to other groups (4.0).</li> </ul>
<b>Outcomes of the intervention</b> Level of clearance		<ul style="list-style-type: none"> <li>Interpretation of the results: a score of 5.0 means that bimekizumab is much better than the comparator in relation to level of clearance achieved.</li> <li>Experts agreed with the results, adding that, for all efficacy criteria, they would have expected an absolute consensus of a 5.0 score in the comparison between BKZ and PBO (median was 5.0 in all).</li> <li>Also, experts believe the results between BKZ vs. SEC and BKZ vs. IXE should have been similar (medians are identical, despite different average scores).</li> <li>Results of the subgroups were similar to the overall scores. The exceptions lie in the comparison BKZ vs. SEC (median: patients: 3.5; other groups: 2.0), and BKZ vs. IXE and RIS (healthcare professionals scored the lowest, whilst managers scored the highest).</li> </ul>

(Continued)

Table 2. (Continued).

Criterion	Scores (box-and-whisker plot) *	Comments
Rapidity of clearance		<ul style="list-style-type: none"> <li>• Interpretation of the results: a score of 5.0 means that bimekizumab is much faster than the comparator in achieving clearance targets.</li> <li>• This results are in line with the evidence analysed, reflecting that the IL-17 (BKZ, SEC, and IXE) are the drugs, which provide the fastest onset of action.</li> <li>• Bimekizumab appears to be the drug that delivers the fastest onset of action.</li> <li>• Subgroup results the same as to those obtained globally, with three exceptions: BKZ vs. SEC (medians; healthcare professionals: 2.0; other groups: 3.0); BKZ vs. IXE (1.0; 2.0, and 2.5 for healthcare professionals, managers, and patients, respectively); BKZ vs. RIS (median; healthcare professionals: 3.0; patients: 3.5; managers: 4.0).</li> </ul>
Persistence of clearance		<ul style="list-style-type: none"> <li>• Interpretation of the results: a score of 5.0 means that bimekizumab is much better than the comparators in maintaining the level of clearance over time.</li> <li>• According to the experts, more long-term results and data from real clinical practice are needed to assess persistence after the first year.</li> <li>• They added that secukinumab is a drug, which usually loses efficacy in the long-run.</li> <li>• Overall, for all comparisons except BKZ vs. PBO, healthcare professionals assigned lower scores (medians between 0.0 and 3.0) in relation to the other groups (managers and patients: 3.0-4.0).</li> </ul>
Safety / tolerability		<ul style="list-style-type: none"> <li>• Interpretation of the results: a score of 5.0 means that bimekizumab is much safer and tolerable than the comparator, whilst a score of -5.0 means that bimekizumab is less safe and tolerable than the comparator.</li> <li>• The experts commented that bimekizumab, overall, has a similar safety/tolerability profile compared to most of the comparators.</li> <li>• Some of the low scores assigned to this drug could be explained by the adverse events related to candidiasis, although the experts highlighted that this is perfectly manageable, not leading to treatment discontinuation.</li> <li>• Variability in the scores was high (SD 1.1-2.6) which could be related to the difference in importance given by each expert to the different types of adverse events (total, serious, severe, etc.) produced by the use of the drugs.</li> <li>• Healthcare professionals and managers tended to assign lower scores (mostly between -1.0 and 1.0) than patients (1.5 to 2.0).</li> </ul>
Patient reported outcomes		<ul style="list-style-type: none"> <li>• Interpretation of the results: a score of 5.0 means that bimekizumab is much better than the comparator in achieving patient reported outcomes.</li> <li>• Patient reported outcomes were valued based on quality-of-life scales and convenience of treatment. The experts mentioned that this made scoring and interpretation more difficult.</li> <li>• According to the experts, there tends to be a correlation between patient reported outcomes and the level of clearance achieved by the use of the drugs. Hence, it became more complex to score this criterion in an independent manner.</li> <li>• Convenience entails aspects, which not only are related to the frequency of doses, but also to the pain caused by the shots and induction periods.</li> <li>• Excluding the comparison between BKZ vs. PBO, the highest scores on patient reported outcomes were assigned by the patients (medians between 2.0 and 3.0), related to other groups (healthcare professionals and managers: 0.0-3.0).</li> </ul>

(Continued)





Table 2. (Continued).

Criterion	Scores (box-and-whisker plot) *	Comments
<p><b>Type of benefit of the intervention</b> Type of therapeutic benefit</p>		<ul style="list-style-type: none"> <li>The drug provides a substantial therapeutic benefit to the patients, as it improves results reported by the patients (quality of life and symptoms such as pain, itching, and flaking), and combines a higher level of clearance, rapidity, and persistence with a similar safety and tolerability profile.</li> <li>Despite of not providing a (desirable) cure, bimekizumab represents a step forward in the treatment of moderate-to-severe psoriasis, even considering the sizable number of alternative therapies available.</li> <li>Managers scored a median of 3.0, whilst the other subgroups had a median score of 4.0.</li> </ul>
<p><b>Consistency of the effect</b></p>		<ul style="list-style-type: none"> <li>Interpretation of the results: a score of 5.0 means that the effects of bimekizumab are much more consistent in the treatment of psoriatic arthritis and specific locations of psoriasis (i.e. scalp, nails, palmoplantar, genitals) that those of the comparator.</li> <li>Some of the experts based their score on the existence of an approval for psoriatic arthritis (i.e. risankizumab has not yet been approved to this indication). Others also considered aspects that stand out in each drug (i.e. secukinumab for the treatment of nail psoriasis, or risankizumab for the treatment of genital psoriasis).</li> <li>There are interrelations between some effects: efficacy of psoriatic arthritis and nail psoriasis; efficacy on general level of clearance and scalp psoriasis.</li> <li>Variability on the answers between subgroups was high, and no clear pattern was revealed (i.e. no group scored the highest or the lowest across all comparisons).</li> </ul>
<p><b>Economic consequences of the intervention</b> Cost of intervention</p>		<ul style="list-style-type: none"> <li>Interpretation of the results: a score of 5.0 means that the acquisition of bimekizumab generates substantial savings to the system versus the comparator, whilst a score of -5.0 means that it generates substantial additional costs.</li> <li>In the absence of a price for bimekizumab in Spain (not defined at the time this study was being carried on), we assumed the same annual acquisition cost per patient as that of an IL-17A inhibitor already marketed, such as secukinumab. Thus, a cost per patient of €19,400 was assumed for the first year and €14,900 for the maintenance period, based on notified prices (laboratory sales prices: PVL). The MEC mentioned that this was a very reasonable assumption.</li> <li>Experts recognized that there is a large difference between the notified price and the ones practiced by the market, especially for the biologics that have biosimilars. For this reason, some of the scores of bimekizumab vs. adalimumab took into account the real cost of adalimumab (indicated to be around €3,500 p.a.). This explains the highest variability observed between the scores assigned in this comparison.</li> <li>Healthcare professionals assigned a score of 0 for all comparisons except BKZ vs. ADA and BKZ vs. PBO. Patients assigned scores between 0.0 and -0.5 (except BKZ vs. PBO) and managers gave scores between -2.0 and 1.0 (except BKZ vs. PBO).</li> </ul>
<p><b>Impact on other direct costs</b></p>		<ul style="list-style-type: none"> <li>Interpretation of the results: a score of 5.0 means that bimekizumab would generate substantial savings in other direct costs (hospitalizations, medical visits, etc.) in relation to the comparator. The median score for all comparisons (except BKZ vs. PBO) was 1.0, and there were no negative scores assigned, reflecting that bimekizumab appears to be slightly superior in terms of the impact that its implementation would have on other direct costs.</li> <li>Experts commented that the results obtained are consistent, given the limited available evidence.</li> <li>Variability was low between subgroups. Median scores for all comparisons (except BKZ vs. PBO) were 1.0 for the managers, between 0 and 1 for healthcare professionals and between 1.0 and 2.5 for patients.</li> </ul>

(Continued)

Table 2. (Continued).

Criterion	Scores (box-and-whisker plot) *	Comments
Impact on indirect costs		<ul style="list-style-type: none"> <li>• Interpretation of the results: a score of 5.0 means that bimekizumab would generate substantial savings in indirect costs (i.e. labor productivity) in relation to the comparator.</li> <li>• The results appear to be consistent, in the opinion of the experts.</li> <li>• The impact of psoriasis on patients' work activity generated certain differences of opinions among the committee members. For some experts, it may have little impact, while for others, this impact may be greater due to logistical issues, such as the need for medical visits, or to pick up medications from the hospital pharmacy. Some commented that, in this sense, home dispensing and teleconsultation have resulted in labor productivity improvements.</li> <li>• Variability was low between groups and no scores were extreme cases. Median scores for all comparisons (except BKZ vs. PBO) were 1.0 for the managers, between 0 and 2 for healthcare professionals and between 1.5 and 2.5 for patients</li> </ul>
<b>Knowledge about the intervention</b>		
Quality of evidence		<ul style="list-style-type: none"> <li>• Interpretation of the results: a score of 5.0 means that the quality of the evidence on which the comparison data are based upon is highly relevant and valid, whilst a score of 0.0 means that it is neither relevant or valid.</li> <li>• The quality of evidence generated by the four head-to-head trials (direct comparisons: BKZ vs. PBO, ADA, UST, and SEC) was considered as very relevant and valid, whilst the indirect comparisons (BKZ vs. IXE and RIS) were considered relatively less relevant, as the comparisons had less scientific rigor ("eyeball" comparisons).</li> <li>• All experts have identical scores for the BKZ vs. IXE and BKZ vs. RIS comparisons. For the head-to-head trials, healthcare professionals assigned median scores of 5.0 (patients: 4.5; managers: 4.0). For the indirect comparisons, median scores from the healthcare professionals and managers were 2.0 (patients: 4.0).</li> </ul>
Expert consensus / CPG		<ul style="list-style-type: none"> <li>• Interpretation of the results: a score of 5.0 means that bimekizumab is or will be better recommended than the comparator, and -5.0 means that the comparator is or will be better recommended than bimekizumab in future clinical practice guidelines updates or expert consensus.</li> <li>• The MEC considered that bimekizumab will be positioned similarly to other first-line biological drugs for the treatment of moderate-to-severe psoriasis in the future updates of clinical practice guidelines.</li> <li>• According to them, some of the elements that could differentiate bimekizumab from the others are the form of administration (every 2 months); the potential approval for the treatment of psoriatic arthritis and the maintenance of efficacy levels.</li> <li>• Overall, patients have assigned the highest scores to this criterion (medians between 1.5 and 3.5, excluding the comparison of BKZ vs. PBO), whilst healthcare professionals and managers assigned similar scores (mostly between 1.0 and 2.0)</li> </ul>

\*The box-and-whisker plot visually represents various descriptive statistics of the scores given for this criterion. The lower and upper limits of the graph represent the minimum and maximum scores. The box represents the central 50% of the scores awarded, as it is bounded by the lower (25%) and upper (75%) quartile. The "x" represents the average value of the scores, and the line dividing the boxes (which is the number that appears on the table) represents the median (in some cases, the median coincides with one of the two quartiles represented graphically). The circles represent the extreme cases ("outliers"), which show scores that deviate more than 1.5 times from the interquartile ranges. Finally, greater distances between the extremes of the box and the graph represent greater dispersion in the responses. CPG: clinical practice guidelines. BKZ: Bimekizumab. PBO: placebo. ADA: Adalimumab. UST: Ustekinumab. IXE: Ixekizumab. SEC: Secukinumab. RIS: Risankizumab.

perfectly manageable, not leading to treatment discontinuation.

The scoring of the criterion ‘patient reported outcomes’ was based on both quality-of-life scales and convenience of treatment, with results ranging from  $4.6 \pm 0.7$  (median: 5.0) for BKZ vs. PBO to  $0.8 \pm 1.3$  (median: 1.0) for BKZ vs. RIS. A score of 5.0 means that bimekizumab provides much better patient reported outcomes than the comparator. According to the MEC, there is a correlation between level of clearance and patient reported outcomes, fact which posed a challenge for an independent assessment of this criterion.

‘Type of therapeutic benefit,’ received a mean score of  $3.6 \pm 0.7$  (median 4.0), reflecting the belief that bimekizumab produces a high therapeutic benefit, given it provides a high level of clearance and a rapid onset of action, which are sustained over time. In addition, the therapeutical benefits were associated with an improvement in patients’ quality of life and the relief of the main symptoms, such as pain, itching, and scaling.

Furthermore, ‘consistency of the effect’ was scored between  $4.5 \pm 0.8$  (median: 5.0) for BKZ vs. PBO, and  $0.9 \pm 1.6$  (median: 0.5) for BKZ vs. IXE. A score of 5.0 means that bimekizumab is much more consistent than the comparator. Some of the experts based their score on whether or not the drug was approved for the indication of psoriatic arthritis, or could potentially receive this indication in the future, based on published or ongoing clinical trials [33,34], while others also considered aspects that stand out in each drug (i.e. secukinumab for the treatment of nail psoriasis).

The economic consequences were appraised in three criteria, the first being ‘cost of the intervention.’ In the absence of a price for bimekizumab in Spain (not defined at the time this study was being carried on), we assumed the same annual acquisition cost per patient as that of an IL-17A inhibitor already marketed, such as secukinumab (€19,400 for the

first year and €14,900 for the maintenance period, based on ‘notified prices’ [laboratory sales prices: PVL]).

Overall mean scores for the criterion ‘cost of the intervention’ ranged from  $0.8 \pm 0.8$  (median: 1.0) for BKZ vs. RIS to  $-3.8 \pm 1.9$  (median:  $-5.0$ ) for BKZ vs. PBO. A score of +5.0 means that the acquisition of bimekizumab generates substantial savings to the system versus the comparator, and  $-5.0$ , substantial additional costs. There was a consensus on the large difference that exists between the notified price reported and the price paid in practice, especially for the biologics for which there are biosimilars. Thereupon, for the scoring of bimekizumab vs. adalimumab, the MEC took into account the real cost of adalimumab, which was informed to be nearly €3500 per year.

The median score for all comparisons (except BKZ vs. PBO) related to the ‘impact on other direct costs’ and the ‘impact on indirect costs’ were 1.0 (SD ranged from 0.6 to 1.2), and no negative scores were given, reflecting that bimekizumab appears to be slightly superior in terms of the impact that its implementation would have on all other costs for the system, such as hospitalizations, medical visits and productivity losses. The experts commented that the results are consistent, based on the narrow evidence available for these criteria.

Overall, the ‘quality of evidence’ provided by the clinical trials analyzed was considered as very relevant and valid (medians between 4.0 and 4.5; SD between 1.0 and 1.2) for the head-to-head comparisons (BKZ vs. PBO, ADA, UST, and SEC), whilst the indirect comparisons (BKZ vs. IXE and RIS) were considered as relatively less relevant (medians:  $2.0 \pm 1.4$ ), as comparisons had less scientific rigor.

The last criterion appraised was ‘expert consensus/clinical practice guidelines’. The MEC considered that bimekizumab will be positioned similarly to other first-line biological drugs for the treatment of moderate-to-severe psoriasis in the future

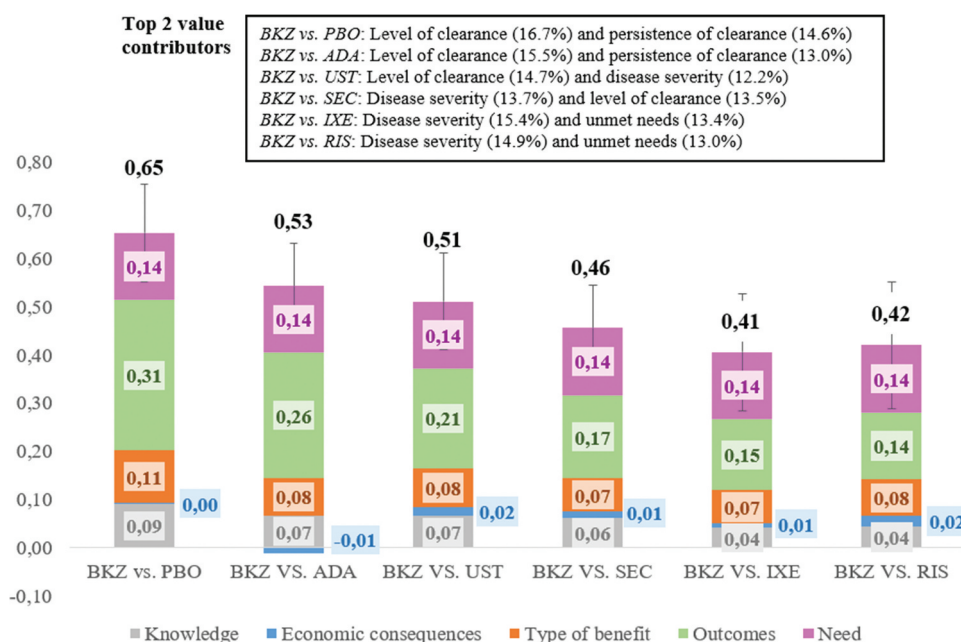


Figure 2. Value contribution of bimekizumab compared to placebo and five biological drugs according to the MCDA framework for the assessment of drugs in moderate-to-severe psoriasis. Mean value contribution per domain and overall value estimates are shown. Error bars show standard deviations across the twelve participants. BKZ: Bimekizumab. PBO: placebo. ADA: Adalimumab. UST: Ustekinumab. SEC: Secukinumab. IXE: Ixekizumab. RIS: Risankizumab.

updates of clinical practice guidelines (medians between 1.0 and 2.0; SD between 1.1 and 2.0). Some of the elements that could differentiate bimekizumab from the others, according to the experts, are the form of administration (every 2 months); the potential approval for the treatment of psoriatic arthritis and the maintenance of efficacy levels.

### 3.3. Value estimates: combining weights and scores

The integration of weights and scores of each panelist resulted in overall value estimates scaling between  $-1$  and  $1$ . Bimekizumab provided a high added value against all comparators analyzed. Specifically, the value contribution of bimekizumab for the treatment of moderate-to-severe psoriasis was: BKZ vs. PBO ( $0.65 \pm 0.10$ ; median:  $0.64$ ), BKZ vs. ADA ( $0.53 \pm 0.09$ ; median:  $0.53$ ), BKZ vs. UST ( $0.51 \pm 0.10$ ; median:  $0.50$ ), BKZ vs. SEC ( $0.46 \pm 0.09$ ; median:  $0.45$ ), BKZ vs. IXE ( $0.41 \pm 0.12$ ; median:  $0.41$ ) and BKZ vs. RIS ( $0.42 \pm 0.13$ ; median:  $0.47$ ) (Figure 2).

The five criteria with the greatest contribution to the final estimated values were the level of clearance (12%–17%), persistence of clearance (10%–15%), disease severity (10%–15%), unmet needs (8%–13%) and type of therapeutic benefit (8%–13%). Negative contributions were only revealed in two comparisons related to the safety criterion and in four comparisons regarding drug acquisition costs, suggesting that BKZ is less safe than PBO and RIS and more costly than PBO, ADA, UST, and IXE.

In the analysis by domains, comparative outcomes of the intervention contributed between 30% and 56% of the final estimated values, followed by the need for the intervention (21%–34%), the type of benefit (11%–22%), the knowledge about the intervention (10%–17%) and the economic consequences of the intervention ( $-4\%$  to  $+9\%$ ) (Supplementary file 2).

### 3.4. Replicability and consistency

The consistency of the weights between the test and the retest was high, with an average intraclass correlation coefficient (ICC) of  $0.8422$ . Similarly, the retest scores were very resemblant to those of the test, in all comparisons performed, with mean intraclass correlation coefficients ranging from  $0.9178$  to  $0.9775$ . The consistency of the final estimated values between the test and the retest was also high, with total average ICCs ranging between  $0.6160$  and  $0.8898$ . The final mean values obtained in the retest were lower than those obtained in the test, with variations between  $-2.8\%$  and  $-10.6\%$ . The final value estimates obtained by the application of an alternative weighting method (direct 1–5 rating scale) were almost identical as the ones obtained by the 100-point distribution method ( $\Delta$ -2.0% to  $+1.3\%$ ) (Supplementary file 3).

## 4. Discussion

The decision-making processes related to the appraisal of new drugs in moderate-to-severe psoriasis are complex, as they involve the need to balance multiple needs from a wide

range of stakeholders [1]. The mainstream methodological approach currently used to support evaluations are cost-effectiveness models [2].

However, the MCDA methodology can be particularly useful as a complement to this approach, as it consists of a structured (validated stepwise methodology), multi-dimensional (participation of experts from a broad range of professional fields), transparent (criteria, weights, and scores are explicit) and systematic approach (replicable), incorporating various criteria and their individual value contribution to the decision or allocation problem [3]. Its popularity has become evident in the healthcare field in the recent years, both nationally and internationally [3,35–38], in diverse areas, such as oncology [39–42], rare diseases [43–46] and dermatology [23,24].

This study has adopted a holistic and transparent methodological approach in the assessment of the value contribution of bimekizumab in comparison to placebo and five biological drugs for the treatment of moderate-to-severe psoriasis in Spain, through a multidisciplinary panel of experts involved in the clinical, management, and political decision-making aspects of the pathology. The EVIDEM framework was adapted into a set of 15 criteria relevant to the drug appraisal context of psoriasis. Notably, this is the first MCDA to include three efficacy criteria in a disaggregated manner (level of clearance, rapidity, and persistence of clearance), as well as to integrate another relevant criterion to this setting, which is consistency of the effect in the treatment of other indications and specific psoriasis locations.

This is also the first MCDA in moderate-to-severe psoriasis that has included six comparators, which were evaluated against bimekizumab by a MEC with a broader professional profile in relation to previous MCDA in this area. In other MCDA conducted in Spain in the area of moderate-to-severe psoriasis, the EVIDEM framework was used without any adaptations, with a smaller number of comparators, and expert committees that lacked the vision of the profiles included in this MCDA, such as nursing, psychology, and political professions [23,24]. In one of them, 45 experts (national and regional evaluators in Spain) weighted the 13 criteria of the EVIDEM framework, and five of them (two hospital pharmacists, one regional payer, one psoriasis expert, and one patient representative) scored ixekizumab versus four comparators [23]. In another, which was performed through a committee of 10 experts (three dermatologists, four patients, two regional payers, and one health economist), the EVIDEM framework was also applied in a comparison between secukinumab and three other drugs [24].

According to this MCDA, bimekizumab provides a positive value contribution in the treatment of moderate-to-severe psoriasis in Spain, in comparison to all drugs analyzed. The final estimated values ranged from  $0.42$  (vs. risankizumab) to  $0.65$  (vs. placebo). These results, despite the methodological differences explained above, are in line with those obtained in the other two MCDA applied to moderate-to-severe psoriasis in Spain [23,24]. The final values estimated by Badia et al. (2017) for ixekizumab



ranged between 0.36 (vs. secukinumab) and 0.45 (vs. adalimumab) [23], whilst Zozaya et al. (2018) estimated values for secukinumab between 0.39 (vs. ustekinumab) and 0.45 (vs. etanercept) [24].

In any case, the importance of this type of study does not lie so much in the exact amounts of the value estimates, but in understanding the value drivers of the drug that is being evaluated. In this sense, the multidisciplinary debate generated was key to understanding the strengths and weaknesses of bimekizumab compared to other drugs in each of the attributes considered, from a qualitative perspective based on insights provided by the MEC.

This study is not exempt from certain limitations, inherent to any MCDA, which should be pointed out. The first limitation stems from the composition of the expert committee itself, as the limited number of experts may not be representative of the opinions of all the stakeholders involved. On the other hand, the small panel size facilitated discussions and sharing of insights, allowing for a more in-depth analysis of different value contributors. Secondly, the evidence matrix gathered information which were limited to the publicly available data at the time of the study, and some evidence was scarce (i.e. impact on other direct and indirect costs). Hence, results could be different if faced with new information, meaning that a follow-up of this study could be of added value in the future. Thirdly, misinterpretation of some evidence or scoring scale may have occurred, due to the cognitive complexity of the exercise. To minimize this potential limitation, scoring was preceded by a thorough explanation of the MCDA methodology, the assumptions made and the interpretation of the values. Fourthly, for two of the comparisons done in this MCDA (BKZ vs. IXE and BKZ vs. RIS), there were no head-to-head trials available, so that value judgment was mainly based on evidence from indirect comparisons, through studies, which were undertaken in different patient populations and conditions. This added difficulty was partially gathered by the MCDA methodology, as one criterion allows for a weighting according to the quality of evidence. Fifthly, all data related to pricing and, when applicable, to other criteria, were based on the Spanish reality, and results may differ if applied in other countries. Finally, this MCDA could have been enhanced by the addition of some aspects, such as the inclusion of all comparators available, the use of real practiced prices (versus notified prices), or the inclusion of the qualitative criteria.

## 5. Conclusions

Under this methodology of increasing use in the healthcare, bimekizumab has been evaluated by a multidisciplinary committee as a drug that adds value to the treatment of moderate-severe psoriasis, by providing a high degree of clearance, rapidly and persistently over time, with a very similar safety profile to other drugs.

Exercises of this type allow us to understand where the value of health interventions lies for the different agents, encourage communication between them and can serve as a reference in decision-making on evaluation, financing, and reimbursement. In the future, it would be desirable to continue advancing in the development of the MCDA

methodology and to extend its use, so that health care decision making can be carried out in a framework of greater transparency, consistency, and efficiency.

## Authors contributions

N Zozaya and A Hidalgo participated in the conception and design of the work. N Zozaya, F Abdalla, S Alfonso, J Balea, J Carrascosa, O Delgado, F Dolz, A Garcia-Ruiz, P Herranz, A Manfredi, J Martinez, P Morales de los Rios Luna, L Puig and S Ros have contributed to the acquisition of data. N Zozaya and F Abdalla have analyzed and interpreted the data. F Abdalla has drafted the manuscript, and N Zozaya has substantively reviewed it. All authors have approved the manuscript and have agreed both to be personally accountable for the author's contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

## List of abbreviations

ADA Adalimumab  
 AEMPS Spanish Medicines and Healthcare Products Agency  
 BKZ Bimekizumab  
 EMA European Medicines Agency  
 EVIDEME Evidence and Value: Impact on DEcision Making  
 IL Interleukin inhibitors  
 IXE Ixekizumab  
 MCDA Multi-Criteria Decision Analysis  
 MEC Multidisciplinary Experts Committee  
 PASI Psoriasis Area and Severity Index  
 PBO Placebo  
 RIS Risankizumab  
 SEC Secukinumab  
 TNF Tumor Necrosis Factor inhibitors  
 UST Ustekinumab

## Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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## Declaration of interest





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Papers of special note have been highlighted as either of interest (\*) or of considerable interest (\*\*\*) to readers.

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