PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost-effectiveness analysis of ixekizumab versus secukinumab in patients with psoriatic arthritis and concomitant moderate-to-severe psoriasis in Spain
AUTHORS	Schweikert, Bernd; Malmberg, Chiara; Núñez, Mercedes; Dilla, Tatiana; Sapin, Christophe; Hartz, Susanne

VERSION 1 – REVIEW

REVIEWER	Laura Coates University of Oxford UK I have received honoraria from Eli Lilly for consultations and talks. I have not been involved in this project.
REVIEW RETURNED	18-Jul-2019

GENERAL COMMENTS	This is an interesting paper using the York HE modelling to compare the use of secukinumab and ixekizumab in a Spanish population. Major comments: 1. I think the methodology is robust but I am concerned about the conclusions. Although the authors do state a modest difference, they lead by saying that ixekizumab is shown to be superior in outcome to secukinumab and I don't think the magnitude of difference can support this claim given the potential variation in costs within the model. 2. Age and gender distribution are taken from the SPIRIT trials but we know that in real life, patients differ significantly from trial populations. 3. I don't really understand why the timepoint for induction is different for secukinumab and ixekizumab? 4. While I agree that a combination of joint and skin response is optimal, this is obviously quite a high bar to meet and is probably not realistic in practice. Usually these are considered separately and there is a significant discrepancy between PsARC which is quite a low bar compared to PASI which is a high target. 5. What doses were modelled? For patients with PsA, lower doses with mild to moderate psoriasis may use significantly lower doses. In real practice that represents around 80% of the population in rheumatology clinics. 6. We know very little about the annual discontinuation rate on these drugs as they are relatively new but this will affect the model significantly.

REVIEWER	Luis Puig Hospital de la Santa Creu i Sant Pau, Spain.

	Receipt of grants/research supports or participation in clinical trials (paid to Institution) Abbvie, Almirall, Amgen, Boehringer Ingelheim, Celgene, Janssen, Leo-Pharma, Lilly, Novartis, Pfizer, Regeneron, Roche, Sanofi, UCB Receipt of honoraria or consultation fees (paid to myself) Abbvie, Almirall, Amgen, Baxalta, Biogen, Boehringer Ingelheim, Celgene, Fresenius-Kabi, Gebro, Janssen, Leo-Pharma, Lilly, Merck-Serono, MSD, Mylan, Novartis, Pfizer, Regeneron, Roche, Sandoz, Samsung-Bioepis, Sanofi, UCB. Participation in a company sponsored speaker's bureau Celgene, Janssen, Lilly, MSD, Novartis, Pfizer Stock shareholder None Other support (please specify) None
REVIEW RETURNED	29-Nov-2019

GENERAL COMMENTS	I have found no references regarding the input parameters for ixekizumab and secukinumab: "For efficacy inputs, the convergence diagnostics and output analysis of the Bayesian NMA (?) was used instead of applying parametric distributions. The input parameters included PsARC and PASI response rates (?), changes in HAQ-DI based on response criterion (?), costs based on HAQ-DI and PASI (?), discontinuation rates (?), various healthcare-related costs and the use of resources..."

REVIEWER	Lorenzo Sabatelli Incyte Biosciences International Sarl, Lausanne, Switzerland (employer) & GLOBMOD Health, Barcelona, Spain (currently on leave) I am currently employed by and own shares of Incyte Biosciences International Sarl, in Lausanne, Switzerland I am also the founder and sole proprietor of GLOBMOD Health, in Barcelona, Spain, a company with interests in health data, decision sciences for HEOR and Access, and healthcare R&D. This review is based solely my personal technical expertise, and solely reflects my personal views.
REVIEW RETURNED	16-Jan-2020

GENERAL COMMENTS	This study assesses the cost-effectiveness of ixekizumab versus secukinumab in patients with psoriatic arthritis and concomitant moderate-to-severe psoriasis from the perspective of the Spanish health system. This topic is important for patient outcome optimization, and in the context of healthcare resource allocation in Spain. Before I can perform a more in-depth review, I would like the authors to clarify a few points about the available evidence used to parameterize the model. If necessary, I would recommend providing a separate supplementary file or an appendix to the manuscript. In particular, additional information is needed with reference to: 1. The comparability of trial populations and outcomes of ixekizumab versus secukinumab: was an ITC performed or used? (if so please provide details and specify whether it takes into any account results from recent trials. If not, I would recommend to

	specify which assumptions were made and if/how they were tested); 2. How the induction periods were defined and what their sources are (there seems to be a difference between the modeling assumptions and what the label suggests for treatment initiation and time to response, please see text below); 3. The utility values used for each state of the model should be reported; 4. The derivation/adaptation of the costs to the Spanish healthcare system associated with PsA severity ; 5. The distributions and parameters used for the probabilistic sensitivity analysis. Thanks in advance for your feedback.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Laura Coates
Comment 1 (page 15): I think the methodology is robust but I am concerned about the conclusions. Although the authors do state a modest difference, they lead by saying that ixekizumab is shown to be superior in outcome to secukinumab and I don't think the magnitude of difference can support this claim given the potential variation in costs within the model.

Response: Thank you for your in-depth review of the manuscript and for providing feedback on areas that could be improved. We acknowledge that the differences between ixekizumab and secukinumab are small, and have rephrased the text accordingly to further emphasise this (Conclusion, page 13). In addition, a sentence has been added in the 'Discussion' (third paragraph, page 12) noting that, while the model employs list prices, the true drug acquisition costs in clinical practice (potentially including confidential discounts or similar) will have an impact on the real-world cost differences.

Comment 2 (page 8): Age and gender distribution are taken from the SPIRIT trials but we know that in real life, patients differ significantly from trial populations.

Response: Patient demographics, particularly with regards to age and gender, from the SPIRIT trials do not differ greatly from real-world populations in Spain (Queiro et al. Arthritis Research & Therapy 2017;19:72). Therefore, we feel that using real-world age and gender distribution is unlikely to have a major impact on the results of the analysis.

Comment 3 (pages 8–9): I don't really understand why the timepoint for induction is different for secukinumab and ixekizumab?

Response: In the manuscript, we mention that the induction periods were chosen in alignment with the follow-up period commonly observed in clinical practice in Spain (Methods – Model overview, third paragraph, page 7). This choice has also been confirmed by a local medical expert panel consulted on this topic, and is intended to make the analysis more relevant to decision making in clinical practice. The difference in the length of induction period between the two drugs also acknowledges a degree of difference in the availability of clinical trial data for ixekizumab and secukinumab (i.e., across the included studies, more week 16 than week 12 data is available for secukinumab). In addition, when it comes to the impact of this selection on the model results, based on the mechanics of the model a longer induction period for secukinumab is a conservative approach, which might favour secukinumab rather than ixekizumab in the analysis. A similar sentence has been added to better clarify why different time points were used in the model (Methods – Model overview, third

paragraph, page 7).

Comment 4 (page 8): While I agree that a combination of joint and skin response is optimal, this is obviously quite a high bar to meet and is probably not realistic in practice. Usually these are considered separately and there is a significant discrepancy between PsARC which is quite a low bar compared to PASI which is a high target.

Response: As this analysis is comparing two interleukin (IL)-17A antagonists, which both have proven high efficacy and effectiveness on skin symptoms, we feel that the choice of a high PASI threshold is reasonable and relevant for the respective decision making in clinical practice. In Spain, most psoriatic arthritis (PsA) patients treated with ixekizumab and secukinumab have been observed to also have concomitant psoriasis (Busquets-Pérez et al. Clin Rheumatol 2012;31:139–143; de Vlam et al. Rheumatol Ther 2018;5:423–436). Therefore skin response, in addition to joint response, is a key treatment goal in clinical practice. This is reflected in our analysis, modelling a patient population with PsA and concomitant moderate-to-severe psoriasis.

Comment 5 (page 9): What doses were modelled? For patients with PsA, lower doses with mild to moderate psoriasis may use significantly lower doses. In real practice that represents around 80% of the population in rheumatology clinics.

Response: Doses were modelled as per European market authorisation (Methods – Treatment sequences, first paragraph, page 7). Please refer to Table 2 in the manuscript, which states the modelled doses (page 20). As elaborated above, most patients treated with the two drugs under consideration may be assumed to have concomitant moderate-to-severe psoriasis, for which the respective dosages apply.

Comment 6 (page 9): We know very little about the annual discontinuation rate on these drugs as they are relatively new but this will affect the model significantly.

Response: We fully agree that there is, at present, still a lack of data to update the assumptions around the annual discontinuation rate in the model. Although it would be desirable to use real-world treatment discontinuation or drug survival data to confirm or correct the current parameters, these data are still limited, especially for newer agents, such as ixekizumab and secukinumab. We therefore followed the established approach of the York model; however we are in full agreement that this issue presents a research need for future updates. A sentence has been added in the ‘Discussion’ (third paragraph, page 12) acknowledging this.

Reviewer 2: Luis Puig
Comment 1 (page 12): I have found no references regarding the input parameters for ixekizumab and secukinumab:
a) “For efficacy inputs, the convergence diagnostics and output analysis of the Bayesian NMA was used instead of applying parametric distributions.”

Response: We thank you for your concise review of our manuscript.

The efficacy input parameters for ixekizumab and secukinumab are derived from a network meta analysis (NMA), which has just been published and is available at https://rmdopen.bmj.com/content/6/1/e001117 (Ruyssen-Witrand et al. RMD Open 2020;6:e001117. doi: 10.1136/rmdopen-2019-001117). The selection of endpoints considered is based on and aligned with the York model, which is the current “gold standard” in economic modelling in PsA.
To make these inputs more transparent, we have added a table with the full list of respective parameters in a supplementary appendix (Supplementary Table 1). For efficacy data a non-

parametric approach was chosen by directly using the values from the outputs of the NMA models ("CODA", convergence diagnostics and output analysis), as opposed to drawing from a parametric distribution. This approach allows preserving the correlation structure between the variables from the NMA.

b) "The input parameters included PsARC and PASI response rates,"

Response: PASI and PsARC response are based on the current standard of modelling and are referenced in the manuscript (Methods – Treatment effect, first paragraph, pages 7–8). In addition, efficacy input data from a related NMA have been included in Supplementary Table 1.

c) "changes in HAQ-DI based on response criterion,"

Response: Similarly, this is referenced in the manuscript (Methods – Treatment effect, first paragraph, page 7–8).

d) "costs based on HAQ-DI and PASI,"

Response: The inclusion of health state related costs follows the York model, and accounts for costs caused by the disease besides drug acquisition and monitoring costs. Please see 'Methods – Resource use and costs' (second paragraph, page 9) in the manuscript for the reference. Additional text has been added to clarify further.

e) "discontinuation rates,"

Response: Please see 'Methods – Treatment sequences' (first paragraph, page 7) in the manuscript, which includes the references.

f) "various healthcare-related costs and the use of resources"

Response: Please see 'Methods – Resource use and costs' (first paragraph, page 9) and Table 2 in the manuscript for the references.

Reviewer 3: Lorenzo Sabatelli
This study assesses the cost-effectiveness of ixekizumab versus secukinumab in patients with psoriatic arthritis and concomitant moderate-to-severe psoriasis from the perspective of the Spanish health system. This topic is important for patient outcome optimization, and in the context of healthcare resource allocation in Spain.
Before I can perform a more in-depth review, I would like the authors to clarify a few points about the available evidence used to parameterize the model. If necessary, I would recommend providing a separate supplementary file or an appendix to the manuscript. In particular, additional information is needed with reference to:

Comment 1 (page 21): The comparability of trial populations and outcomes of ixekizumab versus secukinumab: was an ITC performed or used? (if so please provide details and specify whether it takes into any account results from recent trials. If not, I would recommend to specify which assumptions were made and if/how they were tested).

Response: We thank you for taking the time to review our manuscript and providing valuable feedback. The comparative efficacy inputs for ixekizumab and secukinumab are derived from a NMA, which has just been published and is available at https://rmdopen.bmj.com/content/6/1/e001117 (Ruyssen-Witrand et al. RMD Open 2020;6:e001117. doi: 10.1136/rmdopen-2019-001117). The

baseline study characteristics including trial populations and outcomes have been adequately evaluated before conducting the comparative efficacy analysis to investigate heterogeneity and ensure comparability; this is discussed in more detail in the publication noted above.
For transparency, we have provided a table detailing the efficacy input data used in the economic analysis in the supplementary appendix (Supplementary Table 1).

Comment 2 (pages 8–9): How the induction periods were defined and what their sources are (there seems to be a difference between the modeling assumptions and what the label suggests for treatment initiation and time to response, please see text below).

Response: The induction periods were chosen in alignment with the follow-up period commonly observed in clinical practice in Spain (Methods – Model overview, third paragraph, page 7). This choice has been confirmed by a local medical expert panel, and is intended to make the analysis more relevant to decision making in clinical practice. The difference in the length of induction period between the two drugs also acknowledges a degree of difference in the availability of clinical trial data for ixekizumab and secukinumab (i.e., across the included studies, more week 16 than week 12 data is available for secukinumab). A similar sentence has been added for further clarification (Methods – Model overview, third paragraph, page 7).

Comment 3 (pages 8): The utility values used for each state of the model should be reported.

Response: In line with the approach used in the York model, utilities in our model are not allocated to health states per se, but are modelled through equations linking in each cycle treatment- and time-dependent HAQ-DI and PASI to EQ-5D based utilities. This is briefly explained in the 'Methods – Health utilities' (pages 8–9).

Comment 4 (page 11): The derivation/adaptation of the costs to the Spanish healthcare system associated with PsA severity.

Response: Besides the costs for drug acquisition and monitoring, the model assumes that the disease severity will cause additional financial burden. The respective costs, related to HAQ-DI and PASI, have been estimated in the past and have been used in the York model, as well as in subsequent models. In the absence of more recent or more local data, the existing costs thus derived have been updated and converted to 2018 Euros.

Comment 5 (pages 11–12): The distributions and parameters used for the probabilistic sensitivity analysis.

Response: We have included details on the parameters used in the probabilistic sensitivity analysis in a supplementary appendix (see Supplementary Table 2).

We hope that these responses and amendments adequately address the reviewers' comments and that the revised manuscript is now acceptable for publication in BMJ Open.

Thank you again for your time and efforts in the consideration of our work.

VERSION 2 – REVIEW

REVIEWER	Laura Coates NDORMS, University of Oxford UK
REVIEW RETURNED	30-Mar-2020

GENERAL COMMENTS	Thank you for addressing my comments. I am still not completely sure why the modelling would only use the higher dose of secukinumab. I think it is important that IL-17 inhibitors are seen a reasonable option for PsA not just for severe psoriasis. Therefore I think it would be helpful to consider the mixed doses. The H2H studies of TNF and IL-17 inhibitors showed around 10-20% of patients with severe psoriasis requiring the higher dose.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1: Laura Coates

Comment: Thank you for addressing my comments. I am still not completely sure why the modelling would only use the higher dose of secukinumab. I think it is important that IL-17 inhibitors are seen a reasonable option for PsA not just for severe psoriasis. Therefore I think it would be helpful to consider the mixed doses. The H2H studies of TNF and IL-17 inhibitors showed around 10-20% of patients with severe psoriasis requiring the higher dose.

Response: Thank you for your further review of the manuscript. We acknowledge that the proportion of patients with PsA and concomitant moderate-to-severe psoriasis requiring the higher dose of secukinumab in H2H studies of TNF and IL-17 inhibitors is small. However, in this model we are focused on a population of patients with moderate-to-severe psoriasis from a Spanish perspective, which we consider of interest to decision makers and stakeholders as described in the manuscript. The higher dose of secukinumab is in-line with European and local recommendations for this patient population.

We hope that these responses and amendments adequately address the reviewer's comments and that the revised manuscript is now acceptable for publication in *BMJ Open*.

Thank you again for your time, efforts and consideration of our work.