PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

(This paper received five reviews from its previous journal but only four reviewers agreed to published their review.)

ARTICLE DETAILS

TITLE (PROVISIONAL)	Effectiveness and safety of golimumab in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis under real-life clinical conditions: non-interventional GO-NICE study in Germany
AUTHORS	Krueger, Klaus; Burmester, Gerd; Wassenberg, Siegfried; Bohl-Bühler, Martin; Thomas, Matthias

VERSION 1 – REVIEW

REVIEWER	Fonseca, Joao Rheumatology and Metabolic Bone Diseases Department, Hospital de Santa Maria, CHLN, Rheumatology Research Unit, Instituto de Medicina Molecular, Faculty of Medicine, University of Lisbon, Lisbon Academic Medical Centre, Portugal
REVIEW RETURNED	18-Nov-2017

GENERAL COMMENTS	1- Abstract and introduction: no need for the alpha after TNF 2- introduction: rephrase last sentence of the first paragraph. Sounds strange as it stands. The message is just that TNF is a Key player in RA, AS and PsA. 3- Methods: It is said that no explicit exclusion criteria was formulated. However, for practical purposes patients were for sure included only if the common clinical exclusion criteria for using these drugs were absent. The reviewer suggests making a comment on this. Particularly important in the case of TB. Maybe alluding to local guidelines or EULAR guidelines. 4- Methods: How was data captured? Was a specific clinical record form developed? Was data captured from a registry? 5- Results: Did dermatologists scored joint counts? 6- Results: Why ASDAS was not calculated? This would increase the interest of the results. Is data available for that? If yes it should be included in the paper. 7- Results: How was the screening status for TB done in the patients that developed TB? How many months after treatment initiation did TB appear? 8- Results: Is it really impossible to retrieve information on the deaths? Why?

REVIEWER	van riel, piet

	Radboud Institute for Health Sciences, IQ healthcare
REVIEW RETURNED	24-Nov-2017

GENERAL COMMENTS	Effectiveness and safety of golimumab in patients…. I do agree with the authors that it is important to collect and publish data from daily clinical practice about the treatments of patients to add this to the results and experiences of randomized clinical trials. The combination of these two sources of information gives us a good idea about the effectiveness and safety of the used treatments. Therefore I appreciate the efforts of the group to report about the data collected in daily clinical practice. However it is important, like in RCT's, to report carefully about the population and the withdrawals/lost to follow-up over time and make sure that correct conclusions are being drawn. I agree that the data about safety are correctly presented: all adverse events etc about the patients who had received at least one dose of the drug are being presented. I do however have problems with the presentation and conclusions of the efficacy data. Data about for instance remission rate and disease activity are being given for less than 50% of the original patients after 2 years. It is not correct for instance to state that 44.6% of the patients are being in remission after 24 months as about 60% have been withdrawn due to inefficacy. Yes 44.6 % of the remaining patients are in remission . I don't understand the analyses of all patients (N=474) over the 24 month period, what happened with the DAS28 of patients for instance who dropped out at week 16 due to lack of efficacy? (Figure 5) Figure 3: numbers are missing for low disease activity

REVIEWER	Montecucco, Carlomaurizio University of Pavia; Early Arthritis Clinic, IRCCS Policlinico S. Matteo Foundation, Rheumatology
REVIEW RETURNED	30-Nov-2017

GENERAL COMMENTS	This is a 24 months observational study evaluating effectiveness and safety of GLM in all the three main indications in rheumatology (RA, PsA, SpA). The study is well conducted, the number of enrolled patients is highly significant and the paper reads well. I just wonder why retention rate has not been specifically addressed in results and discussion. This could give additional relevant information and allow comparison with several recently published studies on Golimumab in real life (e.g. Iannone F et al, Semin Arthritis Rheum 2017; Svedbom A et al. Patient Prefer Adherence 2017; Manara M et al, Clin Exp Rheumatol 2017) in addition to RCTs.

REVIEWER	Gómez-Reino, Juan J. Hospital Clinico Santiago de Compostela, Rheumatology
REVIEW RETURNED	03-Dec-2017

GENERAL COMMENTS	In this study based on an open-label, multicenter, prospective observational study of the effectiveness and safety of golimumab in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis under real-life clinical conditions, Klaus Krueger et al. conclude that GLM SC once monthly led to remarkable improvements in clinical effectiveness in patients with various inflammatory rheumatic diseases in a real-life setting in Germany. The article has important drawbacks

	1. Although the authors state that a significant number of patients were followed prospectively, the data does not support this assertion. A total of 661 of 1,458 patients discontinued the treatment prematurely. 2. The overall 24-month retention rate was 45% (40% for RA, 46% for PsA, and 51 for AS). This is not a "remarkable improvement in clinical effectiveness" 3. Missing data are frequently encountered in observational studies. Estimates based on complete-case analysis might be biased if patients with missing data and complete data differ. The STROBE guidelines (Lancet, 370:1453-1457, 2007) recommend that observational studies should report the amount of missing data, the number of individuals used for analysis at each stage of the study, reasons for non-response and the method used to handle missing data in the analyses. The authors report the results according to these guidelines just in part. More specific, they should describe the reason for discontinuation for all patients. According to the data provided, reason for discontinuation is missing in 169 patients. More important, missing data is not accounted for. All in all, the analysis is the analysis of completers at 24-month 4. What the authors call "all AR" and "all AS" populations at months 18, 21 and 24 is constituted largely by the completers. The overlapping of the effectiveness in "all populations" and completers is expected.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Comments to the Author
1- Abstract and introduction: no need for the alpha after TNF
Response: The –α was omitted.

2- introduction: rephrase last sentence of the first paragraph. Sounds strange as it stands. The message is just that TNF is a Key player in RA, AS and PsA.
Response: The sentence: "Tumour necrosis factor (TNF) acts as a key cell signalling protein (cytokine) involved in systemic inflammation, and is a treatment target in the named manifestations of inflammatory arthritis" was replaced by "Tumour necrosis factor (TNF) is a key player in RA, PsA and AS."

3- Methods: It is said that no explicit exclusion criteria was formulated. However, for practical purposes patients were for sure included only if the common clinical exclusion criteria for using these drugs were absent. The reviewer suggests making a comment on this. Particularly important in the case of TB. Maybe alluding to local guidelines or EULAR guidelines.
Response: The sentence "No explicit exclusion criteria were formulated in order to avoid patient selection bias" was replaced by: "While no explicit exclusion criteria were formulated to avoid patient selection bias, GLM was to be prescribed in line with the specifications of the drug labelling including the contraindications for use."

4- Methods: How was data captured? Was a specific clinical record form developed? Was data captured from a registry?
Response: We added the following sentence to the methods section (data management and statistics): "Investigators or their staff entered data from the patient charts via a secure internet connection into a standardized data entry form."

5- Results: Did dermatologists scored joint counts?
Response: Yes. Only 4.9% of physicians were dermatologists.

6- Results: Why ASDAS was not calculated? This would increase the interest of the results. Is data available for that? If yes it should be included in the paper.
Response: When the study was initiated in 2010, the Ankylosing Spondylitis Disease Activity Score was less established as it is today: neither its cut-off values for disease activity states nor the endorsement of the definitions of disease activity states and improvement scores of the Outcome Measures in Rheumatology (OMERACT) 10 conference were available at this time.
The complete data for calculation of this score are unfortunately not available.

7- Results: How was the screening status for TB done in the patients that developed TB?
Response: Tuberculosis (TBC) is a contraindication for GLM treatment. Therefore, a tuberculosis screening (Mendel Mantoux test or Interferon-γ test) was to be performed in each patient before start of GLM. The following text was added to the results (safety) section: "In the evaluated population the Mendel-Mantoux test was done for 397 (27.2%) and the interferon gamma test for 1097 (75.2%) out of 1458 patients."

How many months after treatment initiation did TB appear?
Response: Unfortunately, there are no narrative on these cases available.

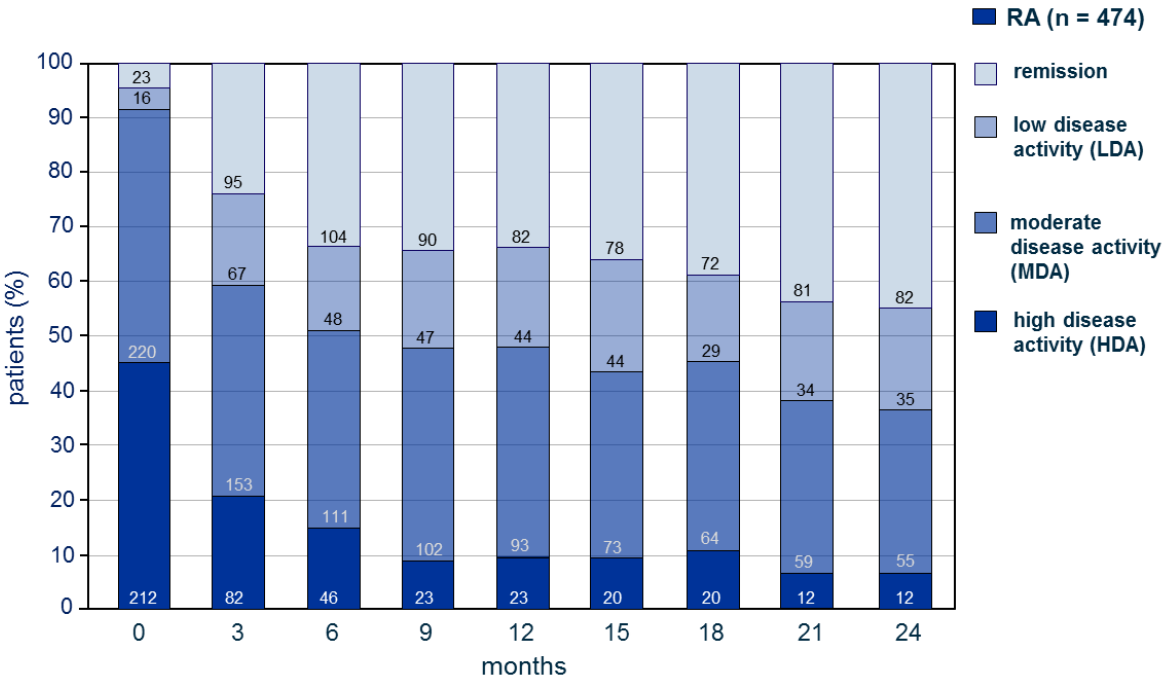
8- Results: Is it really impossible to retrieve information on the deaths? Why?
Response: The documenting rheumatologists (or dermatologists) did not receive detailed information from the institutions which documented the death cases (family physicians or hospitals). There were (unsuccessful) attempts to retrieve details on the death.

Reviewer: 2

Comments to the Author
Effectiveness and safety of golimumab in patients….

I do agree with the authors that it is important to collect and publish data from daily clinical practice about the treatments of patients to add this to the results and experiences of randomized clinical trials. The combination of these two sources of information gives us a good idea about the effectiveness and safety of the used treatments. Therefore I appreciate the efforts of the group to report about the data collected in daily clinical practice.
However it is important, like in RCT's, to report carefully about the population and the withdrawals/lost to follow-up over time and make sure that correct conclusions are being drawn. I agree that the data about safety are correctly presented: all adverse events etc about the patients who had received at least one dose of the drug are being presented. I do however have problems with the presentation and conclusions of the efficacy data. Data about for instance remission rate and disease activity are being given for less than 50% of the original patients after 2 years. It is not correct for instance to state that 44.6% of the patients are being in remission after 24 months as about 60% have been withdrawn due to inefficacy. Yes 44.6 % of the remaining patients are in remission . I don't understand the analyses of all patients (N=474) over the 24 month period, what happened with the DAS28 of patients for instance who dropped out at week 16 due to lack of efficacy? (Figure 5)
Response: In the revision, we highlighted the high discontinuation rates and reworded the conclusions.

Figure 3: numbers are missing for low disease activity
Response: We have revised the figure; it now contains the patient numbers for low disease activity.



Reviewer: 3
Comments to the Author
This is a 24 months observational study evaluating effectiveness and safety of GLM in all the three main indications in rheumatology (RA, PsA, SpA). The study is well conducted, the number of enrolled patients is highly significant and the paper reads well.

I just wonder why retention rate has not been specifically addressed in results and discussion. This could give additional relevant information and allow comparison with several recently published studies on Golimumab in real life (e.g. Iannone F et al, Semin Arthritis Rheum 2017; Svedbom A et al. Patient Prefer Adherence 2017; Manara M et al, Clin Exp Rheumatol 2017) in addition to RCTs.
Response: we added a section to the discussion citing these new publications, and added a third one (Dalen et al Rheumatol Int 2016): “Retention rate. Results must be considered in the context of the low retention rate of the GO-NICE study. Less than half of the originally included patients could be documented at 2 years. A recent observational study on GLM performed in real-life found higher retention rates: 416 RA, PsA and AS patients in Italian centers had a global 2 years drug retention rate 70.2%, with no different hazard of discontinuation among diseases or line of biologic treatment.[16] However, similar rates as in GO-NICE were found in the LORHEN registry which was conducted at the same time in Italy: the 2-year retention rate of 180 patients with RA was 47.3%, of 110 patients with PsA 48%, and of 120 patients with AS 62.8%, with similar results when given as first or second line of treatment.[17] In a retrospective, observational register analysis (Swedish Prescribed Drug Register) at 24 months the median retention rate (calculated by Kaplan-Meier analysis) was 46% for GLM. This rate was higher compared to 40%, 39%, or 40% for adalimumab, etanercept or certolizumab, respectively. [18]„

Reviewer: 5

Comments to the Author
In this study based on an open-label, multicenter, prospective observational study of the effectiveness and safety of golimumab in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis under real-life clinical conditions, Klaus Krueger et al. conclude that GLM SC once monthly led to remarkable improvements in clinical effectiveness in patients with various inflammatory rheumatic diseases in a real-life setting in Germany. The article has important drawbacks
1. Although the authors state that a significant number of patients were followed prospectively, the data does not support this assertion. A total of 661 of 1,458 patients discontinued the treatment prematurely.
Response: Please see the response on the low retention rates for reviewer 3. We added a section in the discussion section.

2. The overall 24-month retention rate was 45% (40% for RA, 46% for PsA, and 51 for AS). This is not a “remarkable improvement in clinical effectiveness”
Response: In the abstract we added the this information “664 patients completed follow-up [New:](2-year retention rate 45.5%).
Further, the conclusion in the abstract was reworded as follows: “ GLM SC once monthly led to remarkable improvements in clinical effectiveness [new:] in patients who could be followed up with various inflammatory rheumatic diseases in a real-life setting in Germany [end of insertion]. The treatment was well-tolerated, and the safety profile of GLM was consistent with that observed in the previous randomised controlled trials.”

3. Missing data are frequently encountered in observational studies. Estimates based on complete-case analysis might be biased if patients with missing data and complete data differ. The STROBE guidelines (Lancet, 370:1453-1457, 2007) recommend that observational studies should report the amount of missing data, the number of individuals used for analysis at each stage of the study, reasons for non-response and the method used to handle missing data in the analyses. The authors report the results according to these guidelines just in part. More specific, they should describe the reason for discontinuation for all patients. According to the data provided, reason for discontinuation is missing in 169 patients. More important, missing data is not accounted for. All in all, the analysis is the analysis of completers at 24-month.
Response: The problem of relatively low retention is now addressed in the abstract, in a new section in the discussion, and the conclusion. The conclusion was reworded as follows: “Golimumab (GLM) 50mg SC once monthly was an effective treatment in patients with RA, PsA and AS in a real-life setting in Germany. [new text:] The suboptimal retention rate in this study was comparable with other recent studies [end of insertion]. During the 24-month observation, [new text] in patients available for follow-up [end of insertion], good treatment response and effectiveness were observed in the three indications.

4. What the authors call “all AR” and “all AS” populations at months 18, 21 and 24 is constituted largely by the completers. The overlapping of the effectiveness in “all populations” and completers is expected.
Response: As noted above, we highlighted and discussed the problem of the high discontinuation rates and the non-availability of data from non-completers in the discussion, conclusion and abstract.

VERSION 2 – REVIEW

REVIEWER	Adrian Richter Institute for Community Medicine, University Medicine Greifswald
REVIEW RETURNED	07-Feb-2018

GENERAL COMMENTS	The authors edited an interesting topic and consolidated results for Golimumab treatment in real-life patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. The study has relevance since observational studies add considerable knowledge to what is known from RCTs. Nonetheless, this reviewer considers some aspects of the manuscript, some of them were already mentioned by previous reviewers, are (still) inadequately presented or discussed. Abstract, page 39, line 50: As Reviewer 5 already noted, the presented results do not show a remarkable improvement particularly since methodological limitations in the analysis prevail. I suggest replacing “remarkable” by “substantial”. Strength and limitations of this study, page 41: the strongest limitation in this analysis is that high drop-out rates were not accounted for in a statistical manner. Neither imputation techniques,

	weighting nor likelihood methods were applied to address selection bias induced during follow-up. The above mentioned limitation is not adequately considered in several paragraphs of the manuscript: Results, page 46/47: comparison of disease activity at baseline and after 24 month using statistical tests are only valid for completers, i.e. those who tolerate the treatment very well. Discussion: the low follow-up rate is discussed in terms of comparability to other real life studies. It should be discussed in terms of biased estimates of clinical improvement. Figure 2 and 5: I recommend to delete the sentence: “Results did not differ relevantly between the evaluable and the completer population.”. This conclusion is misleading and it is possibly erroneous if no formal test has been applied. Further, the populations compared are getting more and more similar along with the follow-up. In the end, identical patients contribute to both groups as seen at month 24. Regarding the safety analysis the manuscript would gain relevance if AEs and SAEs are presented for each of the three diseases. Further, relating the number of events to patients included in the study is misleading. This reviewer suggests calculating event (incidence) rates per 100 patient years for each disease and to replace percentages in Table 2. Table 2: the numbers of AEs do not sum up to 2,125.

REVIEWER	Tsutomu Takeuchi Keio University School of Medicine, Tokyo, Japan
REVIEW RETURNED	07-Mar-2018

GENERAL COMMENTS	Kruger et al. described the real life experience of glimumab in RA, PsA, and AS patients in GO-NICE study in Germany. The study with prospective, non-interventional 24 months observation per patient showed remarkable efficacy and well tolerability. The manuscript is well prepared and written, and the topics are very important in clinical practice. There are several minor points as shown below. #1: No imputation was used for missing-data, so that there is a possibility to result in the better efficacy based on the as-observe results. The authors may add this to limitation of this manuscript. #2: The reasons for the patients with drop-out was not fully described. What are the reasons for 171 patients among 661 patients with drop-out. Are there any imbalances for the drop-out patients among the diseases? #3: It is surprised to note the mean duration of RA in this cohort was ten years, while biologics naïve patients were more than 60%. Is this situation common in Germany in real life? Given the retention rate was low in RA, compared to PsA and AS, are there any reasons? Is this relates to efficacy or safety? #4: Are there any imbalances of severe AE among the diseases? What are the frequent SAE in the total population and those in individual disease?

VERSION 2 – AUTHOR RESPONSE

Editor Comments to Author:
Please complete and include a STROBE checklist, ensuring that all points are included and state the page numbers where each item can be found. The checklist can be downloaded from here: http://www.strobe-statement.org/?id=available-checklists
Response: The checklist was filled and added to the submission package.
Please provide another copy of your figures with better qualities and please ensure that figures are of better quality or not pixelated when zooming in. NOTE: They can be in TIFF or JPG format and make sure that they have a resolution of at least 300 dpi. Figures in PDF, DOCUMENT, EXCEL and POWER POINT format are not acceptable.
Response: Figures are now provided in better quality (high resolution).

Please include Figure legends at the end of your main manuscript. *Figure 1 and Figure 3 legend missing
Response: Legends to all figures are described on page 14. In Figures 2,4 and 5, the text was omitted: Results did not differ relevantly between the evaluable and the completer populations
Reviewer: 1
Reviewer Name: Adrian Richter
Institution and Country: Institute for Community Medicine, University Medicine Greifswald Please state any competing interests or state 'None declared': None declared.
The authors edited an interesting topic and consolidated results for Golimumab treatment in real-life patients with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. The study has relevance since observational studies add considerable knowledge to what is known from RCTs. Nonetheless, this reviewer considers some aspects of the manuscript, some of them were already mentioned by previous reviewers, are (still) inadequately presented or discussed.
Abstract, page 39, line 50: As Reviewer 5 already noted, the presented results do not show a remarkable improvement particularly since methodological limitations in the analysis prevail. I suggest replacing "remarkable" by "substantial".
Response: As recommended by the review, in the abstract "remarkable" was replaced by "substantial".

Strength and limitations of this study, page 41: the strongest limitation in this analysis is that high drop-out rates were not accounted for in a statistical manner. Neither imputation techniques, weighting nor likelihood methods were applied to address selection bias induced during follow-up.
The above mentioned limitation is not adequately considered in several paragraphs of the manuscript:
Results, page 46/47: comparison of disease activity at baseline and after 24 month using statistical tests are only valid for completers, i.e. those who tolerate the treatment very well.
Discussion: the low follow-up rate is discussed in terms of comparability to other real life studies. It should be discussed in terms of biased estimates of clinical improvement.
Response: To address the methodological limitations, the text was changed as follows:

- Page 13, methodological limitations: [new text as proposed by the reviewer] „The strongest limitation in this analysis observational study is that high drop-out rates were not accounted for in a statistical manner and which is considerably higher compared to the controlled studies on the drug. Neither imputation techniques, weighting nor likelihood methods were applied to address selection bias induced during follow-up. "
- Summary and conclusion: "The suboptimal retention rate in this study, while being comparable to other recent observational studies, is a notable limitation."

• On page 3, under “Strengths and limitations of this study” we added the limitation: “Further, there was a relatively high rate of patients lost to follow-up [new text] with no information on outcomes, who were not accounted for in a statistical manner.”

Results, page 46/47: comparison of disease activity at baseline and after 24 month using statistical tests are only valid for completers, i.e. those who tolerate the treatment very well.
Response: In the “results” section, we deleted the sentence in the sections on RA, PsA und AS “similar results were seen in the completer patients as in evaluable patients”. It is no longer needed since the “completers” are identical to “evaluated” patients at months 24.
Discussion: the low follow-up rate is discussed in terms of comparability to other real life studies. It should be discussed in terms of biased estimates of clinical improvement.
a) Page 12, results (Effectiveness) the text was added: Substantial and clinically relevant improvements [new:] (in patients with available follow-up data) [end of insertion] in disease activity and response in the various indications were seen early at 3 months and were maintained throughout the 24-month observation period.
b) Methodological limitations: The strongest limitation in this analysis is that high drop-out rates were not accounted for in a statistical manner, and which is considerably higher compared to the controlled studies on the drug.

Figure 2: I recommend to delete the sentence: “Results did not differ relevantly between the evaluable and the completer population.” This conclusion is misleading and it is possibly erroneous if no formal test has been applied. Further, the populations compared are getting more and more similar along with the follow-up. In the end, identical patients contribute to both groups as seen at month 24.
Response: In the “results” section, we deleted the sentence in the sections on RA, PsA und AS “similar results were seen in the completer patients as in evaluable patients”. It is no longer needed since the “completers” are identical to “evaluated” patients at months 24.

Regarding the safety analysis the manuscript would gain relevance if AEs and SAEs are presented for each of the three diseases. Further, relating the number of events to patients included in the study is misleading. This reviewer suggests calculating event (incidence) rates per 100 patient years for each disease and to replace percentages in Table 2.
Response: a revised, more detailed table 2 was generated as recommended by the reviewer. The number of documented patient years was 620/720/725 PY RA/PsA/AS.
Table 2: the numbers of AEs do not sum up to 2,125.
Response: in the old table, only AEs > 5% were shown. The new table also contains infrequent events, so the number of AEs now sums up to 2125.

Reviewer: 2
Reviewer Name: Tsutomu Takeuchi
Institution and Country: Keio University School of Medicine, Tokyo, Japan Please state any competing interests or state ‘None declared’: no
Kruger et al. described the real life experience of glimumab in RA, PsA, and AS patients in GO-NICE study in Germany. The study with prospective, non-interventional 24 months observation per patient showed remarkable efficacy and well tolerability. The manuscript is well prepared and written, and the topics are very important in clinical practice. There are several minor points as shown below.
#1: No imputation was used for missing-data, so that there is a possibility to result in the better efficacy based on the as-observe results. The authors may add this to limitation of this manuscript.
Response: Page 13, methodological limitations: [new text as proposed by the reviewer] „The strongest limitation in this analysis observational study is that high drop-out rates were not accounted for in a statistical manner and which is considerably higher compared to the controlled studies on the

drug. Neither imputation techniques, weighting nor likelihood methods were applied to address selection bias induced during follow-up. “
As stated in the response to reviewer #1, we described this limitation in several sections of our manuscript.
#2: The reasons for the patients with drop-out was not fully described. What are the reasons for 171 patients among 661 patients with drop-out. Are there any imbalances for the drop-out patients among the diseases?
We added further information on page 7: “During follow-up, 661 patients discontinued the treatment prematurely [new text:] and/or switched to other bDMARDs or sDMARDS. [end of insertion] The most common reasons for discontinuation were lack of effectiveness [new text:] (n=292/661; 46.2% of RA, 41.6% of PsA and 39.3% of AS patients), adverse events (n=142/661; 15.9% of RA, 24.7% of PsA, and 25.1% of AS patients) [end of insertion], change of physician or relocation (n=38), symptom-free status (n=12), and family planning or pregnancy (n=8). [new text:] The rest of patients did not provide reasons.
#3: It is surprised to note the mean duration of RA in this cohort was ten years, while biologics naïve patients were more than 60%. Is this situation common in Germany in real life?
Response: We added the following sentence to the discussion section „ The patients in the RA cohort of GO-NICE were very similar to patients in the contemporary RABBIT RA registry in Germany in terms of age (72.8 vs 74.8 years), disease duration (9.8 vs 9.1 years), and mean DAS28 score (5.0 in both studies).19
Given the retention rate was low in RA, compared to PsA and AS, are there any reasons? Is this relates to efficacy or safety?
We added further information on page 7: “During follow-up, 661 patients discontinued the treatment prematurely. The most common reasons for discontinuation were lack of effectiveness [new text:] (n=292/661; 46.2% of RA, 41.6% of PsA and 39.3% of AS patients), adverse events (n=142/661; 15.9% of RA, 24.7% of PsA, and 25.1% of AS patients) [end of insertion], change of physician or relocation (n=38), symptom-free status (n=12), and family planning or pregnancy (n=8). [new text:] The rest of patients did not provide reasons. [end of insertion]

#4: Are there any imbalances of severe AE among the diseases?
Response: we revised table 2 and provided details on exposure (patent years) and overall SAE rates. In the discussion, the following text was added: ”On descriptive analysis, AEs and SAEs were more frequent in patients with RA in line with the higher mean age in this group.”
What are the frequent SAE in the total population and those in individual disease?
Response: the revised table 2 now contains the SAE distribution in a top-level view. It was not described as subset to the MedDRA classes due to the relatively low number in each cell.

VERSION 3 – REVIEW

REVIEWER	Dr. Adrian Richter Institut für Community Medicine, University Medicine Greifswald, Germany
REVIEW RETURNED	02-Apr-2018

GENERAL COMMENTS	The revised manuscript on Golimumab treatment in real-life patients with RA, PsA and AS has gained considerable improvement. The authors rephrased several paragraphs of the manuscript which preclude now false interpretation of results. Methodological flaws are now correctly described and highlighted as limitations of the study. Further, extensive data on the safety profile of Golimumab in different patient populations was added. This reviewer considers all previously mentioned issues as being resolved. However, augmenting Table 2 by disease-specific (S)AE-rates has

	introduced some errors: (a) a probably false calculation of event rates (ER) and (b) inconsistent calculation of ERs. Regarding (a): please consider for example the n=204 serious adverse events in the „Total“ column with 1991.9 patient years. They will rather represent an ER of ≥10 events / 100py but certainly not „306“. Regarding (b), given column-wise similar numbers of events the ERs should be identical; please see for example lines 26/27 in the „Total“ column. A minor issue: in Table 2, line 9 replace „pro“ by „per“. In summary, this manuscript provides interesting results on the course of three different diseases each of them was treated using the same biologic DMARD therapy. If corrections in Table 2 are applied this reviewer has no more issues.

REVIEWER	Tsutomu Takeuchi Keio University School of Medicine, Japan
REVIEW RETURNED	03-Apr-2018

GENERAL COMMENTS	The authors appropriately revised the manuscript by the reviewers' comments.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 1 Reviewer Name: Dr. Adrian Richter

The revised manuscript on Golimumab treatment in real-life patients with RA, PsA and AS has gained considerable improvement. The authors rephrased several paragraphs of the manuscript which preclude now false interpretation of results. Methodological flaws are now correctly described and highlighted as limitations of the study. Further, extensive data on the safety profile of Golimumab in different patient populations was added. This reviewer considers all previously mentioned issues as being resolved.

However, augmenting Table 2 by disease-specific (S)AE-rates has introduced some errors: (a) a probably false calculation of event rates (ER) and (b) inconsistent calculation of ERs. Regarding (a): please consider for example the n=204 serious adverse events in the „Total“ column with 1991.9 patient years. They will rather represent an ER of ≥10 events / 100py but certainly not „306“. Regarding (b), given column-wise similar numbers of events the ERs should be identical; please see for example lines 26/27 in the „Total“ column.

A minor issue: in Table 2, line 9 replace „pro“ by „per“.

In summary, this manuscript provides interesting results on the course of three different diseases each of them was treated using the same biologic DMARD therapy. If corrections in Table 2 are applied this reviewer has no more issues.

Response: We thank Dr. Richter for his positive assessment and in particular, his valuable comments on Table 2:

• Data were corrected as shown in the screenshot.

• Line 9 was redundant to the information “Patient n(%) /evens per 100 patient years” and therefore could be omitted without losing any information.

O Lines 26/27: unchanched, as the information is correct: (b) given column-wise similar numbers of events the ERs should be identical; please see for example lines 26/27 in the „Total“ column.

O Line 26: Gastrointestinal 101 patients (6.3%) with 146 events / 7.3 events /100 PYs

O Line 27: Musculoskeletal 101 patients(6.3%) with 138 events / 6.9 events /100 PYs

Table 2. Adverse events (AEs) overall and by System Organ Class

	Rheumatoid arthritis (RA)	Psoriatic arthritis (PsA)	Ankylosing spondylitis (AS)	Total
	~~N~~n=524 (100.0%)	~~N~~n=546 (100.0%)	~~N~~n=543 (100.0%)	~~N~~n=1613 (100.0%)
		~~Patients n (%) / events (pro 100PY)~~		
Patient years	597.3	690.5	704.1	1,991.9
Adverse events (AEs) total				
Patients n (%) / events per 100 patient years	320 (61.1) / 127.~~7~~6	309 (56.6) / 106.~~0~~2	281 (51.7) / 89.5	910 (56.4) / 106.7
~~serious~~Serious AEs (SAEs)				
Patients n (%) / events per 100 patient years	75 (14.3)/ ~~11~~19.8	70 (12.8)/ ~~10~~15.1	59 (10.9)/ ~~8~~11.9	204 (12.6)/ ~~30~~15.3
AEs sorted by System Organ Class	**Patients n (%) / events per 100 patient years**			
General disorders and administration site conditions	171 (32.6) / 33.3	155 (28.4) / 25.3	124 (22.8) / 21.0	450 (27.9) / 26.2
Infections and infestations	83 (15.8) / 20.8	92 (16.8) / 20.4	88 (16.2) / 16.2	263 (16.3) / 19.0
Skin and subcutaneous tissue disorders	44 (8.4) / 9.0	51 (9.3) / 9.1	55 (10.1) / 9.8	150 (9.3) / 9.3
Surgical and medical procedures	40 (7.6) / 8.5	38 (7.0) / 5.9	26 (4.8) / ~~5.8~~4.1	104 (6.4) / 6.1
Gastrointestinal disorders	29 (5.5) / 7.4	40 (7.3) / 8.7	32 (5.9) / 6.0	101 (6.3) / 7.3
Musculoskeletal and connective tissue disorders	39 (7.4) / 8.9	22 (4.0) / 4.3	40 (7.4) / 7.8	101 (6.3) / 6.9
Nervous system disorders	39 (7.4) / 8.9	29 (5.3) / 5.1	27 (5.0) / 4.4	95 (5.9) / 6.0
Investigations	18 (3.4) / 4.4	29 (5.3) / 5.4	21 (3.9) / 3.8	68 (4.2) / 4.5
Respiratory, thoracic and mediastinal disorders	29 (5.5) / 6.7	24 (4.4) / 3.9	15 (2.8) / 2.4	68 (4.2) / 4.2
Injury, poisoning and procedural complications	19 (3.6) / 3.7	17 (3.1) / 3.5	16 (2.9) / 2.4	52 (3.2) / 3.2
Vascular disorders	15 (2.9) / 3.0	13 (2.4) / 1.9	10 (1.8) / 1.6	38 (2.4) / 2.1
Psychiatric disorders	9 (1.7) / 1.5	12 (2.2) / 2.2	12 (2.2) / 1.9	33 (2.0) / 1.9
Cardiac disorders	14 (2.7) / 2.5	10 (1.8) / 1.9	7 (1.3) / 1.1	31 (1.9) / 1.8
Eye disorders	10 (1.9) / 1.8	3 (0.5) / 0.7	12 (2.2) / 2.~~3~~3	25 (1.5) / 1.6
Neoplasms benign, malignant and	10 (1.9) / 2.0	7 (1.3) / 1.2	5 (0.9) / 0.7	22 (1.4) / 1.3

Reviewer: 2 Reviewer Name: Tsutomu Takeuchi

The authors appropriately revised the manuscript by the reviewers' comments.

Response: We thank Dr. Takeuchi for his helpful comment on the previous version and his current favorable statement on our work.