PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of Guselkumab, a selective IL-23 inhibitor, in Preventing Arthritis in a Multi-center Psoriasis At-Risk cohort (PAMPA): protocol of a randomized, double-blind, placebo controlled multicenter trial
AUTHORS	Haberman, Rebecca; MacFarlane, Katrina; Catron, Sydney; Samuels, Jonathan; Blank, Rebecca; Toprover, Michael; Uddin, Zakwan; Hu, Jiyuan; Castillo, Rochelle; Gong, Cinty; Qian, Kun; Piguet, Vincent; Tausk, Francisco; Yeung, Jensen; Neimann, Andrea; Gulliver, Wayne; Thiele, Ralf; Merola, Joseph; Ogdie, Alexis; Rahman, Proton; Chakravarty, Soumya; Eder, Lihi; Ritchlin, C; Scher, Jose

VERSION 1 – REVIEW

REVIEWER	CHANDRAN, VINOD University of Toronto None for this study/paper, but I belong to the same institution and collaborate with a few of the authors.
REVIEW RETURNED	09-May-2022

GENERAL COMMENTS	The protocol or the study is largely well described. I have a few suggestions. 1. Please clearly provide rationale for the design. Why is arm 3 not randomized? Are subjects in arm 3 going to be recruited from all the centres participating? 2. It is mentioned that up to 30% of subjects with psoriasis 'progress' to PsA. What has however been shown is that up to 30% of patients with psoriasis have PsA in cross-sectional studies. 3. Abstract- the study description mention 'wait-list'. That term is unclear to me. 4. Exclusion criteria- define mid-high positive RF and/or ACPA. 5. Assessment schedule- Why is dactylitis not assessed? 6. Primary end-point- what is modified CASPAR criteria? 7. Explain IDEOM MSK 8. 8. Instead of simply stating SPARCC, indicate SPARCC enthesitis index.

REVIEWER	Sticherling, Michael University of Erlangen-Nuremberg investigator, speaker, consultant or an advisory board member for Abbvie, Amgen, BMS, Celgene, Galderma, GSK, Janssen Cilag, Leo, Lilly, MSD, Mundipharma, Novartis, Regeneron, Pfizer, Sanofi, UCB, clinical studies Abbvie, BMS, Amgen, Celgene, Galderma, GSK, Janssen Cilag, Leo, Novartis, Pfizer, Regeneron, Sanofi , UCB
REVIEW RETURNED	05-Jun-2022

GENERAL COMMENTS	Haberman et al. present present the outline of a clinical controlled study on the effects of guselkumab on the development of psoriasis arthritis (PsA) in psoriasis patients. Following comments: Arm 3 comprising patients who decline biologic therapy is not really controlled, but heavily biased by personal attitude of individual patients. What should results from this arm prove? Are fumarates allowed as current systemic therapy? BSA 3 is very low. Is this on systemic treatment? Is a placebo arm with regard to recent results really ethical? Table 2: 96 weeks are not two years? Bos1: what are genetic, immune cell phenotyoe and microbiome changes? Cutaneous and/or intestinal microbiom? Page 12, line 12: which therapeutic agent in TICOPA study? Page 12, line 52: what is protopathic bias? Page 13, line 15: why ultrasound? Why not micro-CT or MRI? Page 14, line 24: what is advanced psoriasis? Page 25, line 27: medio-carpal? Page 25, line 26ff: only hand jounts: why just ultrasound? Why not micro-CT or MRI?

REVIEWER	Miyagawa, Ippei University of Occupational and Environmental Health Japan
REVIEW RETURNED	01-Aug-2022

GENERAL COMMENTS	This is a very interesting study (protocol). No further comments.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
The protocol or the study is largely well described. I have a few suggestions.
We thank the reviewer and have incorporated his suggestions below.

1. Please clearly provide rationale for the design. Why is arm 3 not randomized? Are subjects in arm 3 going to be recruited from all the centres participating?
Thank you for pointing this out as it was not made explicit. Arm 3 is not randomized as this group consists of participants who do not agree to go on any biologic immunotherapies. We do not think it would be ethical (or feasible) to withhold advanced therapies for 2 years in participants with psoriasis who would otherwise want to go on these therapies. We have made this clearer by amending and adding the following sentences: “A third arm (Arm 3) will consist of participants who do not receive any study drug followed prospectively as the natural history comparator arm based on their personal preference to avoid biologic therapy. No participants will be randomized into Arm 3 as it was deemed neither feasible nor ethical to withhold systemic treatment for 96 weeks, and assuming many of them may want to initiate immunomodulatory therapy during that time period.”

All sites will recruit for Arm 3 and we have added the following: “Participants in all arms will be screened and enrolled from five study sites (community and academic) across North America.”

2. It is mentioned that up to 30% of subjects with psoriasis 'progress' to PsA. What has however been shown is that up to 30% of patients with psoriasis have PsA in cross-sectional studies.
We thank the reviewer for this important distinction. We have changed the sentence to now read: “Up

to 30% of patients with psoriasis have inflammatory arthritis and the rate of progression from psoriasis to PsA occurs at up to 3% per year."

3. Abstract- the study description mention 'wait-list'. That term is unclear to me.
A wait-list design refers to Arm 2: participants who initially do not receive the treatment will go on to receive guselkumab at six months during the open label phase of the study. However, because this term may be confusing to the reader, it has been removed from the abstract.

4. Exclusion criteria- define mid-high positive RF and/or ACPA.
Mid to high positive RF and/or ACPA is defined as two times the upper limit of normal. We have added this into Table 1: "Mid-high positive rheumatoid factor and/or anti-citrullinated protein antibodies (greater than 2 times the upper limit of normal)"

5. Assessment schedule- Why is dactylitis not assessed?
Thank you for pointing this out as a dactylitis count will be assessed. It has been added with the following phrase: "...musculoskeletal assessments (66/68 tender/swollen joint count and Spondyloarthritis Research Consortium of Canada enthesitis index, dactylitis count)…". This has also been added to Table 2 (Assessment Schedule).

6. Primary end-point- what is modified CASPAR criteria?
Modified CASPAR criteria adds dactylitis to the stem. This is defined on page 7 "…and will be evaluated for fulfillment of modified CASPAR criteria (dactylitis added to the stem) to determine if they have converted to PsA".

7. Explain IDEOM MSK 8.
We agree that this new measure needs more explanation. Since the submission of the original version, the IDEOM MSK-8 has now been renamed IDEOM MSK-Q and this has been changed throughout. We also added the following sentence: "The IDEOM MSK-Q is a PRO aimed at identifying musculoskeletal symptoms and measuring their intensity and impact on health-related quality of life in patients with psoriatic disease (further details can be found in the Supplement)." Additionally, the Supplement now includes details on its development, domains, and validity. The IDEOM MSK-Q is now finalized as has been accepted as a late-breaking abstract at the European Academy of Dermatology and Venereology and the final manuscript is actively being submitted.

8. Instead of simply stating SPARCC, indicate SPARCC enthesitis index.
Thank you- we have changed SPARCC to SPARCC enthesitis index in Table 2 and in the text have changed the word "score" to "index" so the sentence now reads: "…66/68 tender/swollen joint count and Spondyloarthritis Research Consortium of Canada enthesitis index, dactylitis count…"

Reviewer 2
Haberman et al. present the outline of a clinical controlled study on the effects of guselkumab on the development of psoriasis arthritis (PsA) in psoriasis patients.

Arm 3 comprising patients who decline biologic therapy is not really controlled, but heavily biased by personal attitude of individual patients. What should results from this arm prove?
We thank the reviewer for this comment and agree with this statement. However, this is the most pragmatic comparator arm for this study as it would not be ethical (or feasible) to withhold systemic medication for 96 weeks in patients with psoriasis who are interested in beginning these medications. Without any comparator arm, however, we would be unable to assess progression rate.

We have more clearly stated that is a comparator arm, rather than a control and clarified why this population was chosen: "A third arm (Arm 3) will consist of patients who do not receive any study drug

followed prospectively as the natural history comparator arm". We have also further clarified the role of Arm 3 and the reasoning behind it: : "A third arm (Arm 3) will consist of patients who do not receive any study drug followed prospectively as the natural history comparator arm based on their personal preference to avoid biologic therapy. No participants will be randomized into Arm 3 as it was deemed neither feasible nor ethical to withhold systemic treatment for 96 weeks, and assuming many of them may want to initiate immunomodulatory therapy during that time period.

We also added this to the limitations section in the discussion: "We also acknowledge, in the assessment of progression, Arm 3 is not a direct comparator for Arms 1 and 2 as these participants are choosing not to be exposed to biologics, creating an inherent selection bias. However, this remains the only feasible and ethical comparator group."

Are fumarates allowed as current systemic therapy?
To enter into Arms 1 and 2, participants cannot be on any systemic medication for psoriasis. Additionally, fumarates are not currently approve for use in the US or Canada.

BSA 3 is very low. Is this on systemic treatment?
To enter into the study, patients will need at least 3% body surface area. This number was chosen as it corresponds to the FDA approved indication for guselkumab in moderate to severe plaque psoriasis. Therefore, all participants who enroll in the study meet criteria to receive this drug. However, there is no upper limit to body surface area and we aim to enroll participants with a wide range of skin severity. Participants may be on methotrexate or apremilast at the time of recruitment, but need to stop at the time of enrollment. Participants may also be using topicals or UV light therapy, but cannot be currently using (or have previously used) any biologics or JAK inhibitors.

Is a placebo arm with regard to recent results really ethical?
Participants who enroll into the drug arms (Arm 1 and 2) will receive either drug or placebo for 6 months, and then all participants will receive the drug. During this 6-month time period, participants can continue to use topicals or UV therapy to control their psoriasis. We have made this more explicit by adding the sentence: "Participants may continue to use topical treatments or phototherapy throughout the duration of the study." This study has also gone through the IRB at 5 separate institutions without any concerns for ethics. Again, these participants have psoriasis, but not psoriatic arthritis, therefore the risks of delayed treatment of arthritis do not apply. If a participant (in any arm) develops arthritis during the study, they immediately exit and can be started on treatment by their primary physicians.

Table 2: 96 weeks are not two years?
Thank you for pointing this out—this is correct. We have changed 2 years to 96 weeks throughout the protocol.

Box1: what are genetic, immune cell phenotype and microbiome changes? Cutaneous and/or intestinal microbiome?
For participants who agree, both skin swabs and stool samples will be obtained to understand both the cutaneous and intestinal microbiome. This was added to Box 1 with the following bullet point: "Genetic, immune cell phenotype, and microbiome changes (cutaneous and intestinal) and their interactions with treatment assignment"

We have also amended the following sentence to make our goals clearer: "…includes biosampling of participants, will also allow us to make contributions to our understanding of the underlying pathogenesis and immune endotypes in the psoriasis to PsA continuum."

Page 12, line 12: which therapeutic agent in TICOPA study?
Thank you for pointing this out. The line now reads: “The TICOPA study, an open label randomized control trial using methotrexate, showed significant…”

Page 12, line 52: what is protopathic bias?
The sentence describing protopathic bias has been edited to more clearly reflect the definition: “These studies are also susceptible to protopathic bias, where a certain therapy (i.e., biologics) may be prescribed because patients have symptoms of, or undiagnosed, disease (i.e., PsA) which are not captured.”

Page 13, line 15: why ultrasound? Why not micro-CT or MRI?
Ultrasound is a commonly used imaging modality for the detection of synovitis, enthesitis, and other musculoskeletal abnormalities. We have added the following sentence regarding why it was chosen: “While other imaging modalities, such as high-resolution peripheral quantitative computed tomography or MRI, have been used, ultrasound is easily accessible, has few (if any) contraindications, and is already being applied in clinical settings.”

Page 14, line 24: what is advanced psoriasis?
Thank you for this comment. We have amended the statement as follows: “… based on moderate to severe psoriasis involvement…”

Page 25, line 27: medio-carpal?
Thank you for this comment. We have confirmed that mid-carpal (used in our supplement) and medio-carpal can be used interchangeably.

Page 25, line 26ff: only hand joints: why just ultrasound? Why not micro-CT or MRI?
The ultrasound will assess 36 joints and 34 pericarticular structures that are based on the PsASon scoring system, a well-used and validated scoring system of US abnormalities in psoriatic disease. While other imaging modalities (high resolution peripheral quantitative CT and MRI in particular) have been used, ultrasound has been shown to assess abnormalities well (i.e., Savage et al Arthritis Rheumatol 2019). Further, we added the following sentence: “While other imaging modalities, such as high-resolution peripheral quantitative computed tomography or MRI, have been used, ultrasound is easily accessible, has few (if any) contraindications, and is already being applied in clinical settings.”

Reviewer 3
This is a very interesting study (protocol).
No further comments.
We thank the reviewer for their time

VERSION 2 – REVIEW

REVIEWER	Sticherling, Michael University of Erlangen-Nuremberg Advisory boards: Abbvie, Amgen, BMS, Boehringer Mannheim, Celgene, Janssen Cilag, Leo, Lilly, Pfizer, MSD, Novartis, Sanofi, UCB Speaker board for Abbvie, Amgen, Boehringer Mannheim, Celgene, Janssen Cilag, Leo, Novartis, Pfizer Clinical studies Abbvie, Amgen, Boehringer Mannheim , Celgene, Galderma, GSK, Janssen Cilag, Leo, Novartis, Pfizer, Regeneron, Sanofi
REVIEW RETURNED	10-Dec-2022

GENERAL COMMENTS	The authors have amply answered all major reviewers' comments.