PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) among patients with systemic lupus erythematosus: protocol for an international observational effectiveness study

Authors

MOSCA, MARTA; Chen, Samuel; Carty, Lucy; Waratani, Miina; Seo, Caroline; Sorrentino, Alessandro; Emmas, Cathy; Nan, Cassandra; Stirnadel-Farrant, Heide A.; Chen, Stephanie

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Fanouriakis, Antonis**
Affiliation	**University of Athens**
Date	**16-Apr-2024**
COI	**None**

Thank you for the opportunity to review this manuscript. This is a study protocol of a real-world study on the efficacy and safety of anifrolumab in SLE, which aims to combine clinician- and patient-reported data. The manuscript is well-written and I have only minor comments in the direction of improving clarity.

1) Introduction, first paragraph: The typical course of SLE is alternating periods of disease activity and quiescence, but the latter does not necessarily equal DORIS remission. For example, some patients may reach low disease activity states, but never remission with this particular definition. This should be rephrased.

2) Introduction, second paragraph: What we call "standard-of-care" in SLE for the past ten years also includes belimumab, not only conventional drugs. Depending on availability, a significant proportion of SLE patients receives belimumab in real-world settings. The respective sentence could thus also be rephrased.

3) Methods, study desing, first paragraph: The way the study design is written may create some confusion, specifically the phrase "1 year retrospective baseline period". Obviously,

this is meant to examine whether anifrolumab reduces the rate of flares compared to the year prior to its start. I would simplify by saying that the date of anifrolumab initiation marks the index date, and that data will also be collected for the 12 months prior to the index date to document flares etc.

4) Table 1: I believe that the primary endpoint(s) should be more succinct, in bullet form.

5) Table1, Exploratory: It is DORIS remission, rather than clinical remission.

6) Figure 1: SoC visit is an awkward term. I would suggest changing to "index visit" or something of this nature.

Reviewer	**2**
Name	**Piantoni, Silvia**
Affiliation	**University of Brescia**
Date	**03-May-2024**
COI	**No competing interests to declare.**

GENERAL COMMENTS

In this manuscript Mosca M and colleagues are proposing the protocol of a multicentric observational clinical study focused on anifrolumab in SLE. I suggest minor clarifications before publication.

MINOR COMMENTS

1-The enrolment is already started (more than one year ago) when the manuscript will be published. Furthermore, in some large Countries, anifrolumab was officially available before the beginning of the enrolment (such as in Germany).

-How many patients and in which Countries SLE patients have been already enrolled in this study (at the moment of the publication of this manuscript)?

-The fact that in some Countries the use of anifrolumab has been already started before February 2023 can reduce all the potentiality of the study (/of the enrollment). A comment on this would be useful.

-Are the Countries who have received the approval for the drug before February 2023 excluded from the enrolment in this study?

2-Not all the patients have or are familiar with mobile devices. A device for patients who don’t have the smartphone is available thanks to the Sponsor? A training is provided?

3-500 pts: Europe and North America or Europe and Canada? Clarify

4-Pg 11, line 250: typo “dissemination”

VERSION 1 - AUTHOR RESPONSE

REVIEWER 1 COMMENTS TO THE AUTHOR

1. *Introduction, first paragraph: The typical course of SLE is alternating periods of disease activity and quiescence, but the latter does not necessarily equal DORIS remission. For example, some patients may reach low disease activity states, but never remission with this particular definition. This should be rephrased.*

Response: We thank the reviewer for these comments and the positive feedback on the writing of the manuscript. We have modified the wording of the Introduction to clarify that the typical course of SLE is alternating periods of disease activity and quiescence and explain that quiescence does not necessarily equate to remission. The revised Introduction is as follows:

Introduction (page 4; paragraph 1): "The course of SLE typically includes alternating periods of disease activity and quiescence. However, quiescence does not necessarily equate to remission as defined by Definitions of Remission in SLE (DORIS) criteria (Clinical SLEDAI = 0; evaluator's global assessment <0.5 (0-3); prednisone ≤5 mg/day; and stable antimalarials, immunosuppressives, and biologics);[3] some patients may achieve low disease activity but may not meet the stringent requirements for DORIS remission. Nearly half of patients incur some form of organ damage and increased risk of mortality within 10 years of diagnosis.[4-6]"

2. *Introduction, second paragraph: What we call "standard-of-care" in SLE for the past ten years also includes belimumab, not only conventional drugs. Depending on availability, a significant proportion of SLE patients receives belimumab in real-world settings. The respective sentence could thus also be rephrased.*

Response: We have revised the introduction to reflect accurately the standard of care for SLE over the past ten years, which includes both belimumab and conventional drugs. The revised section of the *Introduction* is as follows:

Introduction (page 4; paragraph 2): "Since its approval in 2011, belimumab has become an important component of SoC therapy; however, rituximab is not yet approved but recommended for off-label use under certain conditions by clinical practice guidelines.[4,15,20]"

3. *Methods, study design, first paragraph: The way the study design is written may create some confusion, specifically the phrase "1 year retrospective baseline period". Obviously, this is meant to examine whether anifrolumab reduces the rate of flares compared to the year prior to its start. I would simplify by saying that the date of anifrolumab initiation marks the index date, and that data will also be collected for the 12 months prior to the index date to document flares etc.*

Response: We thank the reviewer for this suggestion and have clarified the study design as follows:

Methods (pages 5; paragraph 3): “ASTER is a multinational, single-arm, observational, cohort study (clinicaltrials.gov registration: NCT05637112) designed to collect critical real-world evidence about the addition of anifrolumab to SoC therapy for SLE in routine clinical practice (**figure 1**).[33] The date of anifrolumab initiation marks the study index date. Data will be collected for the 12 months prior to the index date to document disease activity, including the rate of flares.”

4. *Table 1: I believe that the primary endpoint(s) should be more succinct, in bullet form.*

Response: We have revised the Primary ‘Endpoints and Definitions’ in Table 1 to be more succinct and presented them in bullet form for clarity as follows:

1. Disease activity assessed by the PGA and SLEDAI-2K
2. Proportion of patients attaining LLDAS[a]

5. *Table1, Exploratory: It is DORIS remission, rather than clinical remission.*

Response: We have corrected the terminology in Table 1, changing “clinical remission” to “DORIS remission” under the Exploratory section.

6. *Figure 1: SoC visit is an awkward term. I would suggest changing to "index visit" or something of this nature.*

Response: We have replaced “SoC visit” in Figure 1 with “pre-infusion visit” to improve clarity.

REVIEWER 2 COMMENTS TO THE AUTHOR

1. *The enrolment is already started (more than one year ago) when the manuscript will be published. Furthermore, in some large Countries, anifrolumab was officially available before the beginning of the enrolment (such as in Germany)*
    - *How many patients and in which Countries SLE patients have been already enrolled in this study (at the moment of the publication of this manuscript)?*
    - *The fact that in some Countries the use of anifrolumab has been already started before February 2023 can reduce all the potentiality of the study (/of the enrollment). A comment on this would be useful.*
    - *Are the Countries who have received the approval for the drug before February 2023 excluded from the enrolment in this study?*

Response: We appreciate the reviewer’s comments and positive feedback on the manuscript. In the revised manuscript, we have included the number of patients enrolled up to the current date. The availability of anifrolumab in some countries before February 2023 does not diminish the study’s potential. The real-world evidence gathered from these regions adds valuable insights into the drug’s use in routine clinical practice, including the benefits of adding anifrolumab to standard-of-care treatment for SLE.

2. *Not all the patients have or are familiar with mobile devices. A device for patients who don't have the smartphone is available thanks to the Sponsor? A training is provided?*

Response: We agree with the reviewer that this is an important consideration, and the Sponsor understands that not all patients have or are familiar with mobile devices. To address this, patients who do not have a smartphone or are unwilling to download the mobile application can still participate in the study without the patient-reported outcome collection. To clarify this, we have revised the Methods section as follows:

Methods (page 7, paragraph 2): "Patients who do not have a smartphone or who are not willing to download the mobile application may still participate in the study without patient-reported outcome collection. During enrollment, each patient downloads the MyReco® app on their personal device(s) and receives an activation code and in-app setup instructions for how to use the application."

3. *500 pts: Europe and North America or Europe and Canada? Clarify*

Response: Patients are being enrolled from sites across Europe and Canada. The Abstract has been corrected accordingly.

4. *Pg 11, line 250: typo "dissemination"*

Response: We have corrected the typo in the revised manuscript.

EDITOR COMMENTS TO THE AUTHOR

1. *Please revise your title so that it includes your study design. This is the preferred format for the journal. Please also state that your manuscript is a study protocol in the title.*

Response: The title has been revised to reflect the preferred format for the journal as follows:

"Anifrolumab Study for Treatment Effectiveness in the Real World (ASTER) among patients with systemic lupus erythematosus: protocol for an international observational effectiveness study"

2. *Please revise the Ethics and Dissemination section in your Abstract so that it includes the names of all ethics committees that have approved your study and details of the planned dissemination of the study results.*

Response: The *Ethics and Dissemination* section of the manuscript has been revised to include the names of the ethics committees and details of the planned dissemination of the study results as follows:

Ethics and Dissemination (page 10; paragraph 3): "Trial results will be published in peer-reviewed journals and presented at national and international congresses."
Ethics and Dissemination (page 10; paragraph 5): "The final version of the protocol, patient informed consent form, and patient-facing materials (eg, app functionality and questions, advertising for recruitment) have been approved in writing by all applicable local Institutional Review Boards/Independent Ethics Committees (IRB/IEC), which will also be required for any future amendments to these materials."

3. *Please revise the first and second bullet points of the 'Strengths and limitations of this study' section of your manuscript (after the abstract). This section should relate specifically to the methods. The novelty or expected impact of the study should not be summarised here. Please also remove the 'Strengths' and 'Limitations' subheadings in this section.*

Response: The 'Strengths' and 'Limitations' subheadings have been removed, and the first and second bullet points have been revised to relate specifically to the methods as follows:

Strengths and limitations of this study (page 3):

- The ASTER study employs clinical assessments and patient-reported outcome data to obtain long-term information on SLE disease progression and risks and benefits of treatment with anifrolumab in clinical practice
- This study uses a multinational approach, incorporating both patient- and clinical-reported outcomes to assess medication usage

4. *Please state that counties where data will be collected in the Methods section.*

Response: A list of countries where the data is being collected has been included in the *Methods* section as follows:

Methods (page 6, paragraph 2): "At the time of publication, the study has enrolled 271 patients from Austria, Belgium, Canada, Denmark, France, Germany, Israel, Italy, Sweden, and the United Arab Emirates."

5. *Please ensure that the information provided in your protocol article is consistent with that included in the trial registry. For example, the eligibility criteria, and the secondary and exploratory outcomes. Please update the manuscript and/or trial registry accordingly.*

Response: We have cross-checked the manuscript with the trial registry and made minor edits to Table 1 and a minor addition to the Study participants subsection in the Methods as follows:

Methods (page 6; paragraph 4): “Patients eligible for ASTER are adults (≥18 years) who meet the 2019 EULAR/ACR criteria for SLE[34] and have received their first prescription of anifrolumab for the treatment of SLE according to the approved country-specific label and any local authorization requirements.”

6. *Can you please clarify whether further ethics approvals will be required?*

Response: Any amendments to the trial protocol, patient informed consent form, or patient-facing materials will require approval by all applicable local IRB/IEC as described:
Ethics and Dissemination (page 10; paragraph 5): “The final version of the protocol, patient informed consent form, and patient-facing materials (eg, app functionality and questions, advertising for recruitment) have been approved in writing by all applicable local Institutional Review Boards/Independent Ethics Committees (IRB/IEC), which will also be required for any future amendments to these materials.”

7. *Please add a funding statement to your manuscript*

Response: A funding statement has been added to the Footnotes section of the manuscript (page 16).

8. *Please add a Patient and Public Involvement statement to your manuscript (this is usually placed at the end of the main text Methods section). If there was no involvement, please state “None.”*

Response: We have included a “Patient and public involvement” subsection to the Methods as follows:

Methods (page 10; paragraph 2): “Patients with SLE were involved in the study design, including endpoint selection, data collection, and advising on the development of the patient-facing mobile application.”

9. *Along with your revised manuscript, please include a copy of the STROBE checklist indicating the page/line numbers of your manuscript where the relevant information can be found (https://strobe-statement.org/index.php?id=strobe-home). Please do not leave blanks and indicate any items that do not apply to your study design as 'Not Applicable'.*

Response: A STROBE checklist indicating page and line numbers of the manuscript has been included in the resubmission.

VERSION 2 - REVIEW

Reviewer **1**

Name **Fanouriakis, Antonis**

Affiliation	**University of Athens**
Date	**16-Oct-2024**
COI	

My comments have been addressed, I have no further comments.

Reviewer	**2**
Name	**Piantoni, Silvia**
Affiliation	**University of Brescia**
Date	**14-Oct-2024**
COI	

Dear Authors,

Thank you for addressing reviewers' comments adequately.

No further comments