ARTICLE DETAILS

**TITLE (PROVISIONAL)**
Study protocol of the global Effisayil™ 1 Phase II, multicentre, randomised, double-blind, placebo-controlled trial of spesolimab in patients with generalised pustular psoriasis presenting with an acute flare

**AUTHORS**
Choon, Siew Eng; Lebwohl, Mark; Marrakchi, Slaheddine; Burden, David; Tsai, Tsen-Fang; Morita, Akimichi; Navarini, Alexander; Zheng, Min; Xu, Jinhua; Turki, Hamida; Rajeswari, Sushmita; Deng, Hongjie; Tetzlaff, Kay; Thoma, Christian; Bachelez, Herve

GENERAL COMMENTS

With interest I have read the manuscript “Design and rationale of the global Effisayil™ 1 Phase II, multicentre, randomised, double-blind, placebo-controlled trial of spesolimab in patients with generalised pustular psoriasis presenting with an acute flare” a clinical trial protocol about the generalised pustular psoriasis which is overall well-written, well-structured and clear. But I would like receive some clarifications:

- After reading the Introduction, I think that could be useful for the readers to know more info about the duration and periodicity of the acute GPP flares. This could help to understand the pathology and the efforts of the authors for assess the evolution of the disease. Also, I would like to read in the introduction a small summary of the adverse events in the Phase I proof-of-concept study.

- Pg. 13; Line 23: “If required, screening and randomisation can occur on the same visit if patients meet the randomisation criteria.” I don’t understand how the investigator can check the exclusion criteria n. 6 (Pg. 30; Line 7) if the screening and randomisation occur in the same visit. Please, perhaps you could shed some light on this.

- Pg. 14; Line 19 “Dose escalation of their maintenance treatment with cyclosporin, retinoids or methotrexate within 2 weeks prior to randomisation”

Usual, in the dermatology clinical trials the use of this treatments require a wash out of 4 weeks, but in your study the subjects can start with the investigation product just after discontinue the treatment with this restricted medication. Can affect the effect of this medications to the results?

Finally I would like to thanks all the authors for the hard work done in
the design of this clinical trial. The GPP is a rare disease without appropriate treatment and I hope that the spesolimab improves the health of the GPP patients. Besides, I would like to mention the efforts of the authors in favor of transparency. I look forward to reading the study results in a medical journal coming soon. Congratulations also on the data sharing statement.

Reviewer: Zelma Chiesa Fuxench
University of Pennsylvania

Review returned: 18-Dec-2020

General comments:
Thank you for the opportunity to review this work. The protocol is well written and clear. Please see below for my comments and suggestions which hope to make the manuscript stronger.

Page 8, line 50: “Although there are therapies specifically indicated for GPP approved in Japan, Taiwan and Thailand, there...” this sentence is similar to the one in Line 35, please consider revising.

Page 12, Line 38; “Are experiencing their first episode of an acute GPP flare of moderate-to-severe intensity; the diagnosis of GPP is to be confirmed retrospectively by a central external expert committee”-while I understand that there may be difficulties in the diagnosis of GPP at first presentation, just out of curiosity, any concerns about potential for misclassification of disease states? Any plans for further sensitivity analysis excluding these patients?

Version 1 – Author response

Reviewer: 1

Comments to the Author
With interest I have read the manuscript “Design and rationale of the global EffisayilTM 1 Phase II, multicentre, randomised, double-blind, placebo-controlled trial of spesolimab in patients with generalized pustular psoriasis presenting with an acute flare” a clinical trial protocol about the generalized pustular psoriasis which is overall well-written, well-structured and clear. But I would like receive some clarifications:

- After reading the Introduction, I think that could be useful for the readers to know more info about the duration and periodicity of the acute GPP flares. This could be helpful to understand the pathology and the efforts of the authors for assess the evolution of the disease. Also, I would like to read in the introduction a small summary of the adverse events in the Phase I proof-of-concept study.

Response from the authors: The reviewer makes an important point regarding the need for more information about the duration and periodicity of acute flares, and this study will hopefully help us to understand this better. GPP is a heterogeneous disease, and to date, very limited information documenting the natural history and disease course of GPP has been published in the literature. For some patients, acute GPP flares may occur frequently, with multiple flares per year, while others may experience flares less frequently, being spaced a year or more apart. Equally the duration and phenotypic characteristics of each flare can vary between patients and even between flares. While there are limited data on the duration of flares, some studies report resolution of pustular flares within weeks and ranges of 1 week to 2 months, but there are also cases in which chronic skin lesions
persist between attacks of GPP (Choon SE, et al. Int J Dermatol 2014;53:676–684; Bachelez H. Acta Derm Venereol 2020;100:adv00034). Importantly, the Effisayil 1 study will enable the natural course of flares to be examined, as it is the first clinical trial in GPP to include a placebo arm, and this will form part of a future publication from this study. We have included minor amendments in the introduction on page 7, lines 19–22, to help clarify the periodicity and duration of flares. Flare duration was also mentioned in the third paragraph of the introduction: “As systemic and skin manifestations of acute GPP flares may remit within 2 months in some patients, (Choon SE, et al. Int J Dermatol 2014;53:676-684) in most of these trials, clinical assessment of endpoints were conducted at Week 16, and did not measure clinically meaningful aspects such as the rapid improvement or resolution of painful pustules.”, page 8, line 16.

Regarding safety results from the Phase I proof-of-concept study, a short statement has been included in the introduction on page 9, lines 8 and 9.

- Pg. 11; Line 23: “If required, screening and randomisation can occur on the same visit if patients meet the randomisation criteria.”

I don’t understand how the investigator can check the exclusion criteria n. 6 (Pg. 30; Line 7) if the screening and randomisation occur in the same visit. Please, perhaps you could shed some light on this.

Response from the authors: In such instances, assessment of key safety parameters, such as that noted by the reviewer, would be conducted by the local laboratory of the investigator’s centre, and the investigator would be informed about selected lab values prior to dosing, to allow the investigator to ensure the patient satisfies the inclusion/exclusion criteria. To help clarify this to the reader, the manuscript has been edited to include this information on page 10, lines 27 and 28.

- Pg. 12; Line 19 “Dose escalation of their maintenance treatment with cyclosporin, retinoids or methotrexate within 2 weeks prior to randomisation” Usually, in the dermatology clinical trials the use of this treatments require a wash out of 4 weeks, but in your study the subjects can start with the investigation product just after discontinue the treatment with this restricted medication. Can affect the effect of this medications to the results?

Response from the authors: We agree with the reviewer that normally, patients would be required to undergo a washout period prior to initiating treatment. There is a possibility that the absence of a washout could potentially influence study results; however, as it was a requirement that patients must be experiencing an acute GPP flare of moderate-to-severe intensity (defined as a GPPGA score of ≥3, new appearance or worsening of existing pustules, a GPPGA pustulation subscore of ≥2, ≥5% body surface covered with erythema and the presence of pustules) prior to randomisation in order to enrol into the trial, it was deemed that any previous administered medication (even if not fully washed out) had failed and therefore any impact on the study findings would be minimal.

- Finally I would like to thanks all the authors for the hard work done in the design of this clinical trial. The GPP is a rare disease without appropriate treatment and I hope that the spesolimab improves the health of the GPP patients. Besides, I would like to mention the efforts of the authors in favor of transparency. I look forward to read the study results in a medical journal coming soon. congratulations also on the data sharing statement.

Response from the authors: We thank the reviewers for their comments and the acknowledgement of the authors’ hard work on the design of this trial. GPP is a severe and rare disease, with no approved therapies in Western countries and no approved therapies for the treatment of acute flares; acute flares can be life threatening and there is a need for effective and tolerable rapid-acting agents. We share the reviewer’s sentiment and also hope that spesolimab will improve the health and quality of life of these patients.
Reviewer: 2

Comments to the Author
Thank you for the opportunity to review this work. The protocol is well written and clear. Please see below for my comments and suggestions which hope to make the manuscript stronger.

- Page 8, line 50: "Although there are therapies specifically indicated for GPP approved in Japan, Taiwan and Thailand, there ..." this sentence is similar to the one in Line 35, please consider revising.

Response from the authors: We thank the reviewer for identifying this repetition of information. The manuscript has been revised to remove the repetition from the first sentence corresponding to line 35 on page 7.

- Page 12, Line 38; "Are experiencing their first episode of an acute GPP flare of moderate-to-severe intensity; the diagnosis of GPP is to be confirmed retrospectively by a central external expert committee"-while I understand that there may be difficulties in the diagnosis of GPP at first presentation, just out of curiosity, any concerns about potential for misclassification of disease states? Any plans for further sensitivity analysis excluding these patients?

Response from the authors: This criterium was introduced to enable the experienced investigators involved in this study the opportunity to enrol such patients if they presented. We anticipate that there will be very few patients enrolled in this manner. In such cases, however, if the outcome of the review by the central external expert committee does not fully support the diagnosis of GPP, there would be the option to exclude such patients from a post hoc sensitivity analysis. No edits have been made to the manuscript.

VERSION 2 – REVIEW

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<tr>
<th>REVIEWER</th>
<th>Jesus Gay-Mimbrera</th>
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| REVIEW RETURNED                  | 28-Jan-2021 |

| GENERAL COMMENTS                  | Congratulations for your work and good luck. |