Design and rationale of Effisayil™ 2, a Phase IIb, multicentre, randomised, double-blind, placebo-controlled study of spesolimab, an anti-interleukin-36 receptor antibody, in preventing flares in patients with generalized pustular psoriasis

P1034

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The Effisayil™ 2 study has been designed to obtain clinically pertinent information on the use of maintenance spesolimab treatment in preventing generalized pustular psoriasis (GPP) flares and providing sustained symptom management

PURPOSE

The main purpose of the Effisayil™ 2 trial is to evaluate the efficacy, safety and tolerability of three dosing regimens of subcutaneous (SC) spesolimab versus placebo as a maintenance treatment of GPP and for the prevention of GPP flares. In addition, the study will assess the efficacy and safety of spesolimab intravenous (IV) rescue treatment of GPP flares.

INTRODUCTION

- GPP is a rare and potentially life-threatening neutrophilic skin disease, characterised by recurrent flares of widespread sterile pustular eruption.[1,2] Between flares, most patients experience skin scaling, lesions and erythema[3]
  - The interleukin-36 (IL-36) pathway has a pivotal role in GPP pathophysiology[4–6]
- Current treatment options for GPP are limited and often inappropriate for lifelong GPP management because of adverse events, existing contraindications or a lack of sustained efficacy
- In the Effisayil™ 1 study, treatment with spesolimab, an anti-IL-36 receptor monoclonal antibody, demonstrated rapid pustular and skin clearance in patients presenting with GPP flares[7]
- Effisayil™ 2 is the first multicentre, double-blind, placebo-controlled Phase IIb study evaluating the efficacy and safety of maintenance treatment with SC spesolimab for the prevention of GPP flares and sustained control of GPP symptoms

CONCLUSIONS

- In the Effisayil™ 1 study, spesolimab provided rapid pustular and skin clearance in patients with GPP flares
- Effisayil™ 2 will provide valuable information on the use of maintenance spesolimab treatment in preventing GPP flares and providing sustained symptom management

PATIENTS AND STATISTICAL ANALYSES

The study plans to randomise 120 patients with a diagnosis of GPP and previous history of GPP flares

- Aged between 12–75 years
- ≥2 past GPP flares
- GPPGA score of 0 (clear) or 1 (almost clear) at screening and randomisation

Rescue treatment with 900 mg IV OL spesolimab in the event of a GPP flare during the treatment period will be permitted

- In case of persistent GPP flare symptoms, patients may receive an additional spesolimab infusion one week after the first infusion
- Subsequent 300 mg SC OL spesolimab q12w, starting 12 weeks later
- This can be escalated to 300 mg q4w if needed, up to Week 44

The primary objective is to evaluate the dose-response relationship for the three dose regimens of spesolimab versus placebo on the primary endpoint, and demonstrate a non-flat dose-response curve

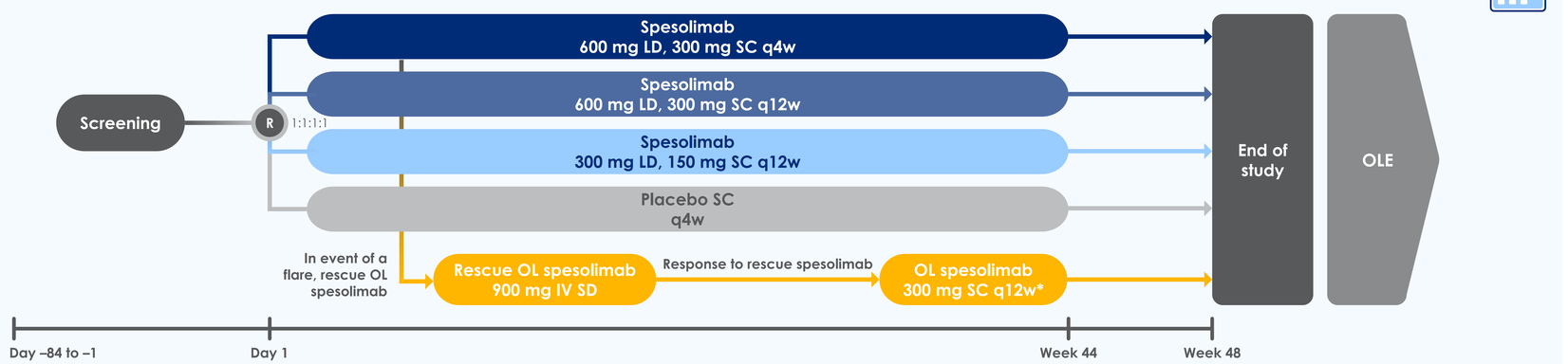
- If the primary objective is met, the secondary objective is to demonstrate the superiority of 300 mg q4w and/or 300 mg q12w spesolimab vs placebo on the primary and key secondary endpoints
- An additional objective is to evaluate the safety of spesolimab in a descriptive manner

GPP, generalized pustular psoriasis; GPPGA, GPP Physician Global Assessment; IV, intravenous; OL, open-label; q4w, every 4 weeks; q12w, every 12 weeks; SC, subcutaneous.

The study plans to randomise 120 patients with a known diagnosis of GPP

STUDY DESIGN

Design of the Effisayil™ 2 study (NCT04399837)



*Patients receiving 300 mg SC OL spesolimab q12w have the option to escalate to 300 mg SC q4w.
IV, intravenous; LD, loading dose; OL, open-label; OLE, open-label extension; q4w, every 4 weeks; q12w, every 12 weeks; R, randomisation; SC, subcutaneous; SD, single dose.

Patients will be randomised 1:1:1:1 to receive one of three spesolimab dosing schedules, or placebo, for 44 weeks

Key inclusion/exclusion criteria

INCLUSION

1. Male or female patients aged ≥12–75 years at screening
2. History of GPP with ≥2 past GPP flares with fresh pustulation (new appearance or worsening)
3. GPPGA score of 0 or 1 at screening and randomisation
4. Patients not on concurrent GPP treatment at randomisation must have had ≥2 flares in the previous year, ≥1 of which must have been associated with fever, elevated CRP or WBC count, asthenia and/or myalgia
5. Patients on concurrent GPP treatment within 12 weeks prior to randomisation must have a history of flaring during, or after dose reduction or discontinuation of, concurrent treatment
6. Patients on concurrent treatment with retinoids, methotrexate and/or cyclosporin must stop this treatment on the day of randomisation

EXCLUSION

1. Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome
2. Primary erythrodermic psoriasis vulgaris
3. Severe, progressive or uncontrolled hepatic disease
4. Acute or chronic infections at randomisation
5. Malignancy within 5 years prior to screening, except for appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of the uterine cervix
6. Pregnant or nursing women, or women planning to become pregnant during the study

CRP, C-reactive protein; GPP, generalized pustular psoriasis; GPPGA, GPP Physician Global Assessment; WBC, white blood cell.

Patients must have a diagnosis of GPP and a history of GPP flares, but must not be experiencing a flare at screening and randomisation

Principal study endpoints

PRIMARY ENDPOINT

Time to first GPP flare (increase of ≥2 in GPPGA total score from baseline and GPPGA pustulation subscore ≥2) onset up to Week 48

KEY SECONDARY ENDPOINT

Occurrence of ≥1 GPP flare up to Week 48

OTHER SECONDARY ENDPOINTS

Time to worsening of PSS score (≥4-point increase in total score from baseline) up to Week 48

Time to first worsening of DLQI (≥4-point increase in total score from baseline)

Sustained remission (GPPGA score of 0 or 1 at all visits up to Week 48)

Occurrence of treatment-emergent adverse events

DLQI, Dermatology Quality of Life Index; GPP, generalized pustular psoriasis; GPPGA, GPP Physician Global Assessment; PSS, Psoriasis Symptom Scale.

The primary study endpoint is time to first GPP flare onset up to Week 48

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Disclosures & Acknowledgements

The authors met criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE). The authors did not receive payment related to the development of the poster. Boehringer Ingelheim was given the opportunity to review the poster for medical and scientific accuracy as well as intellectual property considerations. The study was supported and funded by Boehringer Ingelheim.

AM declares receiving research grants, consulting fees and/or speaker's fees from AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Eisai, Janssen, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe, Nichi-Iko, Nippon Kayaku, Novartis, Sun Pharmaceutical Industries, Taiho Pharmaceutical, Torii Pharmaceutical and Ushio. SEC declares paid activities as an advisor, speaker or consultant for AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, LEO Pharma, Merck Sharp & Dohme, Novartis, Pfizer, Sanofi and UCB. HB declares paid consulting activities for AbbVie, Almirall, Biocad, Boehringer Ingelheim, Celgene, Janssen, Kyowa-Kirin, LEO Pharma, Eli Lilly, Mylan, Novartis and UCB; and grant support from Boehringer Ingelheim, Janssen, LEO Pharma, Novartis and Pfizer. MJA declares paid activities as advisor or consultant for AbbVie, Boehringer Ingelheim, Innovaderm and UCB. SM declares paid consulting activities MZ declares receiving grants, consulting fees and/or speaker's fees from AbbVie, Boehringer Ingelheim, Janssen-Cilag, LEO Pharma China, Novartis, Pfizer and Xian-Janssen. TFT declares conducting clinical trials or received honoraria for serving as a consultant for AbbVie, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, Galderma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, MSD, Novartis International, Pfizer and UCB Pharma. HT declares paid consulting activities for Boehringer Ingelheim. HH is an employee of Boehringer Ingelheim Investment Co. Ltd., Shanghai, China. SR is an employee of Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA. CT is an employee of Boehringer Ingelheim International GmbH, Biberach, Germany. ADB declares paid consulting activities for AbbVie, Almirall, Boehringer Ingelheim, Celgene, Janssen, LEO Pharma, Eli Lilly, Novartis and UCB.

David Murdoch, BSc (Hons), of OPEN Health Communications (London, UK), provided writing, editorial support and formatting assistance, which was contracted and funded by Boehringer Ingelheim.

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