Supplementary file 2

Title: Design and rationale of the global Effisayil™ 1 Phase II, multicentre, randomised, double-blind, placebo-controlled trial of spesolimab in patients with generalized pustular psoriasis presenting with an acute flare

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This supplementary file has been provided by the authors to give readers additional information about their work.

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Generalized Pustular Psoriasis Physician Global Assessment (GPPGA)

GPPGA relies on the clinical assessment of the patient's skin presentation. It is a modified PGA, a physician's assessment of psoriatic lesions, which has been adapted to the evaluation of patients with generalized pustular psoriasis (GPP). The investigator (or qualified site personnel) scores the erythema, pustules and scaling of all psoriatic lesions from 0 to 4. Each component is graded separately, the average is calculated and the final GPPGA is determined from this composite score*. A lower score indicates a lesser severity, with 0 being clear and 1 being almost clear. To receive a score of 0 or 1, the patient should be afebrile in addition to the skin presentation requirements.

Score	Erythema	Pustules	Scaling
0 (clear)	Normal or post-inflammatory hyperpigmentation	No visible pustules	No scaling or crusting
1 (almost clear)	Faint, diffuse pink or slight red	Low density occasional small discrete pustules (noncoalescent)	Superficial focal scaling or crusting restricted to periphery of lesions
2 (mild)	Light red	Moderate density grouped discrete small pustules (noncoalescent)	Predominantly fine scaling or crusting
3 (moderate)	Bright red	High density pustules with some coalescence	Moderate scaling or crusting covering most or all lesions
4 (severe)	Deep fiery red	Very high density pustules with pustular lakes	Severe scaling or crusting covering most or all lesions

*Composite mean score = (erythema + pustules + scaling)/3; total GPPGA score given is 0 if mean = 0 for all three components, 1 if mean 0 to <1.5, 2 if mean 1.5 to <2.5, 3 if mean 2.5 to <3.5, 4 if mean ≥3.5.

Inclusion criteria

Patients will be enrolled (screened) into the trial, if they meet the following criteria:

1.

a. Patients with a GPPGA score of 0 or 1 and a known and documented history of GPP (per ERASPEN criteria) regardless of *IL36RN* mutation status, and in addition with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above the upper limit of normal [ULN]), **OR**

b. Patients with an acute flare of moderate-to-severe intensity meeting the ERASPEN criteria of GPP, with a known and documented history of GPP (per ERASPEN criteria) regardless of *IL36RN* mutation status, and in addition with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN), **OR**

c. Patients experiencing their first episode of an acute GPP flare of moderate-to-severe intensity with evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN). For these patients, the diagnosis will be confirmed retrospectively by a central external expert/committee.

2. Patients may or may not be receiving background treatment with retinoids and/or methotrexate and/or cyclosporine. Patients must discontinue retinoids/methotrexate/cyclosporine prior to receiving the first dose of spesolimab or placebo.

3. Male or female patients, aged 18–75 years at screening.

4. Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP and local legislation prior to start of any screening procedures.

5. Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilisation. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

Exclusion criteria

Patients will not be screened or treated if any of the following criteria apply:

1. Patients with synovitis–acne–pustulosis–hyperostosis–osteitis syndrome.

2. Patients with primary erythrodermic psoriasis vulgaris.

3. Patients with primary plaque psoriasis vulgaris without presence of pustules or with pustules that are restricted to psoriatic plaques.

4. Drug-triggered acute generalized exanthematous pustulosis.

5. Immediate life-threatening flare of GPP or requiring intensive care treatment, according to the investigator's judgement. Life-threatening complications mainly include, but are not limited to, cardiovascular/cytokine-driven shock, pulmonary distress syndrome or renal failure.

6. Severe, progressive or uncontrolled hepatic disease, defined as >3-fold ULN elevation in aspartate transaminase or alanine transaminase or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin.

7. Treatment with:

a. Any restricted medication as specified in **Supplementary Table 1**, or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.

b. Any prior exposure to spesolimab or another IL36R inhibitor.

8. Patients with dose escalation of their maintenance therapy with cyclosporine and/or methotrexate and/or retinoids within the 2 weeks prior to receiving the first dose of spesolimab/ placebo.

9. The initiation of systemic agents such as cyclosporine and/or retinoids and/or methotrexate 2 weeks prior to receiving the first dose of spesolimab/placebo.

10. Patients with congestive heart disease, as assessed by the investigator.

11. Active systemic infections (fungal and bacterial disease) during the last 2 weeks prior to receiving first drug administration, as assessed by the investigator.

12. Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency [e.g. human immunodeficiency virus (HIV)], past organ or stem cell transplantation), as assessed by the investigator.

13. Relevant chronic or acute infections including HIV or viral hepatitis. For patients screened while having a flare (inclusion criteria 1b or 1c), if Visit 1 HIV or viral hepatitis results are not available in time for randomisation, these patients may receive randomised treatment as long as the investigator has ruled out active disease based on available documented history (i.e. negative HIV and viral hepatitis test results) within 3 months prior to Visit 2. A patient can be re-screened if the patient was treated and is cured from acute infection.

14. Active or latent tuberculosis (TB):

QuantiFERON® (or if applicable, T-Spot®) TB test will be performed at screening. If the result is positive, the patient may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. Patients with active TB must be excluded. If presence of latent tuberculosis is established, then treatment should have been initiated and maintained according to local country guidelines. For patients screened while having a flare (inclusion criteria 1b or 1c), if the TB test results are not available in time for randomisation, these patients may receive randomised treatment (provided they meet all other inclusion/exclusion criteria) as long as the investigator has ruled out active disease based on available documented history (i.e. negative for active TB) within 3 months prior to Visit 2.

15. History of allergy/hypersensitivity to a systemically administered trial medication agent or its excipients.

16. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or *in situ* carcinoma of uterine cervix.

17. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s) or receiving other investigational treatment(s).

18. Women who are pregnant, nursing or who plan to become pregnant while in the trial. Women who stop nursing before the study drug administration do not need to be excluded from participating; they should refrain from breastfeeding up to 16 weeks after the study drug administration.

19. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to receiving the first dose of study drug or planned during the study, e.g. hip replacement, aneurysm removal, stomach ligation, as assessed by the investigator.

20. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or any condition) other than GPP, surgical procedure, psychiatric or social problems, medical examination finding (including vital signs and electrocardiogram) or laboratory value at the screening outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial, compromise the safety of the patient or compromise the quality of the data.

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Supplementary Table 1. Restricted medications

Medication or class of medications	Restriction duration (through EoS visit*)
Secukinumab, risankizumab	2 months prior to Visit 2
Tildrakizumab	2 months prior to Visit 2
Rituximab, ustekinumab	2 months prior to Visit 2
Natalizumab, alemtuzumab, guselkumab, ixekizumab, adalimumab, Investigational products for psoriasis (non-biologics)	2 months prior to Visit 2
Brodalumab, efalizumab, visilizumab, briakinumab, infliximab	2 months prior to Visit 2
IL-36R inhibitors	Not allowed before or during trial participation
Etanercept, live virus vaccinations	6 weeks prior to Visit 2
Any investigational device or product (excludes psoriasis products) Other systemic immunomodulating treatments (e.g. corticosteroids†, cyclophosphamide), tofacitinib, apremilast Other systemic psoriasis treatments (e.g. fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g. PUVA). GMA (granulocytes and monocytes adsorptive apheresis)	30 days prior to Visit 2
Phototherapy (e.g. UVA, UVB) topical treatment for psoriasis or any other skin condition (e.g. topical corticosteroids, topical vitamin D analogues, tar, anthralin, topical retinoids)	No treatment initiation of topical treatment 1 week prior to Visit 2, and use of these medications is not allowed post Visit 2
Anakinra	7 days prior to Visit 2
Methotrexate, cyclosporine, retinoids	No treatment initiation 2 weeks prior to Visit 2 No dose escalation within 2 weeks prior to Visit 2 Must be discontinued prior to receiving the first dose of spesolimab/placebo and not allowed post Visit 2

*In case of worsening of the flare (disease worsening) the investigator can treat the patient with standard of care (escape treatment) of their choice. †No restriction on inhaled corticosteroids to treat asthma or corticosteroid drops administered in the eye or ear. EoS: end of study; IL-36R, interleukin 36 receptor; PUVA, psoralen and ultraviolet A; UVA, ultraviolet A; UVB, ultraviolet B.

Supplementary Table 2. Efficacy outcome measures

Outcome measure	Timepoint(s)	Description
Primary outcome		
GPPGA pustulation subscore of 0	Week 1	No visible pustules
Key secondary outcome		
GPPGA score of 0 or 1	Week 1	Composite mean score = (erythema + pustules + scaling)/3; total GPPGA score given is 0 if mean is 0, and 1 if mean 0 to <1.5 for all three components: Erythema, 0 (normal or post-inflammatory hyperpigmentation) to 4 (deep fiery red) Pustules, 0 (no visible pustules) to 4 (very high-density pustules with pustular lakes) Scaling, 0 (no scaling or crusting) to 4 (severe scaling or crusting covering most or all lesions)
Secondary endpoints		
GPPASI 75	Week 4	75% improvement in GPPASI total score. Composite mean score = sum of individual score (as defined per GPPGA) from all body regions. Individual score per body region = body region factor (head = 0.1, upper limb = 0.2, trunk = 0.3, lower limb = 0.4) × body region area score × sum of component severity scores in body region. Patients' overall GPPASI ranges from 0 to 72
Change from baseline in VAS score	Week 4	PRO providing a range of scores from 0 to 100 in a continuous visual scale of 100 mm in length to indicate the severity of the pain of GPP during the previous week. A higher score indicates greater pain intensity
Change from baseline in PSS score	Week 4	PRO providing a range of 0 (none) to 4 (very severe) to assess severity of pain, redness, itching and burning symptoms during the past 24 hours. The symptom scores are added to an unweighted total score, ranging from 0 to 16
Change from baseline in FACIT-Fatigue score	Week 4	PRO consisting of a 13-item questionnaire that assesses self-reported fatigue and its impact upon daily activities and function during the previous week (7 days). Responses of "not at all", "a little", "somewhat", "quite a bit" and "very much" are available for each question, and correspond to scores of 0, 1, 2, 3 and 4, respectively. The total score ranges from 0 to 52
GPPGA score of 0 or 1	Week 4	
GPPGA pustulation subscore of 0	Week 4	
GPPASI 50	Weeks 1 and 4	50% improvement in GPPASI total score

Percentage reduction from baseline in GPPASI	Weeks 1 and 4	
Further endpoints to compare the effects of a single IV dose of spesolimab to placebo, and/or to explore the effects of OL spesolimab use at Day 8 on the subsequent efficacy of GPP acute flare treatment*		
Time to first achievement of a GPPGA score of 0 or 1		
Time to first achievement of a GPPGA pustulation subscore of 0		
Improvement of CGI per JDA severity index	Weeks 1, 2 and 4	CGI-Improvement as per JDA severity index, an observer-rated scale that measures illness global improvement. It is categorised as “worsened”, “no change”, “minimally improved”, “much improved” or “very much improved”
GPPGA total score of 0 or 1*	By visit	
GPPGA pustulation subscore of 0*	By visit	
Change from baseline in GPPGA total score	By visit	
Change from baseline in GPPGA pustulation subscore	By visit	
GPPASI 50*	By visit	
GPPASI 75*	By visit	
Overall percent reduction in GPPASI*	By visit	
Change from baseline in DLQI score	By visit	PRO consisting of a 10-question quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment during the previous week. DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0–1 = no effect on a patient’s life, 2–5 = small effect, 6–10 = moderate effect, 11–20 = very large effect and 21–30 = extremely large effect. A 4-point change from baseline is considered a clinically important difference

Change from baseline in FACIT-Fatigue score*	By visit	
Change in pain VAS score*	By visit	
Change in PSS score*	By visit	
DLQI score of 0 or 1	By visit	
Change from baseline in EQ-5D-5L VAS score	By visit	EQ-5D is a PRO containing questions on different dimensions of health (e.g. mobility, self-care) and one VAS on current health. It is a standardised instrument for use as a measure of health. Response options include a 5-level ordinal scale reporting on the five dimensions of health and a VAS reporting the patient's self-rated health status as a number between 0 and 100

*Endpoints that will be also explored on patients receiving OL spesolimab at Day 8. CGI, Clinical Global Impression; CRP, C-reactive protein; DLQI, Dermatology Life Quality Index; EQ-5D-5L, 5-level EuroQol-5 dimensions; FACIT, Functional Assessment of Chronic Illness Therapy; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; GPPASI, Generalized Pustular Psoriasis Area and Severity Index; IV, intravenous; JDA, Japanese Dermatological Association; OL, open-label; PRO, patient-reported outcome; PSS, Psoriasis Symptom Scale; VAS, visual analogue scale; WBC, white blood cells.