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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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ABSTRACT

Introduction

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening disease characterised by recurrent flares of widespread neutrophilic aseptic skin pustular eruption. Despite the availability of approved biologics for GPP in Japan, Taiwan and Thailand, associated evidence is largely based on uncontrolled studies in which acute flares were not directly assessed. Therefore, there is a high unmet need to investigate new rapid-acting effective treatments that resolve symptoms associated with acute GPP flares. A prior Phase I proof-of-concept study showed rapid improvements in skin and pustule clearance with a single intravenous dose of spesolimab, a novel anti-IL-36 receptor antibody, in patients presenting with an acute GPP flare. Here, we present the design and rationale of Effisayil™ 1, a global, Phase II, placebo-controlled study to evaluate the efficacy, safety and tolerability of spesolimab in patients presenting with an acute GPP flare.

Methods and analysis

At least 51 patients with an acute GPP flare will be randomised 2:1 to receive a single 900 mg intravenous dose of spesolimab or placebo and followed for up to 28 weeks. The primary endpoint is a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 (pustule clearance) at Week 1. The key secondary endpoint is a GPPGA score of 0 or 1 (clear or almost clear) at Week 1. Safety will be assessed over the study duration by the occurrence of treatment-emergent adverse events. Blood and skin biopsies will be collected to assess biomarkers. Superiority of spesolimab over placebo in the proportion of patients achieving the primary and key secondary endpoints will be evaluated.

Ethics and dissemination

The study complies with the ethical principles of the Declaration of Helsinki, the International Council for Harmonisation's Good Clinical Practice and local regulations. Primary results will be published in a peer-reviewed journal.

Trial registration number

NCT03782792; Pre-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this is the first randomised, double-blind, placebo-controlled study in patients presenting with an acute GPP flare
- This study will be the largest randomised, placebo-controlled trial conducted in this population to date
- This study will incorporate clinically relevant disease-specific measures to assess the efficacy of spesolimab, an IL-36 receptor antibody for which rapid improvements in skin and pustule clearance has been observed in a previous Phase I single-arm study in seven patients presenting with acute GPP
- This study will provide robust evidence on the efficacy of spesolimab in patients with acute GPP flares and will allow the natural course of disease to be characterised
- A major challenge for the study is the recruitment challenges common to rare diseases, which will be minimised by the inclusion of a high number of centres and a more favourable chance of receiving active treatment with a 2:1 allocation ratio

KEYWORDS

Psoriasis < DERMATOLOGY

Dermatopathology < DERMATOLOGY

Clinical trials < THERAPEUTICS

INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening autoinflammatory neutrophilic skin disease characterised by episodes of widespread eruption of aseptic, macroscopically visible pustules, which can occur with or without plaque psoriasis, and may be accompanied by systemic inflammation.[1, 2] GPP is usually associated with one or several systemic symptoms such as fever, malaise and fatigue, and extracutaneous manifestations such as arthritis, uveitis, acute respiratory distress syndrome, cardiovascular shock and neutrophilic cholangitis.[3, 4] Common laboratory abnormalities include elevated C-reactive protein, leucocytosis, neutrophilia and liver function abnormalities.[3, 5] Acute GPP flares are associated with significant morbidity, and without appropriate treatment, mortality.[4] Patients with GPP may experience frequent flares, with several episodes per year that may be triggered by infections, stress, medication, medication withdrawal (e.g. corticosteroids) and pregnancy, causing a dramatic reduction in quality of life.[4, 6-9] During the disease course, some patients with GPP may experience relapsing disease with recurrent flares, or persistent disease with intermittent flares. The clinical appearance of the disease can be phenotypically heterogeneous; skin may be clear in between episodic acute flares or patients may have persistent disease characterised by ill-defined erythematous plaques with or without pustules, which may be localised or widespread.[2, 4, 7, 8, 10-12]

Therapeutic intervention in GPP is a major challenge globally, with GPP-specific therapies only approved in a small number of countries (e.g. Japan, Taiwan and Thailand). The rarity of GPP means recruitment of sufficient patients to conduct large, randomised controlled trials to robustly investigate the efficacy and safety of therapeutics is a constant challenge. In addition, the intermittent remission and spontaneously self-limiting episodic pustular flares characteristic of GPP make it difficult to assess the efficacy of any intervention in this population.[9] Therefore, there is still a lack of robust evidence to guide treatment decisions for GPP. Available management guidelines for GPP are widely based on anti-plaque psoriasis strategies, limited case studies and single-arm, open-label studies and generally recommend cyclosporine, retinoids, infliximab and methotrexate as first-line therapies.[11, 13-15] Use of conventional systemic therapy may be associated with cumulative toxicities and limited efficacy, making them inappropriate for long-term disease control.[11, 13, 16] Although there are therapies specifically indicated for GPP approved in Japan, Taiwan and Thailand, there are currently no approved GPP-specific therapies for acute GPP flares globally. In Japan, tumour necrosis factor (TNF)-alpha inhibitors (adalimumab, infliximab and certolizumab pegol), interleukin-(IL-)17/IL-17 receptor (IL-17R) inhibitors

(secukinumab, brodalumab and ixekizumab) and IL-23 inhibitors (risankizumab and guselkumab) are approved for the treatment of patients with GPP who have had an inadequate response to conventional therapy.[13, 15-30] The approval of TNF inhibitors was based largely on case studies, whereas the approval of IL-17/IL-17R and IL-23 inhibitors was based on prospective, but small-scale, open-label, single-arm, Phase III studies, in which non-disease-specific endpoints, such as any improvement in the Clinical Global Impression index, were used to assess efficacy in Japanese patients presenting with mild-to-moderate GPP as per the Japanese Dermatological Association severity score. As systemic and skin manifestations of acute GPP flares may remit within 2 months in some patients,[4] 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. In Taiwan and Thailand, brodalumab was approved for the treatment of adults with pustular psoriasis who are candidates for systemic therapy, or adults with GPP who have had an inadequate response to conventional therapy, respectively, both based on a Japanese open-label study which included only 12 patients with GPP.[31-33]

Effective treatments with a very rapid onset of action for acute GPP flares that can allow early control of skin inflammation and the prevention of complications, including pustule formation and systemic manifestations, and are tolerable for both short- and long-term treatment strategies are needed.[4, 12]

In patients with GPP, overexpression of IL-36 inflammatory cytokines in skin lesions and loss-of-function mutations in the gene coding for the IL-36 receptor antagonist (*IL36RN*), as well as mutations in other genes connected with the IL-36 pathway (e.g. *CARD14*, *AP1S3, SERPINA3*), have been identified in genetic studies for some patients, suggesting that the IL-36 pathway may be central to GPP pathogenesis.[8, 34-36] Reports for the presence of *IL36RN* mutations in patients with GPP have ranged between 10% and 82%, and was lower in cases of GPP associated with plaque psoriasis than in those associated with GPP alone.[37, 38] Moreover, the knockout of the IL-36R in a murine model of deficiency of IL-36R antagonist (DITRA) led to complete resolution of skin inflammation,[39] making the blockade of IL-36R signalling a novel and appealing targeted therapeutic approach for patients with GPP.

Results of a Phase I, proof-of-concept study, in which the safety and efficacy of a single intravenous (IV) dose of spesolimab (BI 655130), an anti-IL-36R humanised monoclonal antibody, was assessed in seven patients with an acute GPP flare, provided the first evidence for targeting the IL-36 pathway.[40] In this study, spesolimab resulted in rapid (within 7 days) and sustained improvements (up to last assessment at Week 20) in clinical signs and symptoms irrespective of *IL36RN* mutation, suggesting that IL-36 plays a

pathogenic role among patients with GPP with different genetic backgrounds; this was accompanied by rapid downregulation of molecular signatures from the innate immune response, including neutrophilic pathways, and Th1/Th17-mediated inflammation.[40, 41] This study showed that spesolimab is a promising targeted therapy for acute GPP.

Effisayil™ 1 is a global, Phase II, multicentre, randomised, double-blind, placebo-controlled study of spesolimab in patients presenting with an acute GPP flare (ClinicalTrials.gov identifier: NCT03782792). GPP-specific clinical measures that assess key manifestations of the disease, the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) and GPPGA pustulation subscore, have been established to evaluate treatment efficacy in this study. The GPPGA is a physician-based assessment of the severity of pustules, erythema, and scaling of GPP lesions; each component is scored on a 5-point scale, ranging from 0 (clear) to 4 (severe), and the average is calculated (see online **supplementary file 1**). To differentiate against placebo with a feasible sample size, a stringent primary endpoint was chosen—achievement of a GPPGA pustulation subscore of 0 (complete pustular clearance) at Week 1. The successful early performance of these scores was demonstrated in the Phase I proof-of-concept study. A GPPGA score of 0 or 1 (clear or almost clear skin) was achieved in five of seven patients by Week 1 and in all patients by Week 4.[40]The acuteness, severity and potentially life-threating consequences of other autoinflammatory diseases, and the effectiveness shown for the blockade of the IL-1 family, such as the achievement of early inactive disease and sustained remission,[42, 43] further support the rationale for using an early efficacy endpoint in patients with GPP. The evaluation of non-pustulation components (erythema and scaling) are to be evaluated as part of the key secondary endpoint, the achievement of a total GPPGA score of 0 or 1.

Here, we describe the rationale, study design and methods of Effisayil™ 1; to our knowledge, this is the first randomised, double-blind, placebo-controlled study in this patient population presenting with an acute GPP flare. This novel and innovative study will inform on the efficacy and safety of targeting the IL-36 pathway in patients with GPP, and will provide insights into the natural progression of untreated GPP disease through the placebo arm, as well as historical clinical data with particular focus on previous occurrence of flares.

METHODS AND ANALYSIS

Study objectives

The primary objective of the Effisayil™ 1 study is to evaluate the efficacy, safety and tolerability of spesolimab versus placebo in patients presenting with an acute GPP flare. Further objectives include the assessment of pharmacokinetics, anti-drug antibodies and pharmacogenomics of spesolimab, and the exploration of biomarkers in acute GPP. In addition, the natural course of GPP in patients receiving placebo, the response of systemic symptoms of GPP flares to spesolimab and the effects of delaying treatment and further dosing with spesolimab in patients with insufficient initial response will also be explored.

Eligibility criteria

Patients aged 18–75 years with GPP, defined by the European Rare And Severe Psoriasis Expert Network (ERASPEN) at screening,[1] who satisfy the inclusion criteria are allowed to enrol into the study regardless of whether they are experiencing a flare at the time of screening, as patients in remission can be monitored for up to 6 months for their next acute flare. If required, screening and randomisation can occur on the same visit if patients meet the randomisation criteria.

Patients will be enrolled if they have previous evidence of fever associated with flares before randomisation, and/or mild asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia above the upper limit of normal, and meet one of the following criteria, regardless of *IL36RN* mutation status:

- Have a GPPGA score of 0 or 1 and a known and documented history of GPP, or
- Are experiencing an acute GPP flare of moderate-to-severe intensity, or
- 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

Patients eligible for this trial must comply with all of the following inclusion and exclusion criteria at randomisation.

Inclusion criteria

Patients must be experiencing an acute GPP flare of moderate-to-severe intensity prior to randomisation, defined in the trial 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

Exclusion criteria

Patients will be excluded if they are presenting with:

- Synovitis-acne-pustulosis-hyperostosis-osteitis syndrome
- Erythrodermic plaque psoriasis without pustules or with pustules restricted to psoriatic plaques
- Drug-triggered acute generalized exanthematous pustulosis
- Immediate life-threatening flare of GPP or requiring intensive care treatment
- Dose escalation of their maintenance treatment with cyclosporin, retinoids or methotrexate within 2 weeks prior to randomisation
- Treatment with any drug, including biologics and systemic drugs considered likely to interfere with the safe conduct of the study or any prior exposure to an IL-36R inhibitor

Full inclusion and exclusion criteria and restricted concomitant medication can be found in the online **supplementary file 1**.

Randomisation and intervention

At least 51 patients presenting with an acute GPP flare are to be randomised to receive a single 900 mg IV dose of spesolimab or placebo in a 2:1 ratio on Day 1. Study drug is allocated using computerised Interactive Response Technology and patients and investigators involved will remain blinded until after database lock, unless emergency unblinding is required. This allocation ratio will enable more patients with a distressing and potentially life-threatening disease to be on treatment. This design is also likely to be more appealing to patients because evidence has shown that patients prefer to participate in clinical trials where there is a greater likelihood of receiving active treatment.[44] As required by some regulatory agencies, and based on the rapid onset of response demonstrated in the Phase I, proof-of-concept study and the lack of licensed active interventions, the use of a placebo-controlled parallel group was considered most appropriate to evaluate the efficacy and safety of spesolimab in patients with an acute GPP flare.[40]

Study locations and timings

The study will enrol patients from across 52 centres in 12 countries; it started in March 2019 and it is expected to complete in 2021. After randomisation, patients will be assessed daily until Day 3. Clinical

visits on Days 4–7 are optional and need not be attended if a patient has already achieved complete pustular clearance (GPPGA pustulation subscore of 0). After patients have received a single dose of spesolimab or placebo at Day 1, patients will be followed for 12–28 weeks based on the subsequent treatment response (**Figure 1**). Patients who have not received escape treatment, and who have a GPPGA ≥2 and a pustular component of GPPGA ≥2 at Week 1, will qualify for treatment with an open-label single IV dose of 900 mg spesolimab on Day 8. All randomised patients will continue through the subsequent visits until the end of study. Patients who show no flare symptoms of moderate-to-severe intensity at the end of the study and meet clinical criteria for treatment response at Week 12, or at the subsequent visit for patients on rescue treatment with open-label spesolimab (**Figure 1**), will be eligible to enter a 5-year open-label extension study (ClinicalTrials.gov identifier: NCT03886246). Those not qualifying to enter the open-label extension study, will be followed for up to an additional 16 weeks. Clinical response, photographs of skin lesions, physical examination, examination of vital signs, fever assessment and safety laboratory tests are to be undertaken at each visit. Optional skin biopsies will be taken on Days 1 and 8 and Week 8. Whole blood for RNA sequencing and serum for soluble protein biomarkers are to be sampled prior to dosing, on Days 1–3 and Day 8, Week 2, 4 and 12 and at the end of study visit. Importantly, the *IL36RN* mutation status is to be determined for all patients.

Escape and rescue medication

If the severity and progression of the disease worsens within the first week after randomisation and requires immediate treatment, the investigator can treat the patient with escape medication, which is the investigator's choice of standard of care (SoC). However, if the disease condition is stable, it is recommended to wait until the primary endpoint visit (Day 8/Week 1) before prescribing a SoC escape medication because there will be an option to administer open-label spesolimab instead at this time. Due to the absence of an approved standard treatment for GPP and a commonly accepted treatment algorithm, patients in this trial are likely to have a heterogenous pre-treatment history, given that different SoC are available in different countries.

After Week 1, only one rescue dose with open-label spesolimab is permitted if a patient who previously achieved a clinical response (GPPGA 0 or 1) experiences recurrence of a GPP flare. Patients who do not achieve a clinical response, but have disease worsening subsequent to Week 1, can receive an escape treatment chosen by the investigator.

Study endpoints

The primary endpoint of the study is a GPPGA pustulation subscore of 0 at Week 1 and the key secondary endpoint is a GPPGA score of 0 or 1 at Week 1. Secondary endpoints at Week 4 included in the statistical strategy are a 75% improvement in the Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI 75), change from baseline in pain visual analogue scale (VAS) score, change from baseline in Psoriasis Symptom Scale (PSS) score and change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score.

The GPP-specific clinical efficacy endpoints (GPPGA, GPPASI) were created with minimal modification of the PGA and PASI (replacement of the induration component with pustulation), which are widely used and understood clinical instruments by dermatologists, and were created with the help of leading global experts in GPP and psoriasis vulgaris. The proposed primary endpoint of a GPPGA pustulation subscore of 0 (clear) at Week 1 and the key secondary endpoint of a GPPGA score of 0 or 1 at Week 1 are clinically meaningful as pustules are the primary lesion of the disease and reflect the desired rapid pustule clearance and overall improvement in GPP skin symptoms. Other secondary endpoints include the occurrence of treatment-emergent adverse events. At each visit, GPPGA and GPPASI will be measured to assess sustained efficacy (**Table 1**).

Table 1. Efficacy outcome measures

Outcome measure	Timepoint(s)
Primary outcome	
GPPGA pustulation subscore of 0	Week 1
Key secondary outcome	
GPPGA score of 0 or 1	Week 1
Secondary endpoints	
GPPASI 75	Week 4
Change from baseline in VAS score	Week 4
Change from baseline in PSS score	Week 4
Change from baseline in FACIT-Fatigue score	Week 4
GPPGA score of 0 or 1	Week 4
GPPGA pustulation subscore of 0	Week 4
GPPASI 50	Weeks 1 and 4
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
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
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

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

At each applicable visit, patients will be asked to complete patient-reported outcomes (PROs) questionnaires. The order of completion for PROs is recommended to be as follows: PSS, Dermatology Life Quality Index (DLQI), pain VAS, FACIT-Fatigue, and 5-level EuroQol-5 dimensions (EQ-5D-5L). Correlations between efficacy endpoints and PROs are to be assessed. The full list of study outcomes is reported in **Table 1** and **Supplementary Table 2**.

The assessment of biomarkers will be exploratory. This will include biochemical and cellular biomarkers in skin and blood samples pre- and post-treatment with spesolimab. Changes in gene and protein expression in optional skin biopsies, in patients who give consent, are to be assessed. Gene expression analysis will include the genes involved in the mechanism of action of spesolimab or the pathology of the disease. Immunohistochemistry for neutrophils, macrophages, keratinocytes, T cells and dendritic cells markers are planned. Serum will be collected to assess changes in soluble protein levels of select IL-36 pathway disease-specific biomarkers. Cellular biomarkers on cells such as T cells and macrophages will be assessed by flow cytometry from whole blood samples. In addition, RNA sequencing from one blood sample of *IL36RN*, *CARD14* and *AP1S3* genes to assess known GPP-associated mutations will be performed in whole blood, and their potential influence on the severity of disease and efficacy of spesolimab will be evaluated.

Statistical analysis

The trial is designed to demonstrate the superiority of spesolimab with regard to the primary endpoint (achievement of pustule clearance at Week 1) and the key secondary endpoint (achievement of GPPGA 0 or 1 at Week 1) relative to placebo. With an expected response rate of 0.6 on spesolimab and 0.1 on placebo for the primary endpoint and key secondary endpoint, and a type I error of <0.025 (1-sided), for a total sample size of 51 patients, this trial will be able to detect an effect of spesolimab relative to placebo, for the primary endpoint and key secondary endpoint simultaneously, with an overall power of 93.9%. The statistical testing on each of the primary, key secondary and selected secondary endpoints will be performed in a hierarchical manner. The primary endpoint and key secondary endpoint will be analysed with the Suissa–Shuster Z-pooled test to compare the proportion of patients who achieve a response with spesolimab versus placebo at Week 1. For the primary estimand concept, any use of escape medication, open-label spesolimab use at Day 8, or rescue medication with spesolimab, prior to the observation of an endpoint will be considered as non-response. All safety data in this study will be descriptively summarised. For the analysis of biomarkers, a staged approach will be applied, in which the initial analysis will focus on selected time points and decision on further analysis will be made based on these results. Subgroup analysis of trial endpoints on baseline categories (e.g. *IL36RN* mutation status, GPPGA score) are planned. An external and independent data monitoring committee will perform an unblinded safety and efficacy assessment at specified intervals.

Ethics and dissemination

The study will be conducted in compliance with the protocol, the ethical principles of the Declaration of Helsinki, in accordance with the International Council for Harmonisation's Guideline for Good Clinical Practice (GCP), and the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, 27 March 1997) and applicable local regulations, and is approved by the ethics committees of participating institutions and countries. Approved amendments of the protocol will be posted on clinicaltrials.gov (last protocol version 3, 26 June 2020). Eligible patients will be provided information and informed consent will be obtained (see online **supplementary file 2**).

On completion of the trial and after finalisation of the clinical trial report, the study results will be published in an international peer-reviewed medical journal and abstracts for congresses.

Data management

Patient privacy will be ensured by using patient identification code numbers. Data protection and data security measures are implemented for the collection, storage and processing of patient data in

accordance with the confidentiality and privacy principle 12 of the World Health Organization GCP handbook.

Patient and public involvement

There was no involvement from patients and the public in the design of this study.

DISCUSSION

Randomised controlled trials are the gold standard for testing the efficacy and safety of new treatments. However, in rare severe diseases, recruitment difficulties and ethical concerns often hamper the possibility of involving a large population in a placebo-controlled randomised trial. Furthermore, although randomised controlled studies have been conducted in rare autoinflammatory syndromes such as cryopyrinopathies with canakinumab,[45] GPP raised an additional major challenge due to the spontaneously self-limiting course of acute flares in its intermittent pattern that can occur in some patients.[7] Therefore, an original study design integrating these parameters was necessary to accurately assess the efficacy of any drug intervention in this rare variant of the psoriatic disease spectrum. Effisayil™ 1 is the first randomised, double-blind, placebo-controlled study conducted in patients presenting with an acute GPP flare. Altogether, the high number of participating countries to minimise the risk of underrecruiting, along with the rapidity of the efficacy assessment and the lack of a suitable comparator, propitiates the ambitious design and conduct of this unique trial in a rare disease. This study aims to address a high unmet medical need and the lack of robust efficacy and safety data in patients with acute GPP flares, assess PROs, systemic symptoms and biomarkers and their correlation with clinical response and severity of disease, and provide insights on the natural disease course of an acute GPP flare. Results from this trial are planned to support the first registration of spesolimab in patients with GPP.

The study will evaluate the efficacy and safety of a single IV injection of spesolimab at Week 1 versus placebo, with an option of an open-label dose at Day 8 for both treatment arms if criteria is met. In addition, the study will allow the duration of efficacy to be assessed for up to 28 weeks, if not rolling over into the open-label extension study. All recurrent flares within 12 weeks after a single or two IV doses of spesolimab will be recorded. Pictures of skin lesions as well as lesion absence will be systematically collected at each visit to provide further visual insights. For each case, naturally occurring

resolution or worsening of symptoms in the placebo arm will provide insights on the natural disease course of GPP flare.

Despite the small population size of the study and the single 900 mg dose, Effisayil™ 1 is designed to be the largest study in patients with GPP, and the first randomised, placebo-controlled trial in this population to date. In addition to this study there are two further studies planned including a 5-year open-label extension study and the Effisayil™ 2 study (ClinicalTrials.gov identifier: NCT04399837), a multi-centre, randomised, parallel-group, double-blind, placebo-controlled, Phase IIb, dose-finding study to evaluate the efficacy and safety of subcutaneous spesolimab compared with placebo in the prevention of GPP flares in patients with a history of GPP. These studies will tackle different disease scenarios that address the limitations of the present study.

Overall, the results of the Effisayil™ 1 trial will provide robust evidence on early intervention with spesolimab for the treatment of acute GPP flares and will establish the relevance of using disease-specific endpoints that are clinically meaningful for patients and their physicians.

Author's contribution: SEC, MGK, SM, ADB, SR, HD, CT and HB were involved in the conception and trial design. HD provided statistical expertise. All authors contributed in drafting the protocol manuscript and critically revised and commented on its previous versions and the final version. All authors will be involved in the analysis and/or interpretation of the data.

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Competing interests: SR is an employee of Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA. HD is an employee of Boehringer Ingelheim Investment Co. Ltd., Shanghai, China. KT and CT are employees of Boehringer Ingelheim International GmbH, Biberach, Germany. SEC declares paid activities as advisor, speaker or consultant for AbbVie, Boehringer-Ingelheim, Eli-Lilly, Janssen, Leo Pharma, MSD, Novartis, Pfizer, Sanofi and UCB. MGL declares paid consulting activities for Aditum Bio, Allergan,

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Data sharing statement:

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html

Prior to providing access, documents will be examined and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can be requested via this link:

https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html

All such requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use https://clinicalstudydatarequest.com to request access to study data.

Figure 1. Study design

*Day 1: 51 screened GPP patients with an accute flare defined as GPPGA ≥3 and GPPGA pustulation subscore of ≥2 will be randomised 2:1 to a single IV dose of 900 mg spesolimab or IV placebo.

†Day 2–7: Escape treatment (SoC) may be offered in case of disease worsening defined as worsening of clinical status or GPP skin and/or systemic symptoms as defined by the investigator.

‡Day 8: Patients with a GPPGA ≥2 and pustular component of GPPGA ≥2 will qualify for treatment with OL spesolimab.

§After Day 8–Week 12: only one rescue dose with OL spesolimab is permitted if a patient who has previously achieved clinical response (GPPGA 0/1) to initial treatment, either with spesolimab or placebo at Day 1, or escape medication or OL spesolimab at Day 8, experiences a recurrence of a GPP flare (≥2-point increase in the GPPGA score and the pustular component of GPPGA ≥2). Subsequent flares will be treated with SoC per physician's choice.

¶Patients who do not require rescue treatment with OL spesolimab are to be followed until Week 12 (EoS) prior to entering into OLE trial. Patients who receive rescue treatment with OL spesolimab between Weeks 2 and Week 6 are to be followed until Week 12 (EoS) prior to entering the OLE trial. If at Week 12 they qualify to enter the OLE trial, then the EoS will be considered for these patients. If not, patients will have an additional 10 weeks' follow-up and have an EoS at Week 16–28. Patients who receive rescue treatment with OL spesolimab between Weeks 7 and 12 are to be followed for an additional 6 weeks and have a response evaluation at Week 13–18; these patients will not have a visit at Week 12. If at Week 13–18 patients qualify to enter the OLE trial, the EoS will be considered for these patients. If not, patients will have an additional 10 weeks follow-up and have an EoS at Week 16–28. Patients who do not qualify to enter the OLE trial are to be followed for 16 weeks (EoS/Week 16–28) after the last dose of trial medication, which is the latest time point of trial medication given during the study (e.g. Day 1, Day 8 if OL spesolimab is given, rescue with OL spesolimab if given).

The white arrow head indicates a single dose of IV spesolimab or placebo at Day 1 or spesolimab at/after Day 8.

EoS, end of study; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; IV, intravenous; OL, open label, OLE, open-label extension; R, randomisation; SoC, standard of care.

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Supplementary file 1

Generalized Pustular Psoriasis Physician Global Assessment (GPPGA)

Inclusion criteria

Exclusion criteria

Supplementary table 1. Restricted medications

Supplementary table 2. Efficacy outcome measures

Supplementary file 2

Information and Consent Form for Trial Subjects template

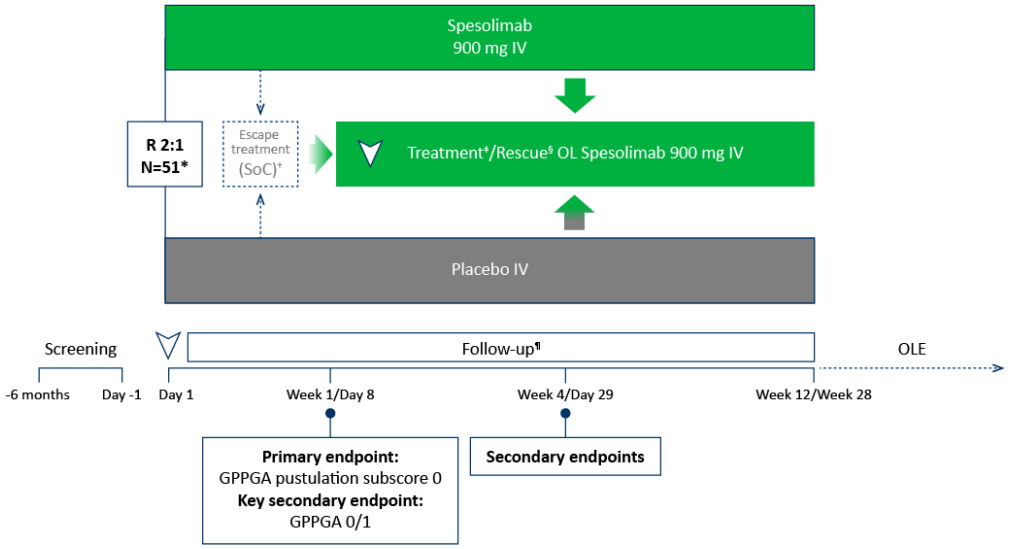

Figure 1. Study design

174x94mm (150 x 150 DPI)

Supplementary file 1

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.

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.

BOEHRINGER INGELHEIM GmbH

Information and Consent Form for Trial Subjects (template)

GENERAL GUIDELINES WHEN WRITING THE CONSENT FORM

(Keep the red text when submitting the trial version to the CT Managers.
Delete these guidelines before submitting to local regulatory authorities)

1. FORMAT:

- Use a consistent font style and size throughout the document; a minimum 12 point font is preferable. Please consider the audience; some patients may require a larger font.
- The pages should contain "Page X of Y" and the version date of the document in the footer.
- **BICTMS number must be added. Localversioning can be added in addition to fulfil local needs.**
- Section headers should not float at the bottom of the page without any text.
- Before using the consent form, please print and review the document for print errors, spelling and grammar, font sizes, floating headers, etc.
- Avoid using tick boxes; this often leads to unnecessary non-compliances.

2. LANGUAGE AND READABILITY:

- Use brief, simple statements (not long, detailed, complicated explanations) using simple, layperson's language aimed at 13 – 15 year olds. Break long sentences into several shorter ones. Express only one major idea per sentence.
- Please do a "Readability Test" in MS Word as an indication check to find out whether the information you prepared is understandable to trial subjectssubjects (e.g. Grade level 8 - 10) included in this trial. Remember that the responsibility for the readability of the document remains exclusively with the author.
- Speak to your reader. Use "you/your" to refer to the potential subject. For example, write, "You must provide consent" not, "Consent must be provided".
- Avoid unfamiliar or confusing words or phrases. Avoid jargon. If a medical terminology is essential, include a layperson's definition. For example, "bruise" should be used instead of "hematoma".

3. GENERAL INSTRUCTIONS FOR USING THIS FORM:

- Instructions and suggested text are printed in 'red', with suggestions to actual text in 'black'. **Delete or replace all red text from this template when finished**.
- Sections highlighted in yellow are mandatory text and if there are any country specific changes , then the responsible CTM must consult and get approval from either local line management and/or local legal and/or local data protection/privacy contact for the requested changes.
- Please delete any parts of the consent template that are not relevant to your particular trial.
- If the consent form contains multiple procedures and/or technical terms, consider using the appendix at the end of the consent form. The use of appendices described in this

template is optional and depends on local regulations. Alternatively, the content in the appendices can be directly incorporated within the main body of the form as usual.

INFORMATION AND CONSENT FORM
FOR TRIAL SUBJECTS

TRIAL LAY TITLE: A study to test BI 655130 in patients with a flare-up of a skin disease called Generalized Pustular Psoriasis

PROTOCOL No.: 1368-0013

TRIAL SUBJECT No.: _____

EudraCT No.: 2017-004231-37

SPONSOR: Boehringer Ingelheim *(to be adapted at country level, CT Manager to insert full corporate legal name of local country)*

TRIAL DOCTOR: Name, address, telephone number

Dear Patient,

You are being asked to participate in this research trial because you have a rare and severe inflammatory skin disease called, Generalized Pustular Psoriasis (GPP) that causes inflammation in the skin and may also affect internal organs. It shows up as a recurrent flare-up (worsening GPP symptoms) with widespread pustules (small bumps on the skin that contain fluid or pus), diffuse erythema (large area of redness of the skin that looks like a sunburn), and scaling (small, hard, dry areas of the skin) accompanied by general symptoms. A flare-up can be serious and requires immediate medical care. Little is known about this rare disease so far, and current treatment options for controlling GPP flare-ups are limited.

Please read the following information carefully. It contains important information to help you decide whether to participate in this research trial. The trial staff will have a detailed interview with you to inform you about the trial and the possible benefits and risks of your participation. Ask questions about anything that is not clear at any time. You may take home an unsigned copy of this information to think about and discuss with your family, friends or family doctor before you make your decision to participate or not.

After reading and discussing the information, you should know:

- Why this research trial is being done;
- What will happen during the trial;
- Any possible benefits to you;
- The possible risks to you;
- Other options you could choose instead of being in this trial;

- How your personal information / health information will be protected during the trial and after the trial is over, and which data privacy rights you have;
- How your data and your biological samples will be collected, stored, processed, transferred and used
- Whether being in this trial could involve any cost to you; and
- What to do if you have problems or questions about this trial.

This document also includes:

- Appendix A: Visit Schedule
- Appendix B: Description of Trial Procedures and Risks
- Appendix C: Known Side Effects (Adverse Events) of the Investigational Drug(s)
- Appendix D: *move* Confidentiality / Privacy and Data Sharing *section to an Appendix if allowed by local authorities / local legal*

Your participation in this trial is voluntary. If you join this trial, you can still stop at any time. You have the right not to sign this consent form. If you do not sign, you cannot take part in this research trial. If you decide to participate, you will be asked to sign and date at the end of this form.

Your signature confirms that you agree and accept to take part in this trial and to the handling of your data as described in this form.
It is important that your personal doctor is aware that you are in a research trial because you may be taking a treatment that could affect your health. With your permission, we will notify him/her that you are taking part in this trial.

PURPOSE OF THE TRIAL

The purpose of this trial is to:

- Compare the safety, effectiveness and side effects of a single intravenous (IV) dose of the investigational drug being studied, BI 655130, with an inactive substance (placebo), in subjects with GPP, who are having a moderate to severe flare-up (GPP symptoms). A placebo is a substance that looks like the investigational drug but contains no active drug.
- Test how the investigational drug is used by the body and how fast or slow it moves through or out of the body.
- Measure the immune response of the investigational drug (when the body detects and defends itself against substances that appear unknown and harmful).
- See how genes (coded instructions for making each cell in your body) may explain and predict the response to the investigational drug.

The investigational drug, BI 655130, works by stopping the effect of a protein called IL-36 receptor involved in the development of GPP. BI 655130 is the first compound of this new class of drugs.

The investigational drug has not been approved as a treatment for any disease by <insert authority> and, thus, its use in this research trial is considered experimental.

We estimate that approximately <enter number of subjects assigned to your OPU> people will participate in this trial in <insert country of OPU> and approximately 51 subjects worldwide.

In this clinical trial, competitive enrolment will be used. This means that when a target number of patients (approximately 51) have entered the trial, all further enrolments will be closed. It is possible that you could be in the screening phase when the target number of patients is reached. If that happens, you may not be able to receive the treatment, even if you meet all the other requirements for entering the clinical trial and receiving the treatment.

THIS TRIAL HAS BEEN APPROVED BY <insert applicable local authorities, if required, otherwise this statement can be deleted>.

DESCRIPTION OF THE TRIAL

This trial compares the effects of the active investigational drug, BI 655130 (spesolimab), with an inactive substance (placebo) in subjects with GPP, who are having a moderate to severe flare-up.

You will be assigned by random choice to receive either the investigational drug, BI 655130, or the placebo at Visit 2 (Day 1) as follows:

- *Group 1 will receive, a single dose of BI 655130, 900 mg, by IV infusion*
- *Group 2 will receive a single dose of placebo, by IV infusion*

This process is called randomization. You will have about 66% chance of being placed in Group 1 and a 33% chance of being placed in Group 2.

The Visit 2 dose of the trial medication (investigational drug or placebo) will be double-blinded. No one (including you and the trial team) will know who is receiving the investigational drug or the placebo. This way the results of the trial will not be favored one way or another. If it becomes necessary for your care, your trial doctor will be able to find out whether you took the placebo or the investigational drug.

TRIAL PROCEDURES

Time to be spent in the trial

The time you will spend in this trial will depend on the time window between the first trial centre visit (when you agree to participate and give your informed consent) and when you have a GPP flare-up and return for the second trial centre visit. This time period can last several days, weeks or even months and cannot be predicted.

Once you have a GPP flare-up and complete Visit 2, your participation will last up to about 28 weeks (about 7 months) and require about 12 to 14 additional visits to the trial centre.

You may be asked to come to the trial centre for additional unscheduled visits. Refer to the Unscheduled Visits section below for more information.

Each trial centre visit may take between 1/2 hour and 4 hours to complete the procedures as described in Appendix A.

If applicable, please consult with your local Legal representative to clarify whether it is acceptable to have the trial tests and procedures listed in an appendix:

In Appendix A of this document you will find a detailed overview and schedule of all the visits which lists the trial tests and procedures planned at each visit. The trial doctor or the trial staff will go through this Appendix with you.

In Appendix B of this document you will find a more detailed description of the different trial tests and procedures including related risks. The trial doctor or the trial staff will go through this Appendix with you.

At trial visits, the trial doctor or trial staff will ask you about how you feel, what medications you have taken and what other health care you have received since the last trial visit.

Before the clinical research starts (screening - Visit 1)

Before any study procedures are done, you will be asked to read and sign this Information and Consent form.

The first trial visit will be a screening visit. The screening visit will include the following procedures:

- You will be asked about your medical history including history of GPP, demographics (gender, ethnicity and race), and your smoking history
- A physical exam including vital signs and your temperature will be taken
- Blood and urine tests, including a blood test for infectious disease testing
- A pregnancy blood test if you are a female able to have a child
- An electrocardiogram (ECG)
- Photographs of skin lesions (areas of your skin affected by GPP)
- You will be asked about how you feel and what medications you are taking
- The trial doctor will obtain information from your personal doctor (if different from the trial doctor) about the mutation (changes to the structure of a gene) of a certain gene (IL-36RN). If this information is not available, you will still be able to participate in this trial

The results of the tests and/or questions at the screening visit will help the trial team decide whether you can continue in this trial. If these tests show that you are eligible to participate in the trial, you will be able to continue in this trial. If you do not meet the eligibility criteria, you will not be able to continue. You should not go to another trial centre to be screened again.

If you are not having a moderate to severe GPP flare-up at the screening visit, you can still take part in this trial and then return to continue your participation when a flare-up occurs. At that time, you will be asked to confirm that you still agree to participate in this trial. If the flare-up occurs after 6 months of signing this consent form, you will be asked to sign another consent form for this trial and repeat your first visit.

INVESTIGATIONAL DRUG VISIT (VISIT 2)

You may be asked to stop taking certain medications before receiving the trial medication. The trial doctor will further discuss this with you.

If you are eligible to participate in this trial and you are having a GPP flare-up at Visit 1, Visit 1 and Visit 2 can be done on the same day.

You will receive the trial medication, BI 655130 or placebo, at Visit 2 (Day 1) by IV infusion. An IV infusion is a slow injection of the trial medication directly into your vein. It will take between 1-1/2 to 3 hours to give you the trial medication.

Your first dose of trial medication will be given to you either at the trial centre or at the hospital. The trial doctor will discuss this with you further.

FOLLOW-UP PERIOD

After receiving the trial medication at Visit 2, you will be followed-up for about 12 to 28 weeks, which includes the End of Study (EOS) Visit (see the EOS section below). The length of the follow-up period will depend on how well you respond to the trial medication.

After you receive your first dose of trial medication, you will return to the trial centre every day during the first week (Day 2 to Day 8). Depending on your response to the trial medication, the trial doctor will let you know if you need to return to the trial centre for visit Days 4 through 7 during the first week.

If your GPP worsens within the first week of receiving the trial medication, the trial doctor will treat you with Standard of Care (SoC) medication(s), which are medications usually given for treating GPP. The trial doctor will tell you the SoC medication(s) you will receive.

At Day 8 (Visit 9), if your GPP did not get better after receiving the initial dose of trial medication, and you did not receive a SoC medication(s) within the first week of receiving the initial dose of trial medication, you may receive a 900 mg dose of BI 655130 by IV infusion. The trial doctor will tell you if you are eligible to receive BI 655130 at this visit.

After Day 8 (Visit 9) and through Week 12 (Visit 14), if you have a second GPP flare-up after achieving a response to one of the following:

- the initial trial medication dose on Day 1 **OR**
- a dose of BI 655130 on Day 8 (if received) **OR**

- the SoC medication(s),

you will be able to receive a 900 mg dose of BI 655130 by IV infusion. This dose is called a rescue treatment.

If you have more than one flare-up after Visit 9, the trial doctor will treat additional flare-ups with SoC medication(s).

If you decide to stop taking the trial medication early, you will be asked to continue with all of your remaining scheduled trial visits as originally planned. If you are not willing to continue with all your remaining scheduled trial visits, you will be asked to return to the trial centre for Visits 9 and 12 (if not already completed), and the End of Study Visit. If you cannot return to the trial centre, the trial staff will contact you when your scheduled visits would have occurred to ask you how you are.

UNSCHEDULED VISITS

During the Follow-up Period you may be asked to come to the trial centre for additional unscheduled visits if you have a GPP flare-up and require a rescue dose of BI 655130 or SoC medication(s), or if the trial doctor thinks the visit(s) are necessary for your safety, or if procedures were missed from a previous visit or need to be repeated.

If you receive BI 655130 at either a scheduled or unscheduled visit after Day 8 (Visit 9), you will complete the Visit 9 procedures (except for certain blood tests) as listed in Appendix A.

END OF STUDY (EOS) VISIT

You will have an "EOS" visit (Visit 14 or 15 or 16) after completing the trial or if you stop the trial early.

Your EOS visit will depend on how you respond to the trial medication and when you have your last dose of trial medication or dose of BI 655130. The trial doctor or trial staff will let you know when your EOS visit will occur.

If you complete all of your scheduled visits and have your EOS visit at either Visit 14 or Visit 15, you may be given the option to participate in an extension of this research trial using the same investigational drug, BI 655130, without the use of a placebo. If you decide to participate in the extension research trial, you will sign another Information and Consent Form.

If you do not join the extension research trial or if you decide to stop the trial early, your EOS visit will be about 16 weeks after you stop the trial medication or dose of BI 655130.

Your trial doctor will discuss your future care, any medications you require, and you will be offered standard medical care.

After your EOS Visit you will have completed this trial.

For your safety, any side effect(s) that continue after your last trial visit will be followed by the trial doctor until the side effect(s) resolve or are stable.

YOUR RESPONSIBILITIES

- You must tell your trial doctor if you previously have participated in this trial, have been in another research trial in the past 30 days or are currently in another research trial. While participating in this trial, you should not take part in another research trial, or in this trial at another site. This is to protect you from possible injury arising from such things as extra drawing of blood samples, potential medication interactions, or other hazards.
- You will receive a Trial Identification Card. It is important that you carry this card with you at all times. If you are treated by another doctor (for example, in an emergency), it is important that you tell them of your participation in this trial by showing this card.
- If you are treated by another doctor, it is important that you tell the trial staff about your treatment and what happened.
- You must follow the trial instructions provided by the trial staff, come to all scheduled trial visits, and be reasonably available for any scheduled telephone visits.
- You must call/tell the trial doctor if you experience any side effects or if you feel unwell, even if you do not know if it has anything to do with this trial.
- You must tell the trial doctor about all prescription and non-prescription drugs, herbal preparations that you are taking or planning to take.
- You will be asked to complete questionnaires (refer to Appendix A). Please complete each of them by yourself, without the help of someone else.

POTENTIAL BENEFITS

You may not personally benefit from participating in this trial, but you may contribute new information that may benefit other patients and provide the medical and scientific community with information about treatment for GPP.

However, receiving BI 655130 may help to reduce GPP symptoms and how long a GPP flare-up lasts. Therefore, you may benefit as a result of your participation in this trial. There is, however, no guarantee for that.

RISKS AND/OR DISCOMFORTS

This section is provided by the TMM for the trial drug. Any changes must be approved by the author of this section.

There are risks to taking part in any research trial. If you receive a placebo, you will not receive an active treatment for your condition. Your condition might not improve or it could get worse during the course of this trial.

If you receive active trial medication, then side effects may occur. Some of those side effects can be treated. Some side effects may go away when you stop taking the trial medication. Some side

effects can be mild, but others may continue longer or become permanent. Some may be life-threatening or fatal.

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or breathing difficulties. If you think you are having an allergic reaction, call the trial doctor right away. If you are having trouble breathing, call <insert regional emergency telephone number>.

Taking BI 655130 may cause you to have one or more of the side effects (or adverse events) listed below: <List all known adverse events of each drug/product here or by using Appendix C>

If applicable, please consult with your local Legal representative to clarify whether it is acceptable to have the side effects listed in an appendix.

If using Appendix C, use the following wording:
In Appendix C of this document you will find a more detailed description of the adverse events of the trial medication including related risks. The trial doctor or the trial staff will go through this Appendix with you.

The trial doctor or the trial staff will go through the description of the known side effects with you. They are willing to discuss any questions you might have about the severity and frequency of risks and other potential discomforts. In addition to the side effects listed, there is always the risk of developing side effects which are not known at this time.

You will be monitored carefully to check for these risks. Your trial participation may be stopped if any signs of drug toxicity or other damage occurs.

You need to tell your trial doctor or a member of the trial team immediately if you experience any side effects.

The trial doctor will discuss with you the risks and benefits of the Standard of Care medication(s) which you may take during your participation in this trial.

ALTERNATIVE TREATMENTS

Instead of participating in this trial, you have other options which may include the following:

- Receive recommended treatment including <specify the standard treatment per your country/OPU>.
- Take part in another research trial.
- Receive no therapy specific to your GPP.
- Receive comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems, fever, headache, and other problems caused by your GPP. It does not treat the GPP directly, but instead tries to treat the symptoms.

Your trial doctor will discuss these options and the important potential risks and benefits with you before you decide whether you will take part in this trial.

NEW INFORMATION ABOUT THE TRIAL

During the trial, you will be notified of changes to trial procedures, newly discovered side effects or significant findings which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this trial.

INFORMATION ON BIRTH CONTROL

Based on the information provided in the Investigator's Brochure (IB) and the Clinical Trial Protocol (CTP), this section must describe the potential risks for a fetus or embryo in case pregnancy occurs during trial participation. For further guidance please refer to Contraception Guideline). This document includes a list of acceptable contraception methods meeting the requirements outlined in ICH M3 (R2).

For Female Trial Subjects

As with any investigational drug, the effect of BI 655130 on the unborn child is unknown. If you decide to take part in this trial and you are able to become pregnant, you must be willing to have a pregnancy test done at the Screening Visit, and regularly at trial visits and at the end of the trial. Further, you must avoid becoming pregnant while you take part in this trial. You cannot participate in this trial if you are pregnant, breastfeeding or plan to become pregnant during your trial participation. You must use a highly effective method of birth control and you should not breastfeed throughout this trial and for up to 16 weeks after receiving the last dose of BI 655130.

Your trial doctor will talk to you about the best method of birth control for you.

Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation
- Progestogen-only hormonal birth control associated with inhibition of ovulation
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion (blocking of the fallopian tubes)
- Vasectomy of sexual partner (proven effective by absence of sperm on the ejaculation).
- Complete sexual abstinence (not to have male-female vaginal sex)

If you are pregnant or think you could be pregnant, it is important for you to tell the trial doctor or trial staff immediately. If you become pregnant during the trial, you will discontinue trial medication and be asked to continue to participate in trial visits. Your health and your baby's health will be monitored throughout your pregnancy. Even if you are no longer in the trial, your trial doctor will contact you after your baby is born to find out about the baby's health.

WITHDRAWAL FROM TRIAL PARTICIPATION

You may choose not to take trial medication or to leave this trial completely at any time. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled. Leaving the trial will not affect your future medical care.

It is important that you tell the trial doctor if you are thinking about stopping or have decided to stop so your trial doctor can evaluate the risks of stopping.

Depending on the protocol, the following section may be adapted. Please ensure the trial site understands that the discussion with the subject and the outcome regarding follow up, vital status collection, discontinuation of trial medication, and withdrawal of consent is documented in the subject's medical records.

Listed below are three possible scenarios that could stop your trial participation. Your study doctor will discuss these scenarios with you.

- **You may stop trial medication, but agree to continue participation and/or continue to be contacted**

If you decide to stop taking the trial medication, you may still continue to participate in trial visits. It is recommended that you come in to the trial centre for all of the remaining trial visits, however if you are unable to come to the trial centre, you will be asked by the trial staff if they can contact you by phone/email/mail or someone you choose (such as your family doctor, a friend, or relative), to ask about your overall health status. This will happen when your scheduled visits would have occurred up to the End of Study Visit. Alternatively, you will be asked for your permission to collect this information from your medical records <or any public records or patient search organisation – if allowed by local regulations> until the end of the trial. This information is important for the scientific value of the trial to interpret the trial results correctly. You are free to refuse this regular contact. Your decision will not affect your future medical care.

- **You may stop trial medication and participation completely and withdraw your consent**

You have the right to withdraw your consent at any time. If you decide to stop trial medication and participation, then the final assessments such as a physical examination, vital signs, laboratory tests, ECG, and questionnaires should be completed as soon as possible. This is important for your safety and well-being. After the final assessments, no further information about you will be entered into the trial database.

All data that had already been collected up to the time of withdrawal of your consent, including data gathered at any of your final assessments, will still be used to ensure the correct completion and documentation of the trial and comply with applicable law.

- **Your trial doctor may decide that you must stop**

Your trial doctor might decide to stop your trial medication or trial participation early without your consent when, in the trial doctor's judgment, it is in your best health interest to do so. Some of the reasons why this might happen are listed below:

- Your condition worsens or does not improve and an alternative treatment is medically indicated.
- The trial treatment or procedures are found to be unsafe or ineffective.
- Your inability to take the medication / participate as instructed.
- Cancellation by the sponsor or regulatory authority.
- Or for other unforeseen reasons that make it necessary to stop your participation in the trial.

If you are removed from the trial, the trial doctor will explain to you why you were removed.

CONFIDENTIALITY / PRIVACY AND DATA SHARING

The wording in this section must preferably be reproduced word-by-word in the trial specific subject information. If any changes to that wording, which would limit our ability to publish or share results and data, are mandated by an Ethics Committee or IRB or are necessary otherwise, then the responsible function (CT Leader or CT Manager) must consult local line management, local legal and/or local data protection/privacy contact. If applicable, please consult with your local legal representative to clarify whether it is acceptable to have the confidentiality, privacy, and data sharing section listed in an appendix, e.g. Appendix D.

Use of Your Personally Identifiable Information

The part of your personal information that directly identifies you, such as your name and address, will remain at the trial site and can be accessed by the trial doctor and other people at the site who are assisting with the trial or your care. This information may also be checked at the trial site by the

- sponsor, or the sponsor's representatives (including monitors hired by the sponsor through a service provider),
- ethics review board/committee that reviewed the ethical aspects of this trial, and/or
- domestic or foreign regulatory agencies such as <insert applicable regulatory bodies here, e.g. the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA)> that approve medicines.

These persons check that the trial is carried out correctly at the trial site. They are bound by a duty of confidentiality.

Coding of Your Data

Your personally identifiable information and health information collected in this trial will be labelled with a unique code number. Coded data may also include data/information such as images (e.g. x-rays) or EEG (electroencephalograms). The code number will be used in place of your name and other information that directly and easily identifies you. Only the trial site will

have the link between your personal information and the coded data. This link will not be provided to the sponsor; only your coded data will be sent to the sponsor. The sponsor will take measures to protect the confidentiality and security of your coded data and your privacy in accordance with current law.

Use of Your Coded Data

The sponsor, its research partners and service providers (like clinical research organizations or laboratories) including companies belonging to sponsor's group, and regulatory authorities such as drug regulators, reimbursement agencies and ethics review boards may use your coded data for the following purposes:

- Analyse it to understand the trial, the trial results and the drug(s) (including side effects and efficacy) or the disease(s) studied, obtain approvals for drug(s) and reimbursements for the drug(s) in countries worldwide.
- Share it with domestic or foreign regulatory, reimbursement or other professional health care agencies worldwide such as <insert applicable regulatory bodies here, e.g. the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA)>, that regulate medicines to fulfil reporting obligations during the trial.
- Analyse it to improve the quality of this trial and other clinical trials.

To support the review of your data, your trial doctor may code and data/information from your medical records. This will be limited to specific information relating to this trial.
The coded data may be transferred within your country or to other countries for analysis. Where the data protection rules in other countries are not as strict as the rules in your country, the sponsor will adopt appropriate measures to provide an adequate level of protection according to EU law.

Additional Use of Your Coded Data

Your coded data from this clinical trial can be combined with data from other trials. The purpose is to learn more about your disease and other diseases, different responses to treatments and new treatment options to improve quality and efficiency in the drug development process. The additional use of your coded data will not be part of another Clinical Trial.

Incidental Findings

The sponsor will only search for results that are directly related to the actual clinical trial question. To do so researchers will obtain results by combining your data with data from a large number of other individuals. Nevertheless, other results which may be of medical importance for you and your family can occur incidentally for all testing techniques applied (so-called incidental findings).
In case of incidental findings that are considered medically actionable because they have clear and immediate medical significance to your health, the Sponsor will take all justifiable efforts to inform your study doctor. Your study doctor may then discuss the impact of these incidental findings with

you.
If you are not interested in receiving this information, please let your trial doctor know.

Sharing of your anonymized data

The sponsor is convinced that access to trial data advances clinical science and medical knowledge and is in the best interest of patients and public health, provided that patient privacy is protected. Therefore, the sponsor may share with credible researchers an anonymized set of your trial data, but only for specified and approved scientific research. Anonymization means that the sponsor will delete or modify any trial data that could identify you.

Storage of your coded data

All coded data, including yours, will be kept by the sponsor. Only your trial doctor will be able to link your unique code number to you.

This link will remain at the trial site for a maximum of 30 years and will then be destroyed by the trial doctor. After that it is not possible to link your unique code number directly back to you.

Rights under data protection laws

You have the right to review which personal data the trial site and sponsor store about you. You can also request that incorrect personal data is corrected or that processing is restricted.

In order to exercise your rights please contact the trial site [if applicable: and its data protection officer (ADD EMAIL)] who will align with the sponsor. You can also ask to receive the personal information you have provided for the trial in a standardized electronic format or to have them transmitted to another person of your choice. You can also contact your local data protection authority in case of questions or concerns about the handling of your personal data. In some cases, your rights can be limited under applicable laws, especially where they conflict with the conduct of the trial and mandatory archiving requirements. In this case you will be informed accordingly.

Clinical Trial Websites and Publication
The following statement must be included and must not be modified. Additional explanations and/or websites may be added.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

The following statement must be included in European studies and is optional for other countries: A description of this trial including a summary of the trial results will also be available on the European Union web-page www.clinicaltrialsregister.eu.

The results of the trial will be published on Boehringer Ingelheim's Trial Web site (http://trials.boehringer-ingelheim.com). The website may also include a summary understandable to a layperson. The results may also appear in other clinical trial/study registries in countries in which the trial is conducted. The results will not include information that can identify you.

The results of the study may also be published in a professional journal or presented at scientific meetings. Your identity will not be disclosed in those presentations.

USE OF SAMPLES FOR THIS TRIAL

The biological samples collected from you during the trial as described under the section "Trial Procedures" and Appendix A and B will be stored, processed, and used under your code number for the purposes of this trial for analyses as follows:

Routine Safety Samples
Blood and urine will be collected for routine safety and blood for pregnancy tests (for women of child bearing potential) and will be sent to a central laboratory for analysis. Leftover samples will be destroyed once the tests are completed. The urine pregnancy testing will be done at the trial centre. The sample will be destroyed at the trial centre once the results are known.

Pharmacokinetic (PK) and Anti-Drug Antibodies/Neutralizing Antibody (ADA/Nab) Samples
Blood will be taken for PK testing to see how your body uses the investigational drug and how fast or slow it moves through or out of your body, and for ADA/Nab testing to measure your immune response to the investigational drug (when the body detects and defends itself against substances that appear unknown and harmful).

After completion of the clinical trial, the samples for PK and ADA/Nab may be used for additional testing to see how the investigational drug reacts over time. These samples will be discarded after the testing is completed but not later than 5 years after the trial is over and the sponsor completes a report that contains the trial results.

Biomarker Samples (in blood)
Blood will be taken for biomarker testing as indicated below. Biomarkers are biological molecules found in blood, other body fluids, or on cells and tissues and are a sign of a normal or abnormal process, or of a condition or disease. Biomarker testing measures how the human body is functioning.

In this study, protein biomarkers will be measured in the blood that could possibly be associated with GPP, to see changes of these biomarkers before and after receiving the trial medication. Biomarkers could be proteins or ribonucleic acid (RNA) sequences (the order of each RNA molecule). Proteins play specific roles for various body functions.

In this study, biomarker testing will be done to:

- See if the biomarkers show how the investigational drug works in your body and how

your body responds to the drug.
- Look at the changes in protein or RNA levels of certain biomarkers to see how severe the disease may be.
- Genetic testing of DNA (deoxyribonucleic acid) will be done to assess certain genes known to have mutations (changes to the structure of a gene) that cause GPP. Genes are a part of your DNA which control things like the colour of your hair or eyes. Your genes affect how you respond to drugs.

Other non-genetic biomarker testing may be done. At this time, it is not known what testing will be done.

Biomarker samples will be stored at the sponsor facilities or by an external vendor (the company hired to store the samples) for backup and will be destroyed after this trial is over and the sponsor completes a report that contains the biomarker and/or the trial results, whichever comes later.

Infectious Disease Testing
Blood will be taken to see if you have infectious diseases, such as hepatitis B or hepatitis C (a disease that affects the liver) or HIV (a blood virus that may lead to AIDS) or tuberculosis (a disease that mainly affects the lungs).

Infectious disease samples will be destroyed once the tests are completed.

For Asian/Pacific region:
Infectious disease samples will be destroyed once the tests are completed with the exception of the HIV confirmation sample (if analysed i.e. in case HIV screen test result is positive). The sample will be stored at least 7 years and then be automatically destroyed.

The samples or parts of them may be transferred to the sponsor, its research partners and service providers (like clinical research organizations or laboratories) including companies belonging to the Boehringer Ingelheim Group of Companies.

SAMPLES FOR OPTIONAL RESEARCH

As an optional part of this trial, you are being asked to allow the collection and storage of blood samples for potential future scientific research.

As another optional part of this trial, you will be asked to have skin biopsies taken at selected trial visits.

You will be provided with separate consent forms with information so that you can decide whether or not you want to participate in these optional parts.

COMPENSATION / COSTS

Sample text provided below. Amend in accordance with local legal requirements or insurance.

This trial is funded by the sponsor. The sponsor will pay the trial doctor and/or institution for his/her expenses, time, and effort to conduct this trial. The trial doctor and the institution/Hospital have no other financial ties to Boehringer Ingelheim.

Sample text if using a CRO; amend as needed.
The sponsor has signed a contract with <insert applicable CRO> to conduct this trial. The sponsor will, on behalf of <CRO> pay the trial doctor and/or institution for his/her expenses, time, and effort to conduct this trial. The trial doctor and the institution/Hospital have no other financial ties to Boehringer Ingelheim.

There will be no additional costs to you for your participation in this trial. All trial procedures including lab work, tests, doctor visits, <include if applicable per your OPU budget: hospital stays to receive the trial medication,> and trial medication are provided to you free of charge by the sponsor, Boehringer Ingelheim, and will not be billed to you or your insurance carrier as long as you are participating in the trial. You will receive <enter amount and/or a description of a payment schedule> to cover out-of-pocket expenses such as meals and parking for visits that are required as part of the trial.

The sponsor will be the owner of the trial results. If commercial products or other valuable discoveries result from research using your samples and/or data, these products and discoveries may be owned, patented, licensed, or otherwise developed for commercial sale by the sponsor, other researchers, or companies. If this should occur, you will not receive any financial benefits or compensation or other proprietary interest from any commercial products or discoveries that may result from such research.

INJURY / INSURANCE

Please work with local legal to ensure that the below follows local regulations.
You will receive necessary medical treatment in the event that an injury or illness results because of your participation in this trial. If your insurance or other third-party coverage does not cover the cost of the necessary medical treatment or care, the sponsor will cover the cost if the injury or illness is due to the trial medication or procedures, and you have followed the trial doctor's instructions. Financial compensation for lost wages, disability or discomfort due to an injury is not generally available. You do not give up any legal rights by signing this form. You do not release the sponsor, institution, trial doctor or their agents from any liability for negligence by signing this form.

EMERGENCY CONTACT / ETHICS CONTACT

Suggested sample text provided below. You can adapt this section and add in any local regulations as needed.
If you have questions concerning side effects, the conduct of the trial, or for any other reason you may contact <*leave the following text intact for each site to customize in their site-specific ICF*> Dr. _____at _____ or the Trial Coordinator, _____, at _____ at ANY TIME. You have the right at any time, upon request, to be informed by the above trial doctor of your condition and the effects of the investigational drug on you.

In case of an emergency, please contact *<leave the following text intact for each site to customize in their site-specific IC>* Dr. _____ at tel. _____ OR go to the nearest hospital emergency department.

If you have any questions about your rights as a trial subject, please contact your family doctor, lawyer, or write to the committee that reviewed the ethical aspects of this trial at: <insert ethics committee name and contact here>

BOEHRINGER INGELHEIM GmbH

Information and Consent Form for Trial Subjects (template)

APPENDIX A: VISIT SCHEDULE

Boxes marked with an X show what will happen at each visit. Descriptions of these procedures are listed in Appendix B.

Trial Procedures	Screening	Treatment Visit	Follow-up Period													
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 or EOS[1]**	**15 or EOS[2]**	**16 EOS[3]**
Visit Week		**1**							**2**		**3**		**8**	**12**	**13-18**	**16-28**
Visit Day	-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**29**	**57**	**85**	**92-127**	**113-197**
Discuss this trial, demographics and medical history, including gene mutation	X															
Physical exam, vital signs, and temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X							X	X	X	X	X	X	X	X
Blood and urine tests for safety,	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood or urine for pregnancy testing for women of child bearing potential	X	X							X	X	X	X	X	X	X	X
Blood for infectious disease testing	X													X	X	X
Blood tests for PK and ADA/Nab		X			X				X	X	X	X	X	X	X	X
Blood tests for: genetic biomarker testing (DNA[4]); RNA and protein biomarkers		X	X	X					X	X				X	X	X
Blood tests for biomarker testing		X							X							
Receive trial medication (BI 655130 or placebo)		X														
Receive BI 655130 (if needed and if eligible)									X				X			
Photographs of skin lesions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete questionnaires		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Visit 14 will be done as your EOS visit only if you did not require a rescue dose with BI 655130 or if you required a rescue dose with BI 655130 before Week 7 and you are eligible to participate in the extension research trial.

[2] Visit 15 will be done as your EOS visit only if you required a rescue dose with BI 655130 after Week 7 and you are eligible to participate in the extension research trial.

[3] Visit 16 EOS will be done 16 weeks after your last dose of trial medication or BI 655130 if you are not eligible to participate in the extension research trial.

[4] DNA testing will only be done at Visit 2.

APPENDIX B: DESCRIPTION OF TRIAL PROCEDURES AND RISKS
<CUSTOMISE THIS LIST AS NEEDED>

Ensure the flowchart in the protocol matches the procedures as described in the CTP text and that all research related procedures are included in the Appendix. The definitions below are suggested descriptions and risks and can be edited as needed. Additional procedural and associated risk definitions may need to be added. It may not be feasible to describe every possible risk; however, subjects must be informed of all risks to consider which may influence their decision to participate.

The trial doctor or the trial staff will go through the description of the trial procedures and related risks with you. Please ask any questions you might have. In addition to the risks listed, there is always the chance of developing risks which are not known at this time.

Procedure	Description	Risks
Blood Tests and Blood Drawing	Approximately 600 mLs (40 tablespoons) of blood samples for the whole trial will be drawn to test your blood for: • Safety and pregnancy • Infectious diseases • PK and ADA/Nab • Biomarkers • Genetic biomarkers At each visit approximately 15-75 mLs (1-5 tablespoons) of your blood will be taken from a vein in your arm. If at any time during this trial your blood tests show there may be a problem with your liver, you will be asked to return for additional tests to see why. Additional blood tests to check your liver function and hepatitis will be done.	As with all blood sampling, there is a risk of mild pain, local irritation, bleeding or bruising (a black and blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.
Blood pressure test	A blood pressure test measures the pressure in your arteries as your heart pumps.	The squeezing of an inflated blood pressure cuff on your arm may be uncomfortable. It usually takes only a few seconds.
ECG (electrocardiogram)	A painless test which measures the electrical activity of your heart.	There may be some skin irritation from the ECG electrode pads or pain when removing these pads from your chest.

Procedure	Description	Risks
Intravenous (IV) Infusion	The investigational drug, BI 655130, or placebo will be given to you by an IV infusion, which is a slow injection of the trial medication directly into your vein using an IV catheter. It will take between 1-1/2 to 3 hours to receive the IV infusion. You will be monitored during the IV infusion and for about 2 hours after receiving BI 655130 or placebo. If you have a reaction to the IV infusion, you may be given medications to help reduce a reaction before you receive another IV infusion.	You may feel mild pain, local irritation, bleeding or bruising (a black and blue mark) at the puncture site (where the needle is inserted). There is also a small risk of light-headedness and/or fainting. In rare cases, the site where the needle is inserted can become infected or nerves may be damaged, and cause long-lasting abnormal sensations, damaged sensation of touch and lasting pain. During an IV infusion, tissue damage can occur if the infusion is not given directly into the vein. Your skin near the vein could become warm, swell, hurt, or get red. A blood clot or an air bubble could form, which could block a blood vessel in another part of your body. There could be an increase or decrease in electrolyte levels (the amount of certain salts and other chemicals in your blood), causing health problems. Some of these side effects could be very serious. Over time, getting a lot of injections or infusions can cause a vein to become hard or scar, which can make it difficult to put a needle into the vein to give you a shot or to take blood.
Photographs	Photographs will be taken of the affected areas of your skin (such as, the front and back trunk, legs and arms). You will not be personally recognized in the photos taken.	Please refer to the "Confidentiality" section of this consent form for information on how your personal information is managed.

Procedure	Description	Risks
	Photographs may be used in a presentation or publication about this trial. The use of the photograph may include news releases, professional conferences, websites and exhibits related to this research trial.	
Physical examination	A routine manual examination your trial doctor performs to check your overall health. The trial doctor will assess your symptoms of GPP.	This examination generally produces little pain or discomfort.
Pregnancy test	A pregnancy test measures a hormone in the body called human chorionic gonadotropin (HCG). This hormone is present in your body when you are pregnant. A pregnancy test is done using your blood and/or your urine. You cannot participate in a clinical trial if you are pregnant or planning to become pregnant.	**Pregnancy tests using blood:** As with all blood sampling, there is a risk of mild pain, local irritation, bleeding or bruising (a black and blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain. **Pregnancy tests using urine**: Because this procedure involves normal urination, there should not be any discomfort and no known risks.

Procedure	Description	Risks
Questionnaires	You will complete the following questionnaires to assess your GPP symptoms: **FACIT-fatigue (Functional Assessment of Chronic Illness Therapy - Fatigue scale):** to see how tired you are. **PSS (Psoriasis Symptom Scale):** to see how bad your GPP symptoms have been. **Pain VAS (Visual Analog Scale):** a measure of how much pain you have. **DLQI (Dermatology Life Quality Index):** to see how your skin problem has affected your life. DLQI will not be completed on Days 2-7. **EQ-5D-5L (EuroQol-5 Dimensions-5 Levels):** a measure of your current health status. It will take about 30 minutes to complete all of the questionnaires. It is important that you complete the questionnaires yourself and not ask others to do it for you. If needed, the trial staff can read the instructions, questions, and response options to you. You can then tell the trial staff member your answer.	You might find the questionnaires are long, or upsetting, or tiring. You might not like some of the questions or feel uncomfortable answering them. You do not have to answer any questions that make your feel uncomfortable.

Procedure	Description	Risks
Urine test (urinalysis)	Urine tests are used to look for the presence of red blood cells (high levels of protein) which may indicate a kidney problem and excreted minerals that can cause kidney stones. A sample of your urine is also likely to be checked for bacteria that cause infection.	Because this procedure involves normal urination, there should not be any discomfort and no known risks.
Vital signs: Temperature, heart rate, breathing rate, and blood pressure	The act of taking vital signs is the recording of body temperature, pulse rate (or heart rate), blood pressure, and respiratory rate, but may also include other measurements. Before receiving the trial medication your temperature will be taken. If you have a fever, the trial doctor may decide to give you medication to treat the fever.	These are routine procedures with little risk. Please also see definition for "blood pressure test" above.

APPENDIX C: KNOWN SIDE EFFECTS (ADVERSE EVENTS) OF THE INVESTIGATIONAL DRUG(S)

Taking BI 655130 may cause you to have one or more of the side effects (or adverse events) listed in the table below. The trial doctor or the trial staff will go through the description of the side effects with you. Please ask any questions you might have. In addition to the side effects listed, there is always the risk of developing side effects which are not known at this time.

As of September 2018, BI 655130 has been given to 212 subjects in ongoing and clinically completed trials. BI 655130 was well tolerated. Most reported adverse events were of mild or moderate intensity, but there have also been a small number of patients experiencing severe or serious adverse events in clinical trials. It is unknown whether these adverse events were caused by BI 655130. Overall adverse events observed in subjects who received BI 655130 were comparable to adverse events observed in those who received placebo and no dose-limiting adverse effects were observed.

If you receive the investigational drug, then adverse events may occur which may or may not be caused by BI 655130. Some of those adverse events can be treated. Some side effects may go away when you stop taking the trial medication. Some adverse events can be mild; but others may by more severe, continue for longer or become permanent. Some may be life-threatening or fatal.

All drugs can potentially cause an allergic reaction. Allergic reactions may vary from mild (rash, hives, itching) to severe (which may include difficulty breathing, swelling of the face or throat, low blood pressure, or passing out). A severe allergic reaction requires immediate medical treatment and could result in permanent disability or death. It is important to tell your trial doctor about any past allergic reactions that you may have had to other drugs including antibody drugs (which are usually given into a vein or injection under the skin).

Giving trial medication into your vein may result in an infusion reaction with symptoms such as fever, flushing of the skin, itching, rash or a decrease in blood pressure. If you are receiving trial medication into your vein, your trial doctor will monitor for signs of an adverse reaction while you are getting the drug into your vein.

Infusion reactions typically resolve after stopping or slowing down the infusion, sometimes additional medication is required. If you think you are having an allergic reaction, call the trial doctor right away. If you are having trouble breathing, call <insert regional emergency telephone number>.

Name of Drug	Known Adverse Events or Side Effects
BI 655130	Currently there are no identified side effects of BI 655130. So far, BI 655130 has been tested in healthy volunteers for up to four weeks of dosing and in one trial in patients with generalized pustular psoriasis (GPP) and palmoplantar pustulosis (PPP). BI 655130 was well tolerated and adverse events were mostly mild or rarely moderate. In the four-week-trial in healthy volunteers, headache appeared to be reported more frequently in subjects treated with 20 mg/kg BI 655130 than in the other treatment groups. Two subjects experienced dyspnoea (shortness of breath) only in the 20 mg/kg group. Additionally, diarrhea, nausea, and nasopharyngitis (inflammation of the nose and throat) appeared to occur more often in subjects who received BI 655130 than in subjects who received placebo. There were no severe or serious adverse events. In the trial investigating the effects of BI 655130 in 7 patients with generalized pustular psoriasis, adverse events reported most frequently were arthralgia (joint pain) (3 patients, 42.9%) and eosinophilia (high levels of a certain type of white blood cell), chills, peripheral oedema (swelling caused by too much fluid in the body tissues), pyrexia (fever), upper respiratory tract infection, and eczema (a condition that causes the skin to become inflamed, itchy, red, cracked, and rough) each reported in 2 patients (28.6%). It is not known whether any of these adverse events were caused by BI 655130. There were no severe or serious adverse events. In the trial investigating the effects of BI 655130 in 59 patients with palmoplantar pustulosis, adverse events reported most frequently were nasopharyngitis (inflammation of the nose and throat) and headache. These adverse events occurred with a comparable frequency in patients treated with BI 655130 and placebo. It is unknown, whether BI 655130 caused any of these adverse events. Based on the preceding trials in healthy volunteers and patients with GPP and PPP, no specific drug-related risks are anticipated. The infusion of any protein can result in local or general allergic reactions. These reactions may also occur by administration of BI 655130. Moreover, there is the risk of local infusion site reactions (swelling, warmth, redness and pain at the infusion site). This usually resolves without any treatment, but can be uncomfortable for a few hours or days.

Name of Drug	Known Adverse Events or Side Effects
BI 655130 – cont'd	Infusion reactions have been reported occasionally in the clinical trials using BI 655130; the event was reported in patients treated with placebo and patients treated with BI 655130. As an inhibitor of the immune mediator IL36R (gene), BI 655130 affects a target of the immune (body defense) system which could decrease the body's defense ability against certain types of infection or tumor diseases. However, repeated dose studies in animals at very high doses and also first data from studies in humans do not suggest that inhibition or absence of IL36R would increase the risk for infectious or tumor diseases.

DECLARATION OF INFORMED CONSENT

This page may be revised as appropriate.

Remember: If the consent and the subject information are two separate documents, the consent form must refer to the version and date of the Subject Information form.

TRIAL SUBJECT No.: _____

My signature on this consent form means that:

- I understand that I am being asked to participate in a research trial to test an investigational drug, BI 655130, in patients with a flare-up of Generalized Pustular Psoriasis.
- I have had this trial explained to me by _____.
- I have read, or have had it read to me, each page of this document including its appendices (Appendix A: Visit Schedule, Appendix B: Description of Trial Procedures and Risks, and Appendix C: Known Side Effects (Adverse Events) of the Investigational Drug) Appendix D; Confidentiality / Privacy and Data Sharing (according to local regulations) and the Declaration of Informed Consent and understood all these documents.
- I have had all of my questions answered fully and to my satisfaction.
- I was given sufficient time to think in peace and quiet and decide whether to participate.
- I have been told that my participation is voluntary and I can withdraw at any time without giving any reasons.
- I voluntarily consent to participate in this trial.
- I will be given a signed copy of this consent document for my records.

Name of Trial Subject (*please print*)	**Consent Signature of Trial Subject**	**Date**

STATEMENT OF INVESTIGATOR / TRIAL DOCTOR / STUDY COORDINATOR:

I certify that I have explained to the above individual(s) the nature and purpose of the trial and the possible benefit and risks associated with participation. I have answered any questions that have been raised and the potential trial subject has received a copy of this signed consent document.

I acknowledge my responsibility for the care and well-being of the above trial subject, to respect the rights and wishes of the subject, and to conduct the trial according to applicable Good Clinical Practice guidelines and regulations.

Name of Health Care Professional (*please print*)	**Signature of Health Care Professional**	**Date**

Study: Effisayil™ 1
IIRB/IECs approvals
Last Updated: 07 Sept 2020

Country	Institutional Review Boards/Medical Ethical Committees
United States	Alpha IRB Suite C #497 1001 Avenida Pico San Clemente California 92673 United States
	Western Institutional Review Board Suite 120 1019 39th Avenue Puyallup Washington 98374 United States
	University of Miami Institutional Review Board Suite 1200A 1400 NW 10th Avenue Miami Florida 33136 United States
	University of Missouri - Columbia Health Services IRB 482 McReynolds Hall Columbia Missouri 65212 United States
	Icahn School of Medicine at Mount Sinai Program for the Protection of Human Subjects Box 1081 One Gustave L. Levy Place New York New York 10029 United States
China	2nd Affiliated Hosp Zhejiang University College of Medical The Second Affiliated Hospital of Zhejing University School of Medicine No. 88, Jiefang road Hangzhou Zhejiang Province 310009 China
	Shanghai Skin Disease Hospital No 1278, Baode Road, Jingan District,Shanghai,200000,China shanghai Shanghai Municipality 200000 China
	Shanghai Huashan Hospital No. 12, Urumqi Road, Shanghai. 200040 Shanghai Shanghai Municipality 200040 China
	Tianjin Medical University General Hospital No.154, Anshan Road, Heping District, Tianjin Tianjin Migration Data 30052 China
	The First Hospital of China Medical University 155 Nanjing Street, Heping District Shenyang Liaoning Province 110001 China
	First Affiliated Hospital of Kunming Medical University Neurology Department No.295 Xichang Road,Kunming Kunming Yunnan Province 650032 China
	Peking Union Medical College Hospital No.41 Damucang

Study: Effisayil™ 1
IIRB/IECs approvals
Last Updated: 07 Sept 2020

	Hutong, Xicheng District/ No. 1 Shuaifuyuan, Dongcheng District Beijing Beijing Municipality 100032 China
	2nd Affiliated Hosp Zhejiang University College of Medical The Second Affiliated Hospital of Zhejing University School of Medicine No. 88, Jiefang road Hangzhou Zhejiang Province 310009 China
France	CCP Sud-Méditerranée IV Hôpital Saint-Eloi Montpellier 34295 France
Germany	Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen Robert-Koch-Straße 9-11 Essen 45147 Germany
Japan	The IRB of Nagoya City University Hospital 1 Kawasumi, Mizuho-cho, Mizuho-ku Aichi, Nagoya 467-8602 Japan
	The IRB of Fukuoka University Hospital 7-45-1 Nanakuma, Jonan-ku Fukuoka, Fukuoka 814-0180 Japan
	The IRB of Asahikawa Medical University Hospital 1-1-1, Higashi2jo, Midorigaoka Hokkaido, Aasahikawa 078-8510 Japan
	The IRB of Tokyo Medical University Ibaraki Medical Center 3-20-1, Chuo, Ami-machi Ibaraki, Inashiki-gun 300-0395 Japan
	The IRB of Mie University Hospital 2-174, Edobashi Mie, Tsu 514-8507 Japan
	The Conjoint IRB of All Tohoku Clinical Trial Review and Audit Organization 1-6-10, Kamisugi, Aoba-ku Miyagi, Sendai 980-0011 Japan
	The IRB of Shinshu University Hospital 3-1-1 Asahi Nagano, Matsumoto 390-8621 Japan
	The IRB of Kindai University Hospital The IRB of Kindai University Hospital 377-2 Onohigashi
	The IRB of Tokyo Medical University Hachioji Medical

Study: Effisayil™ 1
IIRB/IECs approvals
Last Updated: 07 Sept 2020

	Center 1163, Tatemachi Tokyo, Hachioji 193-0998 Japan
	The Conjoint IRB of Nihon University Hospitals 30-1, Oyaguchi kami-cho Tokyo, Itabashi-ku 173-8610 Japan
	The IRB of Tokyo Medical University Hospital 6-7-1 Nishishinjuku Tokyo, Shinjuku-ku 160-0023 Japan
Korea	Seoul National University Hospital Institutional Review Board 101 Daehak-ro Jongno-gu Seoul 03080 Korea, Republic of
	Institutional Review Board Severance Hospital, Yonsei University Health System, Institutional Review Board 50-1 Yonsei-ro, Seodaemun-gu Seoul 03722 Korea, Republic of
Malaysia	Medical Research & Ethics Committee d/a Kompleks Institut Kesihatan Negara Blok A, No 1, Jalan Setia Murni U13/52 Seksyen U 13, Bandar Setia Alam 40170 Shah Alam, Selangor Shah Alam 40170 Malaysia
Singapore	NHG Domain Specific Review Board 3 Fusionopolis Link #03-08 Nexus@One-North Singapore 138543 Singapore 138543 Singapore
Switzerland	Commission cantonale (VD) d'ethique de la recherche sur l'entre humain Chairman: Prof. Dr. Med. Patrik Francioli Avenue de Chailly 23 Lausanne 1012 Switzerland
Taiwan	CHANG GUNG MEDICAL FOUNDATION 199 TUNG HWA NORTH ROAD Taipei Migration Data 10507 Taiwan
Thailand	Ethics committee/IRB of the Institute of Dermatology Institute of Dermatology, 420/7 Rajavithi Road Bangkok 10400 Bangkok 10400 Thailand
	Central Research Ethics Committee Building 2., 5th Fl, The National Research Council of Thailand Building, 196 Ladyao, Catuchak, Bangkok 10900 Thailand
	Office of The Committee for Research

Study: Effisayil™ 1
IIRB/IECs approvals
Last Updated: 07 Sept 2020

	Faculty of Medicine Ramathibodi Hospital Mahidol University 270 Rama 6 Rd. Phayatai Ratchathewi Bangkok 10400 Bangkok 10400 Thailand
Tunisia	Personal protection Committee -South Ethics Committee Higher Institute of Nursing science of Sfax-Avenue Majida BOULILA-Sfax-Tunisia

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Yes, page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Yes, page 3
	2b	All items from the World Health Organization Trial Registration Data Set	Yes, available at clinicaltrial.gov NCT03782792
Protocol version	3	Date and version identifier	Yes, page 13
Funding	4	Sources and types of financial, material, and other support	Yes, page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Yes, page 14
	5b	Name and contact information for the trial sponsor	Yes, page 14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Yes, pages 1, 15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Yes, pages 8, 13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Yes, pages 5, 6, 7

	6b	Explanation for choice of comparators	Yes, page 9
Objectives	7	Specific objectives or hypotheses	Yes, pages 8, 13
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Yes, pages 8–11
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Yes, page 9 and reported in clinicaltrials.gov
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Yes, pages 8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Yes, pages 9, 10, and Figure 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Yes, page 10, and Figure 1
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Yes, pages 4, 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Yes, page 9, and supplementary files
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Yes, pages 11, 12, Table 1 and supplementary Table 2

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Yes, pages 9, 10, and Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Yes, page 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Yes, page 12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Yes, page 9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Yes, page 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Yes, page 9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Yes, pages 9, 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Yes, page 9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Yes, pages 11–14, Table 1 and supplementary Table 2

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Yes, pages 9, 10, and Figure 1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Yes, page 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Yes, page 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Yes, page 13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Yes, page 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Yes, page 12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Yes, page 13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Yes, pages 13, 16
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Yes, page 13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Yes, pages 13, 16, and reported in clinicaltrials.gov
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Yes, pages 12, 16, and supplementary files
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Yes, page 12 and supplementary files
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Yes, pages 16, 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Yes, page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Yes, pages 16, 17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Yes, pages 13, 15, 16, and supplementary files
	31b	Authorship eligibility guidelines and any intended use of professional writers	Yes, page 15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Yes, pages 15, 16

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes, page 16 and supplementary files
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Yes, pages 10, 12

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Study protocol 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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Title: Study protocol 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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ABSTRACT

Introduction

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening disease characterised by recurrent flares of widespread neutrophilic aseptic skin pustular eruption. Despite the availability of approved biologics for GPP in Japan, Taiwan and Thailand, associated evidence is largely based on uncontrolled studies in which acute flares were not directly assessed. Therefore, there is a high unmet need to investigate new rapid-acting effective treatments that resolve symptoms associated with acute GPP flares. A prior Phase I proof-of-concept study showed rapid improvements in skin and pustule clearance with a single intravenous dose of spesolimab, a novel anti-IL-36 receptor antibody, in patients presenting with an acute GPP flare. Here, we present the design and rationale of Effisayil™ 1, a global, Phase II, placebo-controlled study to evaluate the efficacy, safety and tolerability of spesolimab in patients presenting with an acute GPP flare.

Methods and analysis

At least 51 patients with an acute GPP flare will be randomised 2:1 to receive a single 900 mg intravenous dose of spesolimab or placebo and followed for up to 28 weeks. The primary endpoint is a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 (pustule clearance) at Week 1. The key secondary endpoint is a GPPGA score of 0 or 1 (clear or almost clear) at Week 1. Safety will be assessed over the study duration by the occurrence of treatment-emergent adverse events. Blood and skin biopsies will be collected to assess biomarkers. Superiority of spesolimab over placebo in the proportion of patients achieving the primary and key secondary endpoints will be evaluated.

Ethics and dissemination

The study complies with the ethical principles of the Declaration of Helsinki, the International Council for Harmonisation's Good Clinical Practice and local regulations. Ethics committee approvals have been obtained for each centre from all participating countries and are listed in online **supplementary file 1**. Primary results will be published in a peer-reviewed journal.

Trial registration number

NCT03782792; Pre-results.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- To our knowledge, this is the first randomised, double-blind, placebo-controlled study in patients presenting with an acute GPP flare
- This study will be the largest randomised, placebo-controlled trial conducted in this population to date
- This study will incorporate clinically relevant disease-specific measures to assess the efficacy of spesolimab, an IL-36 receptor antibody for which rapid improvements in skin and pustule clearance has been observed in a previous Phase I single-arm study in seven patients presenting with acute GPP
- This study will provide robust evidence on the efficacy of spesolimab in patients with acute GPP flares and will allow the natural course of disease to be characterised
- A major challenge for the study is the recruitment challenges common to rare diseases, which will be minimised by the inclusion of a high number of centres and a more favourable chance of receiving active treatment with a 2:1 allocation ratio

KEYWORDS

Psoriasis < DERMATOLOGY

Dermatopathology < DERMATOLOGY

Clinical trials < THERAPEUTICS

INTRODUCTION

Generalized pustular psoriasis (GPP) is a rare, potentially life-threatening autoinflammatory neutrophilic skin disease characterised by episodes of widespread eruption of aseptic, macroscopically visible pustules, which can occur with or without plaque psoriasis, and may be accompanied by systemic inflammation.[1, 2] GPP is usually associated with one or several systemic symptoms such as fever, malaise and fatigue, and extracutaneous manifestations such as arthritis, uveitis, acute respiratory distress syndrome, cardiovascular shock and neutrophilic cholangitis.[3, 4] Common laboratory abnormalities include elevated C-reactive protein, leucocytosis, neutrophilia and liver function abnormalities.[3, 5] Acute GPP flares are associated with significant morbidity, and without appropriate treatment, mortality.[4] GPP is highly heterogeneous, with some patients experiencing frequent flares, i.e. several episodes per year, while for others, flares may occur less frequently, potentially years apart. Acute GPP flares may be triggered by infections, stress, medication, medication withdrawal (e.g. corticosteroids) and pregnancy, causing a dramatic reduction in quality of life.[4, 6-9] During the disease course, some patients with GPP may experience relapsing disease with recurrent flares, or persistent disease with intermittent flares. The clinical appearance of the disease can be phenotypically heterogeneous; skin may be clear in between episodic acute flares or patients may have persistent disease characterised by ill-defined erythematous plaques with or without pustules, which may be localised or widespread.[2, 4, 7, 8, 10-12]

Therapeutic intervention in GPP is a major challenge globally. The rarity of GPP means recruitment of sufficient patients to conduct large, randomised controlled trials to robustly investigate the efficacy and safety of therapeutics is a constant challenge. In addition, the intermittent remission and spontaneously self-limiting episodic pustular flares characteristic of GPP make it difficult to assess the efficacy of any intervention in this population.[9] Therefore, there is still a lack of robust evidence to guide treatment decisions for GPP. Available management guidelines for GPP are widely based on anti-plaque psoriasis strategies, limited case studies and single-arm, open-label studies and generally recommend cyclosporine, retinoids, infliximab and methotrexate as first-line therapies.[11, 13-15] Use of conventional systemic therapy may be associated with cumulative toxicities and limited efficacy, making them inappropriate for long-term disease control.[11, 13, 16] Although there are therapies specifically indicated for GPP approved in Japan, Taiwan and Thailand, there are currently no approved GPP-specific therapies for acute GPP flares globally. In Japan, tumour necrosis factor (TNF)-alpha inhibitors (adalimumab, infliximab and certolizumab pegol), interleukin-(IL-)17/IL-17 receptor (IL-17R) inhibitors

(secukinumab, brodalumab and ixekizumab) and IL-23 inhibitors (risankizumab and guselkumab) are approved for the treatment of patients with GPP who have had an inadequate response to conventional therapy.[13, 15-30] The approval of TNF inhibitors was based largely on case studies, whereas the approval of IL-17/IL-17R and IL-23 inhibitors was based on prospective, but small-scale, open-label, single-arm, Phase III studies, in which non-disease-specific endpoints, such as any improvement in the Clinical Global Impression index, were used to assess efficacy in Japanese patients presenting with mild-to-moderate GPP as per the Japanese Dermatological Association severity score. As systemic and skin manifestations of acute GPP flares may remit within 2 months in some patients,[4] 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. In Taiwan and Thailand, brodalumab was approved for the treatment of adults with pustular psoriasis who are candidates for systemic therapy, or adults with GPP who have had an inadequate response to conventional therapy, respectively, both based on a Japanese open-label study which included only 12 patients with GPP.[31-33]

Effective treatments with a very rapid onset of action for acute GPP flares that can allow early control of skin inflammation and the prevention of complications, including pustule formation and systemic manifestations, and are tolerable for both short- and long-term treatment strategies are needed.[4, 12]

In patients with GPP, overexpression of IL-36 inflammatory cytokines in skin lesions and loss-of-function mutations in the gene coding for the IL-36 receptor antagonist (*IL36RN*), as well as mutations in other genes connected with the IL-36 pathway (e.g. *CARD14*, *AP1S3, SERPINA3*), have been identified in genetic studies for some patients, suggesting that the IL-36 pathway may be central to GPP pathogenesis.[8, 34-36] Reports for the presence of *IL36RN* mutations in patients with GPP have ranged between 10% and 82%, and was lower in cases of GPP associated with plaque psoriasis than in those associated with GPP alone.[37, 38] Moreover, the knockout of the IL-36R in a murine model of deficiency of IL-36R antagonist (DITRA) led to complete resolution of skin inflammation,[39] making the blockade of IL-36R signalling a novel and appealing targeted therapeutic approach for patients with GPP.

Results of a Phase I, proof-of-concept study, in which the safety and efficacy of a single intravenous (IV) dose of spesolimab (BI 655130), an anti-IL-36R humanised monoclonal antibody, was assessed in seven patients with an acute GPP flare, provided the first evidence for targeting the IL-36 pathway.[40] In this study, spesolimab resulted in rapid (within 7 days) and sustained improvements (up to last assessment at Week 20) in clinical signs and symptoms irrespective of *IL36RN* mutation, suggesting that IL-36 plays a

pathogenic role among patients with GPP with different genetic backgrounds; this was accompanied by rapid downregulation of molecular signatures from the innate immune response, including neutrophilic pathways, and Th1/Th17-mediated inflammation. Four patients (57.1%) had mild-to-moderate drug-related adverse events through Week 20, but no severe or serious adverse events were reported.[40, 41] This study showed that spesolimab is a promising targeted therapy for acute GPP.

Effisayil™ 1 is a global, Phase II, multicentre, randomised, double-blind, placebo-controlled study of spesolimab in patients presenting with an acute GPP flare (ClinicalTrials.gov identifier: NCT03782792). GPP-specific clinical measures that assess key manifestations of the disease, the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) and GPPGA pustulation subscore, have been established to evaluate treatment efficacy in this study. The GPPGA is a physician-based assessment of the severity of pustules, erythema, and scaling of GPP lesions; each component is scored on a 5-point scale, ranging from 0 (clear) to 4 (severe), and the average is calculated (see online **supplementary file 2**). To differentiate against placebo with a feasible sample size, a stringent primary endpoint was chosen—achievement of a GPPGA pustulation subscore of 0 (complete pustular clearance) at Week 1. The successful early performance of these scores was demonstrated in the Phase I proof-of-concept study. A GPPGA score of 0 or 1 (clear or almost clear skin) was achieved in five of seven patients by Week 1 and in all patients by Week 4.[40]The acuteness, severity and potentially life-threating consequences of other autoinflammatory diseases, and the effectiveness shown for the blockade of the IL-1 family, such as the achievement of early inactive disease and sustained remission,[42, 43] further support the rationale for using an early efficacy endpoint in patients with GPP. The evaluation of non-pustulation components (erythema and scaling) are to be evaluated as part of the key secondary endpoint, the achievement of a total GPPGA score of 0 or 1.

Here, we describe the rationale, study design and methods of Effisayil™ 1; to our knowledge, this is the first randomised, double-blind, placebo-controlled study in this patient population presenting with an acute GPP flare. This novel and innovative study will inform on the efficacy and safety of targeting the IL-36 pathway in patients with GPP, and will provide insights into the natural progression of untreated GPP disease through the placebo arm, as well as historical clinical data with particular focus on previous occurrence of flares.

METHODS AND ANALYSIS

Study objectives

The primary objective of the Effisayil™ 1 study is to evaluate the efficacy, safety and tolerability of spesolimab versus placebo in patients presenting with an acute GPP flare. Further objectives include the assessment of pharmacokinetics, anti-drug antibodies and pharmacogenomics of spesolimab, and the exploration of biomarkers in acute GPP. In addition, the natural course of GPP in patients receiving placebo, the response of systemic symptoms of GPP flares to spesolimab and the effects of delaying treatment and further dosing with spesolimab in patients with insufficient initial response will also be explored.

Eligibility criteria

Patients aged 18–75 years with GPP, defined by the European Rare And Severe Psoriasis Expert Network (ERASPEN) at screening,[1] who satisfy the inclusion criteria are allowed to enrol into the study regardless of whether they are experiencing a flare at the time of screening, as patients in remission can be monitored for up to 6 months for their next acute flare. If required, screening and randomisation can occur on the same visit if patients meet the randomisation criteria (laboratory testing to be conducted by a local laboratory in such instances).

Patients will be enrolled if they have previous evidence of fever associated with flares before randomisation, and/or mild asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia above the upper limit of normal, and meet one of the following criteria, regardless of *IL36RN* mutation status:

- Have a GPPGA score of 0 or 1 and a known and documented history of GPP, or
- Are experiencing an acute GPP flare of moderate-to-severe intensity, or
- 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

Patients eligible for this trial must comply with all of the following inclusion and exclusion criteria at randomisation.

Inclusion criteria

Patients must be experiencing an acute GPP flare of moderate-to-severe intensity prior to randomisation, defined in the trial 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

Exclusion criteria

Patients will be excluded if they are presenting with:

- Synovitis-acne-pustulosis-hyperostosis-osteitis syndrome
- Erythrodermic plaque psoriasis without pustules or with pustules restricted to psoriatic plaques
- Drug-triggered acute generalized exanthematous pustulosis
- Immediate life-threatening flare of GPP or requiring intensive care treatment
- Dose escalation of their maintenance treatment with cyclosporin, retinoids or methotrexate within 2 weeks prior to randomisation
- Treatment with any drug, including biologics and systemic drugs considered likely to interfere with the safe conduct of the study or any prior exposure to an IL-36R inhibitor

Full inclusion and exclusion criteria and restricted concomitant medication can be found in the **supplementary file 2** and **supplementary Table 1**.

Randomisation and intervention

At least 51 patients presenting with an acute GPP flare are to be randomised to receive a single 900 mg IV dose of spesolimab or placebo in a 2:1 ratio on Day 1. Study drug is allocated using computerised Interactive Response Technology and patients and investigators involved will remain blinded until after database lock, unless emergency unblinding is required. This allocation ratio will enable more patients with a distressing and potentially life-threatening disease to be on treatment. This design is also likely to be more appealing to patients because evidence has shown that patients prefer to participate in clinical trials where there is a greater likelihood of receiving active treatment.[44] As required by some regulatory agencies, and based on the rapid onset of response demonstrated in the Phase I, proof-of-concept study and the lack of licensed active interventions, the use of a placebo-controlled parallel group was considered most appropriate to evaluate the efficacy and safety of spesolimab in patients with an acute GPP flare.[40]

Study locations and timings

The study will enrol patients from across 52 centres in 12 countries; it started in March 2019 and it is expected to complete in 2021. After randomisation, patients will be assessed daily until Day 3. Clinical visits on Days 4–7 are optional and need not be attended if a patient has already achieved complete pustular clearance (GPPGA pustulation subscore of 0). After patients have received a single dose of spesolimab or placebo at Day 1, patients will be followed for 12–28 weeks based on the subsequent treatment response (**Figure 1**). Patients who have not received escape treatment, and who have a GPPGA ≥2 and a pustular component of GPPGA ≥2 at Week 1, will qualify for treatment with an open-label single IV dose of 900 mg spesolimab on Day 8. All randomised patients will continue through the subsequent visits until the end of study. Patients who show no flare symptoms of moderate-to-severe intensity at the end of the study and meet clinical criteria for treatment response at Week 12, or at the subsequent visit for patients on rescue treatment with open-label spesolimab (**Figure 1**), will be eligible to enter a 5-year open-label extension study (ClinicalTrials.gov identifier: NCT03886246). Those not qualifying to enter the open-label extension study, will be followed for up to an additional 16 weeks. Clinical response, photographs of skin lesions, physical examination, examination of vital signs, fever assessment and safety laboratory tests are to be undertaken at each visit. Optional skin biopsies will be taken on Days 1 and 8 and Week 8. Whole blood for RNA sequencing and serum for soluble protein biomarkers are to be sampled prior to dosing, on Days 1–3 and Day 8, Week 2, 4 and 12 and at the end of study visit. Importantly, the *IL36RN* mutation status is to be determined for all patients.

Escape and rescue medication

If the severity and progression of the disease worsens within the first week after randomisation and requires immediate treatment, the investigator can treat the patient with escape medication, which is the investigator's choice of standard of care (SoC). However, if the disease condition is stable, it is recommended to wait until the primary endpoint visit (Day 8/Week 1) before prescribing a SoC escape medication because there will be an option to administer open-label spesolimab instead at this time. Due to the absence of an approved standard treatment for GPP and a commonly accepted treatment algorithm, patients in this trial are likely to have a heterogenous pre-treatment history, given that different SoC are available in different countries.

After Week 1, only one rescue dose with open-label spesolimab is permitted if a patient who previously achieved a clinical response (GPPGA 0 or 1) experiences recurrence of a GPP flare. Patients who do not achieve a clinical response, but have disease worsening subsequent to Week 1, can receive an escape treatment chosen by the investigator.

Study endpoints

The primary endpoint of the study is a GPPGA pustulation subscore of 0 at Week 1 and the key secondary endpoint is a GPPGA score of 0 or 1 at Week 1. Secondary endpoints at Week 4 included in the statistical strategy are a 75% improvement in the Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI 75), change from baseline in pain visual analogue scale (VAS) score, change from baseline in Psoriasis Symptom Scale (PSS) score and change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score.

The GPP-specific clinical efficacy endpoints (GPPGA, GPPASI) were created with minimal modification of the PGA and PASI (replacement of the induration component with pustulation), which are widely used and understood clinical instruments by dermatologists, and were created with the help of leading global experts in GPP and psoriasis vulgaris. The proposed primary endpoint of a GPPGA pustulation subscore of 0 (clear) at Week 1 and the key secondary endpoint of a GPPGA score of 0 or 1 at Week 1 are clinically meaningful as pustules are the primary lesion of the disease and reflect the desired rapid pustule clearance and overall improvement in GPP skin symptoms. Other secondary endpoints include the occurrence of treatment-emergent adverse events. At each visit, GPPGA and GPPASI will be measured to assess sustained efficacy (**Table 1**).

Table 1. Efficacy outcome measures

Outcome measure	Timepoint(s)
Primary outcome	
GPPGA pustulation subscore of 0	Week 1
Key secondary outcome	
GPPGA score of 0 or 1	Week 1
Secondary endpoints	
GPPASI 75	Week 4
Change from baseline in VAS score	Week 4
Change from baseline in PSS score	Week 4
Change from baseline in FACIT-Fatigue score	Week 4
GPPGA score of 0 or 1	Week 4
GPPGA pustulation subscore of 0	Week 4
GPPASI 50	Weeks 1 and 4
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

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
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

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

At each applicable visit, patients will be asked to complete patient-reported outcomes (PROs) questionnaires. The order of completion for PROs is recommended to be as follows: PSS, Dermatology Life Quality Index (DLQI), pain VAS, FACIT-Fatigue, and 5-level EuroQol-5 dimensions (EQ-5D-5L). Correlations between efficacy endpoints and PROs are to be assessed. The full list of study outcomes is reported in **Table 1** and **supplementary Table 2**.

The assessment of biomarkers will be exploratory. This will include biochemical and cellular biomarkers in skin and blood samples pre- and post-treatment with spesolimab. Changes in gene and protein expression in optional skin biopsies, in patients who give consent, are to be assessed. Gene expression analysis will include the genes involved in the mechanism of action of spesolimab or the pathology of the disease. Immunohistochemistry for neutrophils, macrophages, keratinocytes, T cells and dendritic cells markers are planned. Serum will be collected to assess changes in soluble protein levels of select IL-36 pathway disease-specific biomarkers. Cellular biomarkers on cells such as T cells and macrophages will be assessed by flow cytometry from whole blood samples. In addition, RNA sequencing from one blood sample of *IL36RN*, *CARD14* and *AP1S3* genes to assess known GPP-associated mutations will be performed in whole blood, and their potential influence on the severity of disease and efficacy of spesolimab will be evaluated.

Statistical analysis

The trial is designed to demonstrate the superiority of spesolimab with regard to the primary endpoint (achievement of pustule clearance at Week 1) and the key secondary endpoint (achievement of GPPGA 0 or 1 at Week 1) relative to placebo. With an expected response rate of 0.6 on spesolimab and 0.1 on placebo for the primary endpoint and key secondary endpoint, and a type I error of <0.025 (1-sided), for a total sample size of 51 patients, this trial will be able to detect an effect of spesolimab relative to placebo, for the primary endpoint and key secondary endpoint simultaneously, with an overall power of 93.9%. The statistical testing on each of the primary, key secondary and selected secondary endpoints will be performed in a hierarchical manner. The primary endpoint and key secondary endpoint will be analysed with the Suissa–Shuster Z-pooled test to compare the proportion of patients who achieve a response with spesolimab versus placebo at Week 1. For the primary estimand concept, any use of escape medication, open-label spesolimab use at Day 8, or rescue medication with spesolimab, prior to the observation of an endpoint will be considered as non-response. All safety data in this study will be descriptively summarised. For the analysis of biomarkers, a staged approach will be applied, in which the initial analysis will focus on selected time points and decision on further analysis will be made based on these results. Subgroup analysis of trial endpoints on baseline categories (e.g. *IL36RN* mutation status, GPPGA score) are planned. An external and independent data monitoring committee will perform an unblinded safety and efficacy assessment at specified intervals.

Ethics and dissemination

The study will be conducted in compliance with the protocol, the ethical principles of the Declaration of Helsinki, in accordance with the International Council for Harmonisation's Guideline for Good Clinical Practice (GCP), and the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, 27 March 1997) and applicable local regulations, and is approved by the ethics committees of participating institutions and countries. A list of all ethical approvals is provided in online **supplementary file 1**. Approved amendments of the protocol will be posted on clinicaltrials.gov (last protocol version 3, 26 June 2020). Eligible patients will be provided information and informed consent will be obtained (see online **supplementary file 3**).

On completion of the trial and after finalisation of the clinical trial report, the study results will be published in an international peer-reviewed medical journal and abstracts for congresses.

Data management

Patient privacy will be ensured by using patient identification code numbers. Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the confidentiality and privacy principle 12 of the World Health Organization GCP handbook.

Patient and public involvement

There was no involvement from patients and the public in the design of this study.

DISCUSSION

Randomised controlled trials are the gold standard for testing the efficacy and safety of new treatments. However, in rare severe diseases, recruitment difficulties and ethical concerns often hamper the possibility of involving a large population in a placebo-controlled randomised trial. Furthermore, although randomised controlled studies have been conducted in rare autoinflammatory syndromes such as cryopyrinopathies with canakinumab,[45] GPP raised an additional major challenge due to the spontaneously self-limiting course of acute flares in its intermittent pattern that can occur in some patients.[7] Therefore, an original study design integrating these parameters was necessary to accurately assess the efficacy of any drug intervention in this rare variant of the psoriatic disease spectrum. Effisayil™ 1 is the first randomised, double-blind, placebo-controlled study conducted in patients presenting with an acute GPP flare. Altogether, the high number of participating countries to minimise the risk of underrecruiting, along with the rapidity of the efficacy assessment and the lack of a suitable comparator, propitiates the ambitious design and conduct of this unique trial in a rare disease. This study aims to address a high unmet medical need and the lack of robust efficacy and safety data in patients with acute GPP flares, assess PROs, systemic symptoms and biomarkers and their correlation with clinical response and severity of disease, and provide insights on the natural disease course of an acute GPP flare. Results from this trial are planned to support the first registration of spesolimab in patients with GPP.

The study will evaluate the efficacy and safety of a single IV injection of spesolimab at Week 1 versus placebo, with an option of an open-label dose at Day 8 for both treatment arms if criteria is met. In addition, the study will allow the duration of efficacy to be assessed for up to 28 weeks, if not rolling over into the open-label extension study. All recurrent flares within 12 weeks after a single or two IV doses of spesolimab will be recorded. Pictures of skin lesions as well as lesion absence will be

systematically collected at each visit to provide further visual insights. For each case, naturally occurring resolution or worsening of symptoms in the placebo arm will provide insights on the natural disease course of GPP flare.

Despite the small population size of the study and the single 900 mg dose, Effisayil™ 1 is designed to be the largest study in patients with GPP, and the first randomised, placebo-controlled trial in this population to date. In addition to this study there are two further studies planned including a 5-year open-label extension study and the Effisayil™ 2 study (ClinicalTrials.gov identifier: NCT04399837), a multi-centre, randomised, parallel-group, double-blind, placebo-controlled, Phase IIb, dose-finding study to evaluate the efficacy and safety of subcutaneous spesolimab compared with placebo in the prevention of GPP flares in patients with a history of GPP. These studies will tackle different disease scenarios that address the limitations of the present study.

Overall, the results of the Effisayil™ 1 trial will provide robust evidence on early intervention with spesolimab for the treatment of acute GPP flares and will establish the relevance of using disease-specific endpoints that are clinically meaningful for patients and their physicians.

Author's contribution: SEC, MGL, SM, ADB, SR, HD, CT and HB were involved in the conception and trial design. HD provided statistical expertise. SEC, MGL, SM, ADB, TFT, AM, AAN, MZ, JX, HT, SR, HD, KT, CT and HB contributed in drafting the protocol manuscript and critically revised and commented on its previous versions and the final version. SEC, MGL, SM, ADB, TFT, AM, AAN, MZ, JX, HT, SR, HD, KT, CT and HB will be involved in the analysis and/or interpretation of the data.

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Competing interests: SR is an employee of Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA. HD is an employee of Boehringer Ingelheim Investment Co. Ltd., Shanghai, China. KT and CT are employees of Boehringer Ingelheim International GmbH, Biberach, Germany. SEC declares paid activities

as advisor, speaker or consultant for AbbVie, Boehringer-Ingelheim, Eli-Lilly, Janssen, Leo Pharma, MSD, Novartis, Pfizer, Sanofi and UCB. MGL declares paid consulting activities for Aditum Bio, Allergan, Almirall, Arcutis, Inc., Avotres Therapeutics, BirchBioMed Inc., BMD skincare, Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Evelo, Facilitate International Dermatologic Education, Foundation for Research and Education in Dermatology, Inozyme Pharma, Kyowa Kirin, LEO Pharma, Meiji Seika Pharma, Menlo, Mitsubishi, NeuroDerm, Pfizer, Promius (Dr. Reddy's Laboratories Ltd), Serono, Theravance, and Verrica, and research funds from AbbVie, Amgen, Arcutis, Boehringer Ingelheim, Dermavant, Eli Lilly, Incyte, Janssen Research & Development, LLC, LEO Pharma, Ortho Dermatologics, Pfizer, and UCB. SM and HT declare paid consulting activities for Boehringer Ingelheim. ADB declares paid consulting activities for AbbVie, Almirall, Boehringer-Ingelheim, Celgene, Janssen, LEO Pharma, Lilly, Novartis and UCB. TFT declares conducting clinical trials or paid consulting activities for AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli-Lilly, Galderma, GlaxoSmithKline, Janssen-Cilag, LEO Pharma, Merck Sharp & Dohme, Novartis International, Pfizer and UCB Pharma. AM declares receiving research grants, consulting fees, and/or speaker's fees from AbbVie, Boehringer Ingelheim, Celgene, Eli Lilly, Eisai, Janssen, Kyowa Hakko Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe, Nichi-Iko, Nippon Kayaku, Novartis, Sun Pharmaceutical Industries, Taiho Pharmaceutical, and Torii Pharmaceutical and Ushio. AAN declares being a consultant and advisor and/or receiving speaking fees and/or grants and/or served as an investigator in clinical trials for AbbVie, Almirall, Amgen, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Galderma, GSK, LEO Pharma, Janssen-Cilag, MSD, Novartis, Pfizer, Sandoz, Sanofi, Serono, UCB. MZ declares receiving grants, consulting fees, and/or speaker's fees from AbbVie, Boehringer Ingelheim Janssen-Cilag, LEO Pharma China, Novartis, Pfizer Inc and Xian-Janssen. JX declares receiving grants, consulting fees, and/or speaker's fees from AbbVie, Bayer, Boehringer Ingelheim, Kyowa Kirin, La Roche-Posay China, Novartis, Pfizer Inc and Sanofi. HB declares paid consulting activities for AbbVie, Almirall, BIOCAD, Boehringer-Ingelheim, Celgene, Janssen, Kyowa-Kirin, Leo Pharma, Lilly, Mylan, Novartis and UCB, and grant support from Boehringer-Ingelheim, Janssen, Leo Pharma, Novartis and Pfizer.

Data sharing statement:

To ensure independent interpretation of clinical study results, Boehringer Ingelheim grants all external authors access to all relevant material, including participant-level clinical study data and relevant material as needed by them to fulfil their role and obligations as authors under the ICMJE criteria.

Furthermore, clinical study documents (e.g. study report, study protocol, statistical analysis plan) and participant clinical study data are available to be shared after publication of the primary manuscript in a peer-reviewed journal and if regulatory activities are complete and other criteria met per the BI Policy on Transparency and Publication of Clinical Study Data: https://trials.boehringer-ingelheim.com/transparency_policy.html

Prior to providing access, documents will be examined and, if necessary, redacted and the data will be de-identified, to protect the personal data of study participants and personnel, and to respect the boundaries of the informed consent of the study participants.

Clinical Study Reports and Related Clinical Documents can be requested via this link:

https://trials.boehringer-ingelheim.com/trial_results/clinical_submission_documents.html

All such requests will be governed by a Document Sharing Agreement.

Bona fide, qualified scientific and medical researchers may request access to de-identified, analysable participant clinical study data with corresponding documentation describing the structure and content of the datasets. Upon approval, and governed by a Data Sharing Agreement, data are shared in a secured data-access system for a limited period of 1 year, which may be extended upon request.

Researchers should use https://clinicalstudydatarequest.com to request access to study data.

Figure 1. Study design

*Day 1: 51 screened GPP patients with an accute flare defined as GPPGA ≥3 and GPPGA pustulation subscore of ≥2 will be randomised 2:1 to a single IV dose of 900 mg spesolimab or IV placebo.

†Day 2–7: Escape treatment (SoC) may be offered in case of disease worsening defined as worsening of clinical status or GPP skin and/or systemic symptoms as defined by the investigator.

‡Day 8: Patients with a GPPGA ≥2 and pustular component of GPPGA ≥2 will qualify for treatment with OL spesolimab.

§After Day 8–Week 12: only one rescue dose with OL spesolimab is permitted if a patient who has previously achieved clinical response (GPPGA 0/1) to initial treatment, either with spesolimab or placebo at Day 1, or escape medication or OL spesolimab at Day 8, experiences a recurrence of a GPP flare (≥2-point increase in the GPPGA score and the pustular component of GPPGA ≥2). Subsequent flares will be treated with SoC per physician's choice.

¶Patients who do not require rescue treatment with OL spesolimab are to be followed until Week 12 (EoS) prior to entering into OLE trial. Patients who receive rescue treatment with OL spesolimab between Weeks 2 and Week 6 are to be followed until Week 12 (EoS) prior to entering the OLE trial. If at Week 12 they qualify to enter the OLE trial, then the EoS will be considered for these patients. If not, patients will have an additional 10 weeks' follow-up and have an EoS at Week 16–28. Patients who receive rescue treatment with OL spesolimab between Weeks 7 and 12 are to be followed for an additional 6 weeks and have a response evaluation at Week 13–18; these patients will not have a visit at Week 12. If at Week 13–18 patients qualify to enter the OLE trial, the EoS will be considered for these patients. If not, patients will have an additional 10 weeks follow-up and have an EoS at Week 16–28. Patients who do not qualify to enter the OLE trial are to be followed for 16 weeks (EoS/Week 16–28) after the last dose of trial medication, which is the latest time point of trial medication given during the study (e.g. Day 1, Day 8 if OL spesolimab is given, rescue with OL spesolimab if given).

The white arrow head indicates a single dose of IV spesolimab or placebo at Day 1 or spesolimab at/after Day 8.

EoS, end of study; GPP, generalized pustular psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; IV, intravenous; OL, open label, OLE, open-label extension; R, randomisation; SoC, standard of care.

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Supplementary file 1

Institutional Review Boards/Medical Ethical Committees

Supplementary file 2

Generalized Pustular Psoriasis Physician Global Assessment (GPPGA)

Inclusion criteria

Exclusion criteria

Supplementary table 1. Restricted medications

Supplementary table 2. Efficacy outcome measures

Supplementary file 3

Information and Consent Form for Trial Subjects template

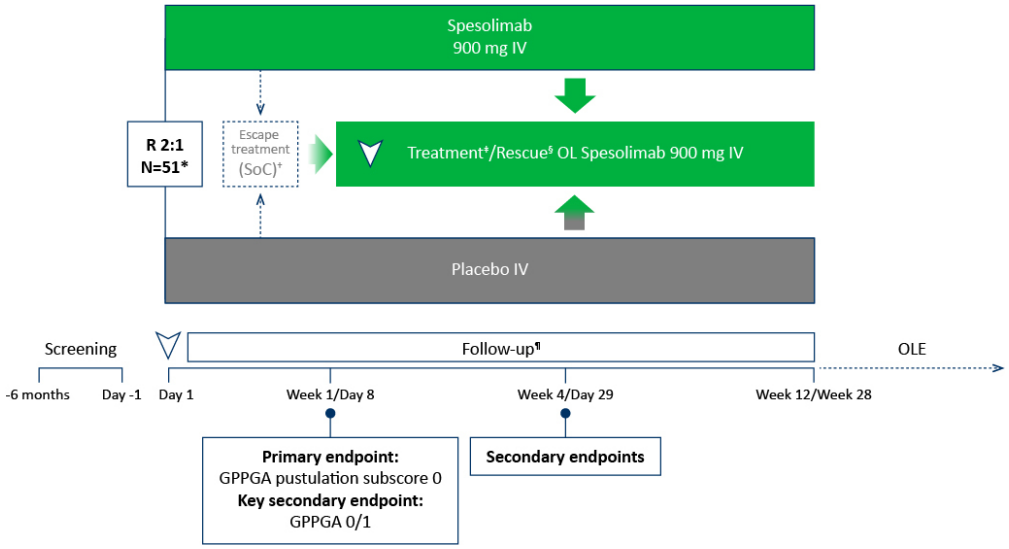

Figure 1. Study design

174x94mm (150 x 150 DPI)

Study: Effisayil™ 1
IRB/IECs approvals

Country	Institutional Review Boards/Medical Ethical Committees
United States	Alpha IRB Suite C #497 1001 Avenida Pico San Clemente California 92673 United States
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	The IRB of Shinshu University Hospital 3-1-1 Asahi Nagano, Matsumoto 390-8621 Japan
	The IRB of Kindai University Hospital 377-2 Onohigashi Japan
	The IRB of Tokyo Medical University Hachioji Medical Centre 1163, Tatemachi Tokyo, Hachioji 193-0998 Japan

Study: Effisayil™ 1
IRB/IECs approvals

	The Conjoint IRB of Nihon University Hospitals 30-1, Oyaguchi kami-cho Tokyo, Itabashi-ku 173-8610 Japan
	The IRB of Tokyo Medical University Hospital 6-7-1 Nishishinjuku Tokyo, Shinjuku-ku 160-0023 Japan
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	Institutional Review Board Severance Hospital, Yonsei University Health System, Institutional Review Board 50-1 Yonsei-ro, Seodaemun-gu Seoul 03722 Korea, Republic of
Malaysia	Medical Research & Ethics Committee d/a Kompleks Institut Kesihatan Negara Blok A, No 1, Jalan Setia Murni U13/52 Seksyen U 13, Bandar Setia Alam 40170 Shah Alam, Selangor Shah Alam 40170 Malaysia
Singapore	NHG Domain Specific Review Board 3 Fusionopolis Link #03-08 Nexus@One-North Singapore 138543 Singapore
Switzerland	Commission cantonale (VD) d'ethique de la recherche sur l'entre humain Chairman: Prof. Dr. Med. Patrik Francioli Avenue de Chailly 23 Lausanne 1012 Switzerland
Taiwan	Chang Gung Medical Foundation 199 Tung Hwa North Road Taipei Migration Data 10507 Taiwan
Thailand	Ethics committee/IRB of the Institute of Dermatology Institute of Dermatology, 420/7 Rajavithi Road Bangkok 10400 Bangkok 10400 Thailand
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Tunisia	Personal protection Committee -South Ethics Committee

Study: Effisayil™ 1
IRB/IECs approvals

	Higher Institute of Nursing science of Sfax-Avenue Majida BOULILA-Sfax-Tunisia

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.

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.

BOEHRINGER INGELHEIM GmbH

Information and Consent Form for Trial Subjects (template)

GENERAL GUIDELINES WHEN WRITING THE CONSENT FORM

(Keep the red text when submitting the trial version to the CT Managers.
Delete these guidelines before submitting to local regulatory authorities)

1. FORMAT:

- Use a consistent font style and size throughout the document; a minimum 12 point font is preferable. Please consider the audience; some patients may require a larger font.
- The pages should contain "Page X of Y" and the version date of the document in the footer.
- **BICTMS number must be added. Localversioning can be added in addition to fulfil local needs.**
- Section headers should not float at the bottom of the page without any text.
- Before using the consent form, please print and review the document for print errors, spelling and grammar, font sizes, floating headers, etc.
- Avoid using tick boxes; this often leads to unnecessary non-compliances.

2. LANGUAGE AND READABILITY:

- Use brief, simple statements (not long, detailed, complicated explanations) using simple, layperson's language aimed at 13 – 15 year olds. Break long sentences into several shorter ones. Express only one major idea per sentence.
- Please do a "Readability Test" in MS Word as an indication check to find out whether the information you prepared is understandable to trial subjectssubjects (e.g. Grade level 8 - 10) included in this trial. Remember that the responsibility for the readability of the document remains exclusively with the author.
- Speak to your reader. Use "you/your" to refer to the potential subject. For example, write, "You must provide consent" not, "Consent must be provided".
- Avoid unfamiliar or confusing words or phrases. Avoid jargon. If a medical terminology is essential, include a layperson's definition. For example, "bruise" should be used instead of "hematoma".

3. GENERAL INSTRUCTIONS FOR USING THIS FORM:

- Instructions and suggested text are printed in 'red', with suggestions to actual text in 'black'. **Delete or replace all red text from this template when finished**.
- Sections highlighted in yellow are mandatory text and if there are any country specific changes , then the responsible CTM must consult and get approval from either local line management and/or local legal and/or local data protection/privacy contact for the requested changes.
- Please delete any parts of the consent template that are not relevant to your particular trial.
- If the consent form contains multiple procedures and/or technical terms, consider using the appendix at the end of the consent form. The use of appendices described in this

template is optional and depends on local regulations. Alternatively, the content in the appendices can be directly incorporated within the main body of the form as usual.

INFORMATION AND CONSENT FORM
FOR TRIAL SUBJECTS

TRIAL LAY TITLE: A study to test BI 655130 in patients with a flare-up of a skin disease called Generalized Pustular Psoriasis

PROTOCOL No.: 1368-0013

TRIAL SUBJECT No.: _____

EudraCT No.: 2017-004231-37

SPONSOR: Boehringer Ingelheim *(to be adapted at country level, CT Manager to insert full corporate legal name of local country)*

TRIAL DOCTOR: Name, address, telephone number

Dear Patient,

You are being asked to participate in this research trial because you have a rare and severe inflammatory skin disease called, Generalized Pustular Psoriasis (GPP) that causes inflammation in the skin and may also affect internal organs. It shows up as a recurrent flare-up (worsening GPP symptoms) with widespread pustules (small bumps on the skin that contain fluid or pus), diffuse erythema (large area of redness of the skin that looks like a sunburn), and scaling (small, hard, dry areas of the skin) accompanied by general symptoms. A flare-up can be serious and requires immediate medical care. Little is known about this rare disease so far, and current treatment options for controlling GPP flare-ups are limited.

Please read the following information carefully. It contains important information to help you decide whether to participate in this research trial. The trial staff will have a detailed interview with you to inform you about the trial and the possible benefits and risks of your participation. Ask questions about anything that is not clear at any time. You may take home an unsigned copy of this information to think about and discuss with your family, friends or family doctor before you make your decision to participate or not.

After reading and discussing the information, you should know:

- Why this research trial is being done;
- What will happen during the trial;
- Any possible benefits to you;
- The possible risks to you;
- Other options you could choose instead of being in this trial;

- How your personal information / health information will be protected during the trial and after the trial is over, and which data privacy rights you have;
- How your data and your biological samples will be collected, stored, processed, transferred and used
- Whether being in this trial could involve any cost to you; and
- What to do if you have problems or questions about this trial.

This document also includes:

- Appendix A: Visit Schedule
- Appendix B: Description of Trial Procedures and Risks
- Appendix C: Known Side Effects (Adverse Events) of the Investigational Drug(s)
- Appendix D: *move* Confidentiality / Privacy and Data Sharing *section to an Appendix if allowed by local authorities / local legal*

Your participation in this trial is voluntary. If you join this trial, you can still stop at any time. You have the right not to sign this consent form. If you do not sign, you cannot take part in this research trial. If you decide to participate, you will be asked to sign and date at the end of this form.

Your signature confirms that you agree and accept to take part in this trial and to the handling of your data as described in this form.
It is important that your personal doctor is aware that you are in a research trial because you may be taking a treatment that could affect your health. With your permission, we will notify him/her that you are taking part in this trial.

PURPOSE OF THE TRIAL

The purpose of this trial is to:

- Compare the safety, effectiveness and side effects of a single intravenous (IV) dose of the investigational drug being studied, BI 655130, with an inactive substance (placebo), in subjects with GPP, who are having a moderate to severe flare-up (GPP symptoms). A placebo is a substance that looks like the investigational drug but contains no active drug.
- Test how the investigational drug is used by the body and how fast or slow it moves through or out of the body.
- Measure the immune response of the investigational drug (when the body detects and defends itself against substances that appear unknown and harmful).
- See how genes (coded instructions for making each cell in your body) may explain and predict the response to the investigational drug.

The investigational drug, BI 655130, works by stopping the effect of a protein called IL-36 receptor involved in the development of GPP. BI 655130 is the first compound of this new class of drugs.

The investigational drug has not been approved as a treatment for any disease by <insert authority> and, thus, its use in this research trial is considered experimental.

We estimate that approximately <enter number of subjects assigned to your OPU> people will participate in this trial in <insert country of OPU> and approximately 51 subjects worldwide.

In this clinical trial, competitive enrolment will be used. This means that when a target number of patients (approximately 51) have entered the trial, all further enrolments will be closed. It is possible that you could be in the screening phase when the target number of patients is reached. If that happens, you may not be able to receive the treatment, even if you meet all the other requirements for entering the clinical trial and receiving the treatment.

THIS TRIAL HAS BEEN APPROVED BY <insert applicable local authorities, if required, otherwise this statement can be deleted>.

DESCRIPTION OF THE TRIAL

This trial compares the effects of the active investigational drug, BI 655130 (spesolimab), with an inactive substance (placebo) in subjects with GPP, who are having a moderate to severe flare-up.

You will be assigned by random choice to receive either the investigational drug, BI 655130, or the placebo at Visit 2 (Day 1) as follows:

- *Group 1 will receive, a single dose of BI 655130, 900 mg, by IV infusion*
- *Group 2 will receive a single dose of placebo, by IV infusion*

This process is called randomization. You will have about 66% chance of being placed in Group 1 and a 33% chance of being placed in Group 2.

The Visit 2 dose of the trial medication (investigational drug or placebo) will be double-blinded. No one (including you and the trial team) will know who is receiving the investigational drug or the placebo. This way the results of the trial will not be favored one way or another. If it becomes necessary for your care, your trial doctor will be able to find out whether you took the placebo or the investigational drug.

TRIAL PROCEDURES

Time to be spent in the trial

The time you will spend in this trial will depend on the time window between the first trial centre visit (when you agree to participate and give your informed consent) and when you have a GPP flare-up and return for the second trial centre visit. This time period can last several days, weeks or even months and cannot be predicted.

Once you have a GPP flare-up and complete Visit 2, your participation will last up to about 28 weeks (about 7 months) and require about 12 to 14 additional visits to the trial centre.

You may be asked to come to the trial centre for additional unscheduled visits. Refer to the Unscheduled Visits section below for more information.

Each trial centre visit may take between 1/2 hour and 4 hours to complete the procedures as described in Appendix A.

If applicable, please consult with your local Legal representative to clarify whether it is acceptable to have the trial tests and procedures listed in an appendix:

In Appendix A of this document you will find a detailed overview and schedule of all the visits which lists the trial tests and procedures planned at each visit. The trial doctor or the trial staff will go through this Appendix with you.

In Appendix B of this document you will find a more detailed description of the different trial tests and procedures including related risks. The trial doctor or the trial staff will go through this Appendix with you.

At trial visits, the trial doctor or trial staff will ask you about how you feel, what medications you have taken and what other health care you have received since the last trial visit.

Before the clinical research starts (screening - Visit 1)

Before any study procedures are done, you will be asked to read and sign this Information and Consent form.

The first trial visit will be a screening visit. The screening visit will include the following procedures:

- You will be asked about your medical history including history of GPP, demographics (gender, ethnicity and race), and your smoking history
- A physical exam including vital signs and your temperature will be taken
- Blood and urine tests, including a blood test for infectious disease testing
- A pregnancy blood test if you are a female able to have a child
- An electrocardiogram (ECG)
- Photographs of skin lesions (areas of your skin affected by GPP)
- You will be asked about how you feel and what medications you are taking
- The trial doctor will obtain information from your personal doctor (if different from the trial doctor) about the mutation (changes to the structure of a gene) of a certain gene (IL-36RN). If this information is not available, you will still be able to participate in this trial

The results of the tests and/or questions at the screening visit will help the trial team decide whether you can continue in this trial. If these tests show that you are eligible to participate in the trial, you will be able to continue in this trial. If you do not meet the eligibility criteria, you will not be able to continue. You should not go to another trial centre to be screened again.

If you are not having a moderate to severe GPP flare-up at the screening visit, you can still take part in this trial and then return to continue your participation when a flare-up occurs. At that time, you will be asked to confirm that you still agree to participate in this trial. If the flare-up occurs after 6 months of signing this consent form, you will be asked to sign another consent form for this trial and repeat your first visit.

INVESTIGATIONAL DRUG VISIT (VISIT 2)

You may be asked to stop taking certain medications before receiving the trial medication. The trial doctor will further discuss this with you.

If you are eligible to participate in this trial and you are having a GPP flare-up at Visit 1, Visit 1 and Visit 2 can be done on the same day.

You will receive the trial medication, BI 655130 or placebo, at Visit 2 (Day 1) by IV infusion. An IV infusion is a slow injection of the trial medication directly into your vein. It will take between 1-1/2 to 3 hours to give you the trial medication.

Your first dose of trial medication will be given to you either at the trial centre or at the hospital. The trial doctor will discuss this with you further.

FOLLOW-UP PERIOD

After receiving the trial medication at Visit 2, you will be followed-up for about 12 to 28 weeks, which includes the End of Study (EOS) Visit (see the EOS section below). The length of the follow-up period will depend on how well you respond to the trial medication.

After you receive your first dose of trial medication, you will return to the trial centre every day during the first week (Day 2 to Day 8). Depending on your response to the trial medication, the trial doctor will let you know if you need to return to the trial centre for visit Days 4 through 7 during the first week.

If your GPP worsens within the first week of receiving the trial medication, the trial doctor will treat you with Standard of Care (SoC) medication(s), which are medications usually given for treating GPP. The trial doctor will tell you the SoC medication(s) you will receive.

At Day 8 (Visit 9), if your GPP did not get better after receiving the initial dose of trial medication, and you did not receive a SoC medication(s) within the first week of receiving the initial dose of trial medication, you may receive a 900 mg dose of BI 655130 by IV infusion. The trial doctor will tell you if you are eligible to receive BI 655130 at this visit.

After Day 8 (Visit 9) and through Week 12 (Visit 14), if you have a second GPP flare-up after achieving a response to one of the following:

- the initial trial medication dose on Day 1 **OR**
- a dose of BI 655130 on Day 8 (if received) **OR**

- the SoC medication(s),

you will be able to receive a 900 mg dose of BI 655130 by IV infusion. This dose is called a rescue treatment.

If you have more than one flare-up after Visit 9, the trial doctor will treat additional flare-ups with SoC medication(s).

If you decide to stop taking the trial medication early, you will be asked to continue with all of your remaining scheduled trial visits as originally planned. If you are not willing to continue with all your remaining scheduled trial visits, you will be asked to return to the trial centre for Visits 9 and 12 (if not already completed), and the End of Study Visit. If you cannot return to the trial centre, the trial staff will contact you when your scheduled visits would have occurred to ask you how you are.

UNSCHEDULED VISITS

During the Follow-up Period you may be asked to come to the trial centre for additional unscheduled visits if you have a GPP flare-up and require a rescue dose of BI 655130 or SoC medication(s), or if the trial doctor thinks the visit(s) are necessary for your safety, or if procedures were missed from a previous visit or need to be repeated.

If you receive BI 655130 at either a scheduled or unscheduled visit after Day 8 (Visit 9), you will complete the Visit 9 procedures (except for certain blood tests) as listed in Appendix A.

END OF STUDY (EOS) VISIT

You will have an "EOS" visit (Visit 14 or 15 or 16) after completing the trial or if you stop the trial early.

Your EOS visit will depend on how you respond to the trial medication and when you have your last dose of trial medication or dose of BI 655130. The trial doctor or trial staff will let you know when your EOS visit will occur.

If you complete all of your scheduled visits and have your EOS visit at either Visit 14 or Visit 15, you may be given the option to participate in an extension of this research trial using the same investigational drug, BI 655130, without the use of a placebo. If you decide to participate in the extension research trial, you will sign another Information and Consent Form.

If you do not join the extension research trial or if you decide to stop the trial early, your EOS visit will be about 16 weeks after you stop the trial medication or dose of BI 655130.

Your trial doctor will discuss your future care, any medications you require, and you will be offered standard medical care.

After your EOS Visit you will have completed this trial.

For your safety, any side effect(s) that continue after your last trial visit will be followed by the trial doctor until the side effect(s) resolve or are stable.

YOUR RESPONSIBILITIES

- You must tell your trial doctor if you previously have participated in this trial, have been in another research trial in the past 30 days or are currently in another research trial. While participating in this trial, you should not take part in another research trial, or in this trial at another site. This is to protect you from possible injury arising from such things as extra drawing of blood samples, potential medication interactions, or other hazards.
- You will receive a Trial Identification Card. It is important that you carry this card with you at all times. If you are treated by another doctor (for example, in an emergency), it is important that you tell them of your participation in this trial by showing this card.
- If you are treated by another doctor, it is important that you tell the trial staff about your treatment and what happened.
- You must follow the trial instructions provided by the trial staff, come to all scheduled trial visits, and be reasonably available for any scheduled telephone visits.
- You must call/tell the trial doctor if you experience any side effects or if you feel unwell, even if you do not know if it has anything to do with this trial.
- You must tell the trial doctor about all prescription and non-prescription drugs, herbal preparations that you are taking or planning to take.
- You will be asked to complete questionnaires (refer to Appendix A). Please complete each of them by yourself, without the help of someone else.

POTENTIAL BENEFITS

You may not personally benefit from participating in this trial, but you may contribute new information that may benefit other patients and provide the medical and scientific community with information about treatment for GPP.

However, receiving BI 655130 may help to reduce GPP symptoms and how long a GPP flare-up lasts. Therefore, you may benefit as a result of your participation in this trial. There is, however, no guarantee for that.

RISKS AND/OR DISCOMFORTS

This section is provided by the TMM for the trial drug. Any changes must be approved by the author of this section.

There are risks to taking part in any research trial. If you receive a placebo, you will not receive an active treatment for your condition. Your condition might not improve or it could get worse during the course of this trial.

If you receive active trial medication, then side effects may occur. Some of those side effects can be treated. Some side effects may go away when you stop taking the trial medication. Some side

effects can be mild, but others may continue longer or become permanent. Some may be life-threatening or fatal.

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or breathing difficulties. If you think you are having an allergic reaction, call the trial doctor right away. If you are having trouble breathing, call <insert regional emergency telephone number>.

Taking BI 655130 may cause you to have one or more of the side effects (or adverse events) listed below: <List all known adverse events of each drug/product here or by using Appendix C>

If applicable, please consult with your local Legal representative to clarify whether it is acceptable to have the side effects listed in an appendix.

If using Appendix C, use the following wording:
In Appendix C of this document you will find a more detailed description of the adverse events of the trial medication including related risks. The trial doctor or the trial staff will go through this Appendix with you.

The trial doctor or the trial staff will go through the description of the known side effects with you. They are willing to discuss any questions you might have about the severity and frequency of risks and other potential discomforts. In addition to the side effects listed, there is always the risk of developing side effects which are not known at this time.

You will be monitored carefully to check for these risks. Your trial participation may be stopped if any signs of drug toxicity or other damage occurs.

You need to tell your trial doctor or a member of the trial team immediately if you experience any side effects.

The trial doctor will discuss with you the risks and benefits of the Standard of Care medication(s) which you may take during your participation in this trial.

ALTERNATIVE TREATMENTS

Instead of participating in this trial, you have other options which may include the following:

- Receive recommended treatment including <specify the standard treatment per your country/OPU>.
- Take part in another research trial.
- Receive no therapy specific to your GPP.
- Receive comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems, fever, headache, and other problems caused by your GPP. It does not treat the GPP directly, but instead tries to treat the symptoms.

Your trial doctor will discuss these options and the important potential risks and benefits with you before you decide whether you will take part in this trial.

NEW INFORMATION ABOUT THE TRIAL

During the trial, you will be notified of changes to trial procedures, newly discovered side effects or significant findings which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this trial.

INFORMATION ON BIRTH CONTROL

Based on the information provided in the Investigator's Brochure (IB) and the Clinical Trial Protocol (CTP), this section must describe the potential risks for a fetus or embryo in case pregnancy occurs during trial participation. For further guidance please refer to Contraception Guideline). This document includes a list of acceptable contraception methods meeting the requirements outlined in ICH M3 (R2).

For Female Trial Subjects

As with any investigational drug, the effect of BI 655130 on the unborn child is unknown. If you decide to take part in this trial and you are able to become pregnant, you must be willing to have a pregnancy test done at the Screening Visit, and regularly at trial visits and at the end of the trial. Further, you must avoid becoming pregnant while you take part in this trial. You cannot participate in this trial if you are pregnant, breastfeeding or plan to become pregnant during your trial participation. You must use a highly effective method of birth control and you should not breastfeed throughout this trial and for up to 16 weeks after receiving the last dose of BI 655130.

Your trial doctor will talk to you about the best method of birth control for you.

Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control associated with inhibition of ovulation
- Progestogen-only hormonal birth control associated with inhibition of ovulation
- Intrauterine device (IUD) and intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion (blocking of the fallopian tubes)
- Vasectomy of sexual partner (proven effective by absence of sperm on the ejaculation).
- Complete sexual abstinence (not to have male-female vaginal sex)

If you are pregnant or think you could be pregnant, it is important for you to tell the trial doctor or trial staff immediately. If you become pregnant during the trial, you will discontinue trial medication and be asked to continue to participate in trial visits. Your health and your baby's health will be monitored throughout your pregnancy. Even if you are no longer in the trial, your trial doctor will contact you after your baby is born to find out about the baby's health.

WITHDRAWAL FROM TRIAL PARTICIPATION

You may choose not to take trial medication or to leave this trial completely at any time. Your decision will not result in any penalty or loss of benefits to which you are otherwise entitled. Leaving the trial will not affect your future medical care.

It is important that you tell the trial doctor if you are thinking about stopping or have decided to stop so your trial doctor can evaluate the risks of stopping.

Depending on the protocol, the following section may be adapted. Please ensure the trial site understands that the discussion with the subject and the outcome regarding follow up, vital status collection, discontinuation of trial medication, and withdrawal of consent is documented in the subject's medical records.

Listed below are three possible scenarios that could stop your trial participation. Your study doctor will discuss these scenarios with you.

- **You may stop trial medication, but agree to continue participation and/or continue to be contacted**

If you decide to stop taking the trial medication, you may still continue to participate in trial visits. It is recommended that you come in to the trial centre for all of the remaining trial visits, however if you are unable to come to the trial centre, you will be asked by the trial staff if they can contact you by phone/email/mail or someone you choose (such as your family doctor, a friend, or relative), to ask about your overall health status. This will happen when your scheduled visits would have occurred up to the End of Study Visit. Alternatively, you will be asked for your permission to collect this information from your medical records <or any public records or patient search organisation – if allowed by local regulations> until the end of the trial. This information is important for the scientific value of the trial to interpret the trial results correctly. You are free to refuse this regular contact. Your decision will not affect your future medical care.

- **You may stop trial medication and participation completely and withdraw your consent**

You have the right to withdraw your consent at any time. If you decide to stop trial medication and participation, then the final assessments such as a physical examination, vital signs, laboratory tests, ECG, and questionnaires should be completed as soon as possible. This is important for your safety and well-being. After the final assessments, no further information about you will be entered into the trial database.

All data that had already been collected up to the time of withdrawal of your consent, including data gathered at any of your final assessments, will still be used to ensure the correct completion and documentation of the trial and comply with applicable law.

- **Your trial doctor may decide that you must stop**

Your trial doctor might decide to stop your trial medication or trial participation early without your consent when, in the trial doctor's judgment, it is in your best health interest to do so. Some of the reasons why this might happen are listed below:

- Your condition worsens or does not improve and an alternative treatment is medically indicated.
- The trial treatment or procedures are found to be unsafe or ineffective.
- Your inability to take the medication / participate as instructed.
- Cancellation by the sponsor or regulatory authority.
- Or for other unforeseen reasons that make it necessary to stop your participation in the trial.

If you are removed from the trial, the trial doctor will explain to you why you were removed.

CONFIDENTIALITY / PRIVACY AND DATA SHARING

The wording in this section must preferably be reproduced word-by-word in the trial specific subject information. If any changes to that wording, which would limit our ability to publish or share results and data, are mandated by an Ethics Committee or IRB or are necessary otherwise, then the responsible function (CT Leader or CT Manager) must consult local line management, local legal and/or local data protection/privacy contact. If applicable, please consult with your local legal representative to clarify whether it is acceptable to have the confidentiality, privacy, and data sharing section listed in an appendix, e.g. Appendix D.

Use of Your Personally Identifiable Information

The part of your personal information that directly identifies you, such as your name and address, will remain at the trial site and can be accessed by the trial doctor and other people at the site who are assisting with the trial or your care. This information may also be checked at the trial site by the

- sponsor, or the sponsor's representatives (including monitors hired by the sponsor through a service provider),
- ethics review board/committee that reviewed the ethical aspects of this trial, and/or
- domestic or foreign regulatory agencies such as <insert applicable regulatory bodies here, e.g. the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA)> that approve medicines.

These persons check that the trial is carried out correctly at the trial site. They are bound by a duty of confidentiality.

Coding of Your Data

Your personally identifiable information and health information collected in this trial will be labelled with a unique code number. Coded data may also include data/information such as images (e.g. x-rays) or EEG (electroencephalograms). The code number will be used in place of your name and other information that directly and easily identifies you. Only the trial site will

have the link between your personal information and the coded data. This link will not be provided to the sponsor; only your coded data will be sent to the sponsor. The sponsor will take measures to protect the confidentiality and security of your coded data and your privacy in accordance with current law.

Use of Your Coded Data

The sponsor, its research partners and service providers (like clinical research organizations or laboratories) including companies belonging to sponsor's group, and regulatory authorities such as drug regulators, reimbursement agencies and ethics review boards may use your coded data for the following purposes:

- Analyse it to understand the trial, the trial results and the drug(s) (including side effects and efficacy) or the disease(s) studied, obtain approvals for drug(s) and reimbursements for the drug(s) in countries worldwide.
- Share it with domestic or foreign regulatory, reimbursement or other professional health care agencies worldwide such as <insert applicable regulatory bodies here, e.g. the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA)>, that regulate medicines to fulfil reporting obligations during the trial.
- Analyse it to improve the quality of this trial and other clinical trials.

To support the review of your data, your trial doctor may code and data/information from your medical records. This will be limited to specific information relating to this trial.
The coded data may be transferred within your country or to other countries for analysis. Where the data protection rules in other countries are not as strict as the rules in your country, the sponsor will adopt appropriate measures to provide an adequate level of protection according to EU law.

Additional Use of Your Coded Data

Your coded data from this clinical trial can be combined with data from other trials. The purpose is to learn more about your disease and other diseases, different responses to treatments and new treatment options to improve quality and efficiency in the drug development process. The additional use of your coded data will not be part of another Clinical Trial.

Incidental Findings

The sponsor will only search for results that are directly related to the actual clinical trial question. To do so researchers will obtain results by combining your data with data from a large number of other individuals. Nevertheless, other results which may be of medical importance for you and your family can occur incidentally for all testing techniques applied (so-called incidental findings).
In case of incidental findings that are considered medically actionable because they have clear and immediate medical significance to your health, the Sponsor will take all justifiable efforts to inform your study doctor. Your study doctor may then discuss the impact of these incidental findings with

you.
If you are not interested in receiving this information, please let your trial doctor know.

Sharing of your anonymized data

The sponsor is convinced that access to trial data advances clinical science and medical knowledge and is in the best interest of patients and public health, provided that patient privacy is protected. Therefore, the sponsor may share with credible researchers an anonymized set of your trial data, but only for specified and approved scientific research. Anonymization means that the sponsor will delete or modify any trial data that could identify you.

Storage of your coded data

All coded data, including yours, will be kept by the sponsor. Only your trial doctor will be able to link your unique code number to you.

This link will remain at the trial site for a maximum of 30 years and will then be destroyed by the trial doctor. After that it is not possible to link your unique code number directly back to you.

Rights under data protection laws

You have the right to review which personal data the trial site and sponsor store about you. You can also request that incorrect personal data is corrected or that processing is restricted.

In order to exercise your rights please contact the trial site [if applicable: and its data protection officer (ADD EMAIL)] who will align with the sponsor. You can also ask to receive the personal information you have provided for the trial in a standardized electronic format or to have them transmitted to another person of your choice. You can also contact your local data protection authority in case of questions or concerns about the handling of your personal data. In some cases, your rights can be limited under applicable laws, especially where they conflict with the conduct of the trial and mandatory archiving requirements. In this case you will be informed accordingly.

Clinical Trial Websites and Publication
The following statement must be included and must not be modified. Additional explanations and/or websites may be added.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

The following statement must be included in European studies and is optional for other countries: A description of this trial including a summary of the trial results will also be available on the European Union web-page www.clinicaltrialsregister.eu.

The results of the trial will be published on Boehringer Ingelheim's Trial Web site (http://trials.boehringer-ingelheim.com). The website may also include a summary understandable to a layperson. The results may also appear in other clinical trial/study registries in countries in which the trial is conducted. The results will not include information that can identify you.

The results of the study may also be published in a professional journal or presented at scientific meetings. Your identity will not be disclosed in those presentations.

USE OF SAMPLES FOR THIS TRIAL

The biological samples collected from you during the trial as described under the section "Trial Procedures" and Appendix A and B will be stored, processed, and used under your code number for the purposes of this trial for analyses as follows:

Routine Safety Samples
Blood and urine will be collected for routine safety and blood for pregnancy tests (for women of child bearing potential) and will be sent to a central laboratory for analysis. Leftover samples will be destroyed once the tests are completed. The urine pregnancy testing will be done at the trial centre. The sample will be destroyed at the trial centre once the results are known.

Pharmacokinetic (PK) and Anti-Drug Antibodies/Neutralizing Antibody (ADA/Nab) Samples
Blood will be taken for PK testing to see how your body uses the investigational drug and how fast or slow it moves through or out of your body, and for ADA/Nab testing to measure your immune response to the investigational drug (when the body detects and defends itself against substances that appear unknown and harmful).

After completion of the clinical trial, the samples for PK and ADA/Nab may be used for additional testing to see how the investigational drug reacts over time. These samples will be discarded after the testing is completed but not later than 5 years after the trial is over and the sponsor completes a report that contains the trial results.

Biomarker Samples (in blood)
Blood will be taken for biomarker testing as indicated below. Biomarkers are biological molecules found in blood, other body fluids, or on cells and tissues and are a sign of a normal or abnormal process, or of a condition or disease. Biomarker testing measures how the human body is functioning.

In this study, protein biomarkers will be measured in the blood that could possibly be associated with GPP, to see changes of these biomarkers before and after receiving the trial medication. Biomarkers could be proteins or ribonucleic acid (RNA) sequences (the order of each RNA molecule). Proteins play specific roles for various body functions.

In this study, biomarker testing will be done to:

- See if the biomarkers show how the investigational drug works in your body and how

your body responds to the drug.
- Look at the changes in protein or RNA levels of certain biomarkers to see how severe the disease may be.
- Genetic testing of DNA (deoxyribonucleic acid) will be done to assess certain genes known to have mutations (changes to the structure of a gene) that cause GPP. Genes are a part of your DNA which control things like the colour of your hair or eyes. Your genes affect how you respond to drugs.

Other non-genetic biomarker testing may be done. At this time, it is not known what testing will be done.

Biomarker samples will be stored at the sponsor facilities or by an external vendor (the company hired to store the samples) for backup and will be destroyed after this trial is over and the sponsor completes a report that contains the biomarker and/or the trial results, whichever comes later.

Infectious Disease Testing
Blood will be taken to see if you have infectious diseases, such as hepatitis B or hepatitis C (a disease that affects the liver) or HIV (a blood virus that may lead to AIDS) or tuberculosis (a disease that mainly affects the lungs).

Infectious disease samples will be destroyed once the tests are completed.

For Asian/Pacific region:
Infectious disease samples will be destroyed once the tests are completed with the exception of the HIV confirmation sample (if analysed i.e. in case HIV screen test result is positive). The sample will be stored at least 7 years and then be automatically destroyed.

The samples or parts of them may be transferred to the sponsor, its research partners and service providers (like clinical research organizations or laboratories) including companies belonging to the Boehringer Ingelheim Group of Companies.

SAMPLES FOR OPTIONAL RESEARCH

As an optional part of this trial, you are being asked to allow the collection and storage of blood samples for potential future scientific research.

As another optional part of this trial, you will be asked to have skin biopsies taken at selected trial visits.

You will be provided with separate consent forms with information so that you can decide whether or not you want to participate in these optional parts.

COMPENSATION / COSTS

Sample text provided below. Amend in accordance with local legal requirements or insurance.

This trial is funded by the sponsor. The sponsor will pay the trial doctor and/or institution for his/her expenses, time, and effort to conduct this trial. The trial doctor and the institution/Hospital have no other financial ties to Boehringer Ingelheim.

Sample text if using a CRO; amend as needed.
The sponsor has signed a contract with <insert applicable CRO> to conduct this trial. The sponsor will, on behalf of <CRO> pay the trial doctor and/or institution for his/her expenses, time, and effort to conduct this trial. The trial doctor and the institution/Hospital have no other financial ties to Boehringer Ingelheim.

There will be no additional costs to you for your participation in this trial. All trial procedures including lab work, tests, doctor visits, <include if applicable per your OPU budget: hospital stays to receive the trial medication,> and trial medication are provided to you free of charge by the sponsor, Boehringer Ingelheim, and will not be billed to you or your insurance carrier as long as you are participating in the trial. You will receive <enter amount and/or a description of a payment schedule> to cover out-of-pocket expenses such as meals and parking for visits that are required as part of the trial.

The sponsor will be the owner of the trial results. If commercial products or other valuable discoveries result from research using your samples and/or data, these products and discoveries may be owned, patented, licensed, or otherwise developed for commercial sale by the sponsor, other researchers, or companies. If this should occur, you will not receive any financial benefits or compensation or other proprietary interest from any commercial products or discoveries that may result from such research.

INJURY / INSURANCE

Please work with local legal to ensure that the below follows local regulations.
You will receive necessary medical treatment in the event that an injury or illness results because of your participation in this trial. If your insurance or other third-party coverage does not cover the cost of the necessary medical treatment or care, the sponsor will cover the cost if the injury or illness is due to the trial medication or procedures, and you have followed the trial doctor's instructions. Financial compensation for lost wages, disability or discomfort due to an injury is not generally available. You do not give up any legal rights by signing this form. You do not release the sponsor, institution, trial doctor or their agents from any liability for negligence by signing this form.

EMERGENCY CONTACT / ETHICS CONTACT

Suggested sample text provided below. You can adapt this section and add in any local regulations as needed.
If you have questions concerning side effects, the conduct of the trial, or for any other reason you may contact <*leave the following text intact for each site to customize in their site-specific ICF*> Dr. _____at _____ or the Trial Coordinator, _____, at _____ at ANY TIME. You have the right at any time, upon request, to be informed by the above trial doctor of your condition and the effects of the investigational drug on you.

In case of an emergency, please contact *<leave the following text intact for each site to customize in their site-specific IC>* Dr. _____ at tel. _____ OR go to the nearest hospital emergency department.

If you have any questions about your rights as a trial subject, please contact your family doctor, lawyer, or write to the committee that reviewed the ethical aspects of this trial at: <insert ethics committee name and contact here>

BOEHRINGER INGELHEIM GmbH

Information and Consent Form for Trial Subjects (template)

APPENDIX A: VISIT SCHEDULE

Boxes marked with an X show what will happen at each visit. Descriptions of these procedures are listed in Appendix B.

Trial Procedures	Screening	Treatment Visit	Follow-up Period													
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14 or EOS[1]**	**15 or EOS[2]**	**16 EOS[3]**
Visit Week		**1**							**2**		**3**		**8**	**12**	**13-18**	**16-28**
Visit Day	-1	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**15**	**22**	**29**	**57**	**85**	**92-127**	**113-197**
Discuss this trial, demographics and medical history, including gene mutation	X															
Physical exam, vital signs, and temperature	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X	X							X	X	X		X	X	X	X
Blood and urine tests for safety,	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood or urine for pregnancy testing for women of child bearing potential	X	X							X	X	X	X	X	X	X	X
Blood for infectious disease testing	X													X	X	X
Blood tests for PK and ADA/Nab		X			X				X	X	X	X	X	X	X	X
Blood tests for: genetic biomarker testing (DNA[4]); RNA and protein biomarkers		X	X	X					X	X				X	X	X
Blood tests for biomarker testing		X							X							
Receive trial medication (BI 655130 or placebo)		X														
Receive BI 655130 (if needed and if eligible)									X				X			
Photographs of skin lesions	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete questionnaires		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[1] Visit 14 will be done as your EOS visit only if you did not require a rescue dose with BI 655130 or if you required a rescue dose with BI 655130 before Week 7 and you are eligible to participate in the extension research trial.

[2] Visit 15 will be done as your EOS visit only if you required a rescue dose with BI 655130 after Week 7 and you are eligible to participate in the extension research trial.

[3] Visit 16 EOS will be done 16 weeks after your last dose of trial medication or BI 655130 if you are not eligible to participate in the extension research trial.

[4] DNA testing will only be done at Visit 2.

APPENDIX B: DESCRIPTION OF TRIAL PROCEDURES AND RISKS
<CUSTOMISE THIS LIST AS NEEDED>

Ensure the flowchart in the protocol matches the procedures as described in the CTP text and that all research related procedures are included in the Appendix. The definitions below are suggested descriptions and risks and can be edited as needed. Additional procedural and associated risk definitions may need to be added. It may not be feasible to describe every possible risk; however, subjects must be informed of all risks to consider which may influence their decision to participate.

The trial doctor or the trial staff will go through the description of the trial procedures and related risks with you. Please ask any questions you might have. In addition to the risks listed, there is always the chance of developing risks which are not known at this time.

Procedure	Description	Risks
Blood Tests and Blood Drawing	Approximately 600 mLs (40 tablespoons) of blood samples for the whole trial will be drawn to test your blood for: • Safety and pregnancy • Infectious diseases • PK and ADA/Nab • Biomarkers • Genetic biomarkers At each visit approximately 15-75 mLs (1-5 tablespoons) of your blood will be taken from a vein in your arm. If at any time during this trial your blood tests show there may be a problem with your liver, you will be asked to return for additional tests to see why. Additional blood tests to check your liver function and hepatitis will be done.	As with all blood sampling, there is a risk of mild pain, local irritation, bleeding or bruising (a black and blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.
Blood pressure test	A blood pressure test measures the pressure in your arteries as your heart pumps.	The squeezing of an inflated blood pressure cuff on your arm may be uncomfortable. It usually takes only a few seconds.
ECG (electrocardiogram)	A painless test which measures the electrical activity of your heart.	There may be some skin irritation from the ECG electrode pads or pain when removing these pads from your chest.

Procedure	Description	Risks
Intravenous (IV) Infusion	The investigational drug, BI 655130, or placebo will be given to you by an IV infusion, which is a slow injection of the trial medication directly into your vein using an IV catheter. It will take between 1-1/2 to 3 hours to receive the IV infusion. You will be monitored during the IV infusion and for about 2 hours after receiving BI 655130 or placebo. If you have a reaction to the IV infusion, you may be given medications to help reduce a reaction before you receive another IV infusion.	You may feel mild pain, local irritation, bleeding or bruising (a black and blue mark) at the puncture site (where the needle is inserted). There is also a small risk of light-headedness and/or fainting. In rare cases, the site where the needle is inserted can become infected or nerves may be damaged, and cause long-lasting abnormal sensations, damaged sensation of touch and lasting pain. During an IV infusion, tissue damage can occur if the infusion is not given directly into the vein. Your skin near the vein could become warm, swell, hurt, or get red. A blood clot or an air bubble could form, which could block a blood vessel in another part of your body. There could be an increase or decrease in electrolyte levels (the amount of certain salts and other chemicals in your blood), causing health problems. Some of these side effects could be very serious. Over time, getting a lot of injections or infusions can cause a vein to become hard or scar, which can make it difficult to put a needle into the vein to give you a shot or to take blood.
Photographs	Photographs will be taken of the affected areas of your skin (such as, the front and back trunk, legs and arms). You will not be personally recognized in the photos taken.	Please refer to the "Confidentiality" section of this consent form for information on how your personal information is managed.

Procedure	Description	Risks
	Photographs may be used in a presentation or publication about this trial. The use of the photograph may include news releases, professional conferences, websites and exhibits related to this research trial.	
Physical examination	A routine manual examination your trial doctor performs to check your overall health. The trial doctor will assess your symptoms of GPP.	This examination generally produces little pain or discomfort.
Pregnancy test	A pregnancy test measures a hormone in the body called human chorionic gonadotropin (HCG). This hormone is present in your body when you are pregnant. A pregnancy test is done using your blood and/or your urine. You cannot participate in a clinical trial if you are pregnant or planning to become pregnant.	**Pregnancy tests using blood:** As with all blood sampling, there is a risk of mild pain, local irritation, bleeding or bruising (a black and blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain. **Pregnancy tests using urine**: Because this procedure involves normal urination, there should not be any discomfort and no known risks.

Procedure	Description	Risks
Questionnaires	You will complete the following questionnaires to assess your GPP symptoms: **FACIT-fatigue (Functional Assessment of Chronic Illness Therapy - Fatigue scale):** to see how tired you are. **PSS (Psoriasis Symptom Scale):** to see how bad your GPP symptoms have been. **Pain VAS (Visual Analog Scale):** a measure of how much pain you have. **DLQI (Dermatology Life Quality Index):** to see how your skin problem has affected your life. DLQI will not be completed on Days 2-7. **EQ-5D-5L (EuroQol-5 Dimensions-5 Levels):** a measure of your current health status. It will take about 30 minutes to complete all of the questionnaires. It is important that you complete the questionnaires yourself and not ask others to do it for you. If needed, the trial staff can read the instructions, questions, and response options to you. You can then tell the trial staff member your answer.	You might find the questionnaires are long, or upsetting, or tiring. You might not like some of the questions or feel uncomfortable answering them. You do not have to answer any questions that make your feel uncomfortable.

Procedure	Description	Risks
Urine test (urinalysis)	Urine tests are used to look for the presence of red blood cells (high levels of protein) which may indicate a kidney problem and excreted minerals that can cause kidney stones. A sample of your urine is also likely to be checked for bacteria that cause infection.	Because this procedure involves normal urination, there should not be any discomfort and no known risks.
Vital signs: Temperature, heart rate, breathing rate, and blood pressure	The act of taking vital signs is the recording of body temperature, pulse rate (or heart rate), blood pressure, and respiratory rate, but may also include other measurements. Before receiving the trial medication your temperature will be taken. If you have a fever, the trial doctor may decide to give you medication to treat the fever.	These are routine procedures with little risk. Please also see definition for "blood pressure test" above.

APPENDIX C: KNOWN SIDE EFFECTS (ADVERSE EVENTS) OF THE INVESTIGATIONAL DRUG(S)

Taking BI 655130 may cause you to have one or more of the side effects (or adverse events) listed in the table below. The trial doctor or the trial staff will go through the description of the side effects with you. Please ask any questions you might have. In addition to the side effects listed, there is always the risk of developing side effects which are not known at this time.

As of September 2018, BI 655130 has been given to 212 subjects in ongoing and clinically completed trials. BI 655130 was well tolerated. Most reported adverse events were of mild or moderate intensity, but there have also been a small number of patients experiencing severe or serious adverse events in clinical trials. It is unknown whether these adverse events were caused by BI 655130. Overall adverse events observed in subjects who received BI 655130 were comparable to adverse events observed in those who received placebo and no dose-limiting adverse effects were observed.

If you receive the investigational drug, then adverse events may occur which may or may not be caused by BI 655130. Some of those adverse events can be treated. Some side effects may go away when you stop taking the trial medication. Some adverse events can be mild; but others may by more severe, continue for longer or become permanent. Some may be life-threatening or fatal.

All drugs can potentially cause an allergic reaction. Allergic reactions may vary from mild (rash, hives, itching) to severe (which may include difficulty breathing, swelling of the face or throat, low blood pressure, or passing out). A severe allergic reaction requires immediate medical treatment and could result in permanent disability or death. It is important to tell your trial doctor about any past allergic reactions that you may have had to other drugs including antibody drugs (which are usually given into a vein or injection under the skin).

Giving trial medication into your vein may result in an infusion reaction with symptoms such as fever, flushing of the skin, itching, rash or a decrease in blood pressure. If you are receiving trial medication into your vein, your trial doctor will monitor for signs of an adverse reaction while you are getting the drug into your vein.

Infusion reactions typically resolve after stopping or slowing down the infusion, sometimes additional medication is required. If you think you are having an allergic reaction, call the trial doctor right away. If you are having trouble breathing, call <insert regional emergency telephone number>.

Name of Drug	Known Adverse Events or Side Effects
BI 655130	Currently there are no identified side effects of BI 655130. So far, BI 655130 has been tested in healthy volunteers for up to four weeks of dosing and in one trial in patients with generalized pustular psoriasis (GPP) and palmoplantar pustulosis (PPP). BI 655130 was well tolerated and adverse events were mostly mild or rarely moderate. In the four-week-trial in healthy volunteers, headache appeared to be reported more frequently in subjects treated with 20 mg/kg BI 655130 than in the other treatment groups. Two subjects experienced dyspnoea (shortness of breath) only in the 20 mg/kg group. Additionally, diarrhea, nausea, and nasopharyngitis (inflammation of the nose and throat) appeared to occur more often in subjects who received BI 655130 than in subjects who received placebo. There were no severe or serious adverse events. In the trial investigating the effects of BI 655130 in 7 patients with generalized pustular psoriasis, adverse events reported most frequently were arthralgia (joint pain) (3 patients, 42.9%) and eosinophilia (high levels of a certain type of white blood cell), chills, peripheral oedema (swelling caused by too much fluid in the body tissues), pyrexia (fever), upper respiratory tract infection, and eczema (a condition that causes the skin to become inflamed, itchy, red, cracked, and rough) each reported in 2 patients (28.6%). It is not known whether any of these adverse events were caused by BI 655130. There were no severe or serious adverse events. In the trial investigating the effects of BI 655130 in 59 patients with palmoplantar pustulosis, adverse events reported most frequently were nasopharyngitis (inflammation of the nose and throat) and headache. These adverse events occurred with a comparable frequency in patients treated with BI 655130 and placebo. It is unknown, whether BI 655130 caused any of these adverse events. Based on the preceding trials in healthy volunteers and patients with GPP and PPP, no specific drug-related risks are anticipated. The infusion of any protein can result in local or general allergic reactions. These reactions may also occur by administration of BI 655130. Moreover, there is the risk of local infusion site reactions (swelling, warmth, redness and pain at the infusion site). This usually resolves without any treatment, but can be uncomfortable for a few hours or days.

Name of Drug	Known Adverse Events or Side Effects
BI 655130 – cont'd	Infusion reactions have been reported occasionally in the clinical trials using BI 655130; the event was reported in patients treated with placebo and patients treated with BI 655130. As an inhibitor of the immune mediator IL36R (gene), BI 655130 affects a target of the immune (body defense) system which could decrease the body's defense ability against certain types of infection or tumor diseases. However, repeated dose studies in animals at very high doses and also first data from studies in humans do not suggest that inhibition or absence of IL36R would increase the risk for infectious or tumor diseases.

DECLARATION OF INFORMED CONSENT

This page may be revised as appropriate.

Remember: If the consent and the subject information are two separate documents, the consent form must refer to the version and date of the Subject Information form.

TRIAL SUBJECT No.: _____

My signature on this consent form means that:

- I understand that I am being asked to participate in a research trial to test an investigational drug, BI 655130, in patients with a flare-up of Generalized Pustular Psoriasis.
- I have had this trial explained to me by _____.
- I have read, or have had it read to me, each page of this document including its appendices (Appendix A: Visit Schedule, Appendix B: Description of Trial Procedures and Risks, and Appendix C: Known Side Effects (Adverse Events) of the Investigational Drug) Appendix D; Confidentiality / Privacy and Data Sharing (according to local regulations) and the Declaration of Informed Consent and understood all these documents.
- I have had all of my questions answered fully and to my satisfaction.
- I was given sufficient time to think in peace and quiet and decide whether to participate.
- I have been told that my participation is voluntary and I can withdraw at any time without giving any reasons.
- I voluntarily consent to participate in this trial.
- I will be given a signed copy of this consent document for my records.

Name of Trial Subject (*please print*)	**Consent Signature of Trial Subject**	**Date**

STATEMENT OF INVESTIGATOR / TRIAL DOCTOR / STUDY COORDINATOR:

I certify that I have explained to the above individual(s) the nature and purpose of the trial and the possible benefit and risks associated with participation. I have answered any questions that have been raised and the potential trial subject has received a copy of this signed consent document.

I acknowledge my responsibility for the care and well-being of the above trial subject, to respect the rights and wishes of the subject, and to conduct the trial according to applicable Good Clinical Practice guidelines and regulations.

Name of Health Care Professional (*please print*)	**Signature of Health Care Professional**	**Date**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Yes, page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Yes, page 3
	2b	All items from the World Health Organization Trial Registration Data Set	Yes, available at clinicaltrial.gov NCT03782792
Protocol version	3	Date and version identifier	Yes, page 13
Funding	4	Sources and types of financial, material, and other support	Yes, page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Yes, page 14
	5b	Name and contact information for the trial sponsor	Yes, page 14
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	Yes, pages 1, 15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Yes, pages 8, 13
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Yes, pages 5, 6, 7

	6b	Explanation for choice of comparators	Yes, page 9
Objectives	7	Specific objectives or hypotheses	Yes, pages 8, 13
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Yes, pages 8–11
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Yes, page 9 and reported in clinicaltrials.gov
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Yes, pages 8, 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Yes, pages 9, 10, and Figure 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Yes, page 10, and Figure 1
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Yes, pages 4, 10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Yes, page 9, and supplementary files
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Yes, pages 11, 12, Table 1 and supplementary Table 2

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Yes, pages 9, 10, and Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Yes, page 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Yes, page 12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Yes, page 9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Yes, page 9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Yes, page 9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Yes, pages 9, 13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Yes, page 9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Yes, pages 11–14, Table 1 and supplementary Table 2

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Yes, pages 9, 10, and Figure 1
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Yes, page 13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Yes, page 13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Yes, page 13
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Yes, page 13
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Yes, page 12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n.a.
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Yes, page 13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Yes, pages 13, 16
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Yes, page 13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Yes, pages 13, 16, and reported in clinicaltrials.gov
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Yes, pages 12, 16, and supplementary files
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Yes, page 12 and supplementary files
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Yes, pages 16, 17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Yes, page 15
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Yes, pages 16, 17
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	n.a.
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Yes, pages 13, 15, 16, and supplementary files
	31b	Authorship eligibility guidelines and any intended use of professional writers	Yes, page 15
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Yes, pages 15, 16

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Yes, page 16 and supplementary files
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Yes, pages 10, 12

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.