Clinical Trial Protocol

	Document Number:	**c36703857-02**
BI Trial No.	1368-0073	
Project No.	1368-P10	
BI Investigational Medicinal Product(s)	Spesolimab, BI 655130	
Title	Multi-centre, open-label, expanded access trial of spesolimab i.v. in patients with generalized pustular psoriasis (GPP) presenting with a flare	
Lay Title	An Expanded Access trial in Japan to provide spesolimab to people with a flare-up in Generalized Pustular Psoriasis who have no other treatment options	
Clinal Trial Leader	[redacted] Tokyo 141-6017, Japan Telephone: [redacted], Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted], Fax: [redacted]	
Current Version and Date	Final Protocol, version 2.0, 06 Jul 2022	
Original Protocol Date	24 Sep 2021	Page 1 of 58

Unless otherwise noted, the term "clinical trial" in the study protocol will be changed to "post marketing clinical trial" upon marketing approval for spesolimab i.v. for GPP indication in Japan

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	24 Sep 2021
Revision date	06 Jul 2022
BI trial number	1368-0073
Title of trial	Multi-centre, open-label, expanded access trial of spesolimab i.v. in patients with generalized pustular psoriasis (GPP) presenting with a flare
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s)	15 ~ 20 sites in Japan
Trial rationale	Current treatment options for controlling flare of GPP, complete resolution of symptoms and prevention of reoccurrence of flares are limited and often do not provide sustained efficacy. Moreover, as the current treatment options have no reports of randomised double-blind trials, evidence supporting those is limited. Some of standard of care therapies are not suitable for life-long treatment due to their side effect profile and existing contraindications. Spesolimab has the potential to provide rapid and effective treatment to patients with GPP presenting with a flare; therefore, this expanded-access clinical trial will offer an opportunity for patients with no satisfactory therapeutic options early access to the investigational drug spesolimab.
Trial objective(s)	The aim of this trial is to provide early access to the investigational drug spesolimab for patients with GPP presenting with a flare. A secondary aim of this trial is to collect additional data on the safety and tolerability of spesolimab.
Trial endpoints	Primary endpoint: • Occurrence of treatment emergent adverse events (TEAEs) Secondary endpoint: Occurrence of: • Treatment emergent serious adverse events (SAEs) • Treatment emergent adverse events of special interest (AESIs).
Trial design	Single-arm, open-label, active treatment

Number of patients entered	There is no recruitment goal for this expanded access trial
Diagnosis	Patients with GPP presenting with a flare
Main in- and exclusion criteria	Main Inclusion Criteria: • Diagnosis of GPP confirmed based on the JDA guidelines for the management and treatment of GPP • Patient is experiencing a flare, defined as new or worsening of widespread eruption of sterile macroscopically visible pustules, with or without systemic inflammation, as assessed by the investigator Male or female patients, aged 18 to 75 years at time of enrollment.Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial. • No satisfactory authorized alternative therapy exists, as assessed by the investigator. Main Exclusion Criteria: • Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in aspartate transaminase (AST) or alanine aminotransferase (ALT) or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin. • Active systemic infections (fungal and bacterial disease) during the last 2 weeks prior to drug administration, as assessed by the investigator. • Relevant chronic or acute infections, including active tuberculosis (TB), HIV infection or viral hepatitis at the time of drug administration. • History of allergy / hypersensitivity to systemically administered spesolimab or its excipients. • Presence of acute demyelinating neuropathy
BI Medicinal product(s)	Spesolimab
dose	900 mg
method and route of administration	Intravenous (i.v.)
Duration of treatment	Single dose, with the potential for a second dose one week after initial infusion, if deemed necessary by the investigator
Statistical methods	Exploratory descriptive statistics of demographic and safety data will be presented as appropriate

FLOW CHART

Trial Period	Screening	Treatment	Follow-up Period			
Visit	**V1[1]**	**V2[1]**	**V3**	**V3-2[4]**	**V4**	**V5/ EoS[2]**
Week			**1**	**2**	**4 / 5[4]**	**16 /17[4]**
Day		**1***	**8**	**15**	**29 / 36[4]**	**113 / 120[4]**
Window			±1d	±3d	±7d	±7d
Informed consent	X					
Infection testing[6]	X					
Demographics	X					
Medical history	X					
Physical examination	X	X[7]	(X)[5]	(X)[5]	(X)[5]	(X)[5]
Vital signs	X	X[7]	(X)[5]	(X)[5]	(X)[5]	(X)[5]
Pregnancy test[8]	X[S]					
Safety laboratory tests (Local lab)[9]	X	(X)[5, 7]	(X)[5]	(X)[5]	(X)[5]	(X)[5]
Review of in-/exclusion criteria	X	X[7]				
IRT transaction	X	X	X[3]			
Dispense/administration study drug		X	X[3]			
Adverse events	X	X[7]	X	X	X	X
Concomitant therapy	X	X[7]	X	X	X	X
Study Completion						X

EoS, end of study; IRT, Interactive Response Technology; V, Visit.

***The day of first study drug administration = Day 1. All subsequent study Days are counted from this Day 1.**

1: Visit 1 and Visit 2 can be on the same day if required (see also footnote 7).
2: Should a patient prematurely discontinue from the treatment, every effort should be made to keep the patient in the trial and complete all of the remaining study visits. If a patient is not willing to follow the whole visit schedule, the EOS Visit (Visit 5) should be conducted at 16 weeks after the last spesolimab administration at a minimum. If patients refuse to return to the study site, early EoS visit should be completed at the timing of prematurely discontinuation and then at least safety information should be collected by phone at 16 weeks after the last spesolimab administration.
3: In case of persistent flare symptoms after a single infusion of spesolimab, a second IV dose can be administered at Visit 3 (Day 8). When a second dose is administered at investigator's discretion, IRT call is required at Visit 3 and all procedures/measurements listed for Visit 3 should be performed prior to dosing.
4: If patients receive a second i.v. dose of spesolimab at Visit 3 (Day 8), additional visit (Visit 3-2) is required at Day 15 and Visit 4 and Visit 5 (EoS) should be shifted by 1 week, i.e. Visit 4 at Week 5 and Visit 5 at week 17.
5: Physical examination, vital signs and safety laboratory test shown with parentheses "(X)" are optional and will be performed according to standard clinical practice and when deemed appropriate by the investigator.
6: Infection testing includes tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see Table 5.2.3:1).
7: These procedures do not need to be repeated/performed when V1 and V2 are performed on the same day.
8: Only applicable for women of childbearing potential. S – serum pregnancy test.
9: Safety laboratory tests at screening visit (Visit 1) include liver function test, haematology test, infection screening test and if a woman of childbearing potential, pregnancy test, and will be performed locally. Please refer to Section 5.2.3 for further details.

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ABBREVIATIONS AND DEFINITIONS

ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
AGEP	Acute Generalized Exanthematous Pustulosis
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
AUC_{0-tz}	Area Under the Curve
BI	Boehringer Ingelheim
CA	Competent Authority
CDC	Complement-dependent cytotoxicity
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, (sometimes referred to as “eCRF”)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
DEDP	Drug exposure during pregnancy
DILI	Drug Induced Liver Injury
DLQI	Dermatology Quality of Life Index
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
EAP	Expanded Access Program
ECG	Electrocardiogram
EOS	End of Study
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue
FcR	Fc Receptor

FDA	Food and Drug Administration
FIH	First in human
GBS	Guillain-Barré syndrome
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPP	Generalized Pustular Psoriasis
GPPASI	Generalized Pustular Psoriasis Area and Severity Index
GPPGA	Generalized Pustular Psoriasis Pysician Global Assessment
GPSP	Good Psot-Marketing Study Practice
GOT	Glutamic-Oxaloacetic Transaminase
GPT	Glutamic-Pyruvic Transaminase
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
i.v.	intravenous
IB	Investigator's Brochure
IC	Inhibitory concentration
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL	Interleukin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITE	Indirect Target Engagement
JDA	Japanese Dermatological Association
KO	Knock Out
LDH	Lactate Dehydrogenase
LPLT	Last Patient Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities

MIP	Macrophage Inflammatory Protein
NCI	National Cancer Institute
NF-κB	Nuclear Factor kappa B
NOAEL	No-Observed Adverse Effect Level
OPU	Operative Unit
PK	Pharmacokinetics
PSS	Psoriasis Symptom Scale
RBC	Red Blood Cell
RCTC	Rheumatology Common Toxicity Criteria
REP	Residual Effect Period
SAE	Serious Adverse Event
SD	Standard Deviation
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TMDD	Target-Mediated Drug Disposition
TNF	Tumour necrosis factor
TS	Treated Set
ULN	Upper Level of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Generalized pustular psoriasis (GPP) is a rare, neutrophilic skin disease characterised by episodes of widespread eruption of sterile, macroscopically visible pustules that can occur with or without systemic inflammation (R17-3403, R19-1562). The clinical course of GPP is heterogeneous and can be characterised as a relapsing disease with recurrent flares, or a persistent disease with intermittent flares (R17-3403, R19-1562). It is distinct from plaque psoriasis in clinical presentation, pathophysiology, histopathology, response to therapies, epidemiology and genetics, although over 65% of patients with GPP may have concurrent plaque psoriasis (R16-1463, R16-0933, R18-2717, P19-10261). GPP has varied prevalence across geographical regions, with estimates ranging from 1.76 per 1,000,000 persons in France to 5 per 10,000 persons in Germany (R16-2698, R18-1635). It is more prevalent in females than males (R16-0933).

Untreated GPP is potentially life-threatening. GPP flares, which are often accompanied by systemic symptoms (extreme fatigue, high fever, peripheral blood neutrophilia, and acute phase response and sepsis), have a risk of rapid deterioration (R16-0933, R16-2698, R20-2767). If inflammation is not controlled quickly, there is sloughing of the skin leaving the body unprotected from external pathogens, resulting in bacteremia and inability to prevent the leakage of essential proteins and electrolytes. The consequence is hypoalbuminemia, peripheral edema, hypovolemic and/or septic shock, with shut down of hepatic and renal function. The morbidity and mortality without supportive care is substantial. Rapid and complete resolution of the skin symptoms (i.e. pustules) and systemic inflammation, and thus to shorten the duration of the flares, is key in the management of GPP flares to reduce negative outcomes. GPP flares are associated with a mean duration of hospitalization of 10 days (range 3–44 days) (R16-0933). Mortality rates attributed to GPP or its treatment are reported to be 2–16% (R16-0933, R16-2698, R20-2767, R17-3605).

Patients with GPP also suffer considerable chronic clinical burden. GPP is a systemic disease that can involve extracutaneous manifestations, including osteoarthritis, uveitis, acute respiratory distress syndrome and cardiovascular shock (R18-2717), often resulting in high concomitant medication usage (R20-3140, R20-2784). As a result of both chronic and acute effects, patients with GPP suffer from a substantial impact on quality of life (R20-2784, R20-1405, R18-1890).

Current treatment options for controlling a GPP flare and maintenance of response are limited and do not provide sustained efficacy (R16-0933). There are no treatments approved specifically for GPP in the US or centrally approved in the EU. In Japan, biologics, including TNF inhibitors (adalimumab, infliximab, and certolizumab pegol), IL-17 inhibitors (secukinumab, brodalumab, and ixekizumab), and IL-23 inhibitors (risankizumab and guselkumab), are approved for treatment of GPP. Approval of these treatment options for GPP in Japan was not based on randomised clinical trials in GPP but on evidence from small (<12 patients), open-label, single-arm trials only, which assessed efficacy at late time points (mostly at Week 12 or Week 16). Response to flare treatment was not evaluated in these trials

and complete pustule and/or skin clearance not demonstrated (R16-1462, R17-3600, R17-3604, R18-2719, R18-2720, R19-1562, R20-1400, R20-2770).

Management guidelines and recommendations for the treatment of GPP generally recommend cyclosporine, retinoids, infliximab or methotrexate as first-line therapies, based on case study reports (R19-1562, R17-3600) and practice for the management of plaque psoriasis. However, long-term use of these treatments is limited owing to side effects and contraindications (retinoids: teratogenicity, severe renal and hepatic dysfunction, ossification abnormalities, pseudotumor cerebri, hair loss; cyclosporine: excessive hair growth, renal toxicity, lymphoma, severe hepatic dysfunction; methotrexate: liver and bone marrow toxicity, lymphoma, hematologic suppression, severe skin reaction, fatal dosing errors). Some of these side effects, such as hair loss, excessive hair growth, and teratogenicity, particularly limit the use of these treatments in women, who are disproportionately affected by GPP. In addition to safety concerns, there is evidence that current treatment options are not optimal. An analysis of 60 patients diagnosed with GPP and enrolled in the Corrona Psoriasis Registry indicated that 35% of patients previously received 1 biologic medication and 25% received 2 or more biologics. This suggests that some patients are cycling through medications in order to find a treatment that provides acceptable control. For patients currently on biologics, the most cited reason for discontinuation of the previous medication was lack of efficacy [data on file].

GPP flare is a severe, life-threatning disease. There are limited treatment options, with available therapies lacking evidence for effectiveness, and no therapies specifically available for the rapid management of flares. As such, there is substantial need for a highly effective treatment that rapidly and sustainably clears pustules and skin manifestations as well as associated systemic symptoms, with a favourable safety profile, in patients with GPP presenting with a flare.

[redacted] *signalling in GPP*

[redacted] is a member of the IL-1 family of cytokines and includes the isoforms [redacted] receptor antagonist [redacted] (R20-2760), which are expressed at high levels in epithelial cells (R18-2717, R20-1386, R16-2297). Dysregulated [redacted] signalling promotes the infiltration of neutrophilic granulocytes into the epidermis, leading to the formation of sterile pustules.

The overexpression of [redacted] or a loss-of-function mutation in the gene encoding [redacted] (*IL36RN*) are central to the pathogenesis of GPP (P19-10261, R14-5158). Such loss-of-function mutations have been identified in patients with GPP, in addition to mutations in other genes associated with the [redacted] pathway, including [redacted] (R14-5158, R16-0929, R16-0928, R20-2761). Notably, mutations in [redacted] are associated with an earlier age of onset of GPP and more severe disease ((R18-2717). Furthermore, biomarker analysis of skin biopsies from GPP lesions demonstrates significantly increased levels of all [redacted] isoforms versus non-lesional skin ((R18-2717).

In summary, there is strong genetic link between the [redacted] signaling pathway and GPP, with experimental data identifying [redacted] as the dominant cytokine driving GPP (R17-3602).

Therefore, there is a strong scientific rationale to support that inhibition of [redacted] signaling with the humanized anti-[redacted] antibody spesolimab would be beneficial in treatment of GPP.

1.2 DRUG PROFILE

1.2.1 Mode of action

Spesolimab is a humanized monoclonal IgG1 antagonistic antibody that blocks human [redacted] signaling. Binding of spesolimab to [redacted] is anticipated to prevent the subsequent activation of [redacted] and downstream activation of proinflammatory and pro-fibrotic pathways. The aim is to reduce epithelial cell / fibroblast / immune cell-mediated inflammation and interrupt the inflammatory processes that drive pathogenic cytokine production in inflammatory diseases, including GPP.

Key pharmacokinetic characteristics
Spesolimab has been characterized by typical IgG1 monoclonal antibody pharmacokinetics. PK data showed that exposure increased with increasing dose in a dose proportional manner from 0.3 mg/kg to 20 mg/kg following i.v. administration of spesolimab to healthy volunteers. The half-life of spesolimab was approximately four weeks in the linear dose range in healthy volunteers and approximately three weeks in patients with GPP. PK data suggest target-mediated drug disposition (TMDD) kinetics for spesolimab at doses lower than 0.3 mg/kg. Comparing the exposures between the 300 mg SC dose and 300 mg i.v. dose, a SC bioavailability of ~70% was determined. No differences in PK were observed between Caucasian and Japanese subjects.

Residual Effect Period
The Residual Effect Period (REP) of spesolimab is 16 weeks. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.

1.2.2 Nonclinical pharmacology

Preclinical studies
Spesolimab binds to [redacted] with a binding avidity of less than 1 pM. Spesolimab inhibits [redacted] activation in transformed epithelial cells as well as primary human keratinocytes, dermal fibroblasts and intestinal myofibroblasts, with IC90 values in a consistent range of 0.7 to 3.7 nM. Spesolimab also inhibits IL-8 release and IFNγ secretion in vitro. Mutations of two key residues (L234 and L235) to alanine were made to spesolimab to abrogate FcR binding activity and function. Direct assessment of the impact of the mutations in the IgG1 FcR binding sites on both antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) effector functions revealed that the mutations abrogate both ADCC and CDC effector functions and indicate that spesolimab will be a non-depleting therapy in vivo.

Toxicology studies
Spesolimab [redacted] in species commonly studied for toxicological evaluation. Therefore, meaningful toxicity studies of spesolimab itself cannot be performed

in any animal species. However, in i.v. toxicity studies of up to 26 weeks in duration in mice, no adverse effects of [redacted] antagonism were seen, using a surrogate mouse antibody that closely resembles the human antibody, at a dose that was 5-fold higher than the dose that was protective in an experimental mouse colonic inflammation model. In the 26-week toxicity study, male and female mice (20–30/sex/group at 0, 10 and 50 mg/kg/day) were administered the surrogate monoclonal antibody twice weekly for 26 weeks by intravenous injection via the caudal vein. There were no test article-related changes in clinical observations, body weights, food consumption, ophthalmology, clinical pathology parameters (haematology, clinical chemistry), organ weights, macroscopic or microscopic examinations. The no-observed-adverse-effect level (NOAEL) was considered to be 50 mg/kg/day. The in vitro cytokine release and tissue cross-reactivity assays demonstrate that the risk of transient cytokine release in humans is low and that, as expected, spesolimab stains epithelium in a variety of tissues. There were no signs of local irritation after single, 1 mL injections of the subcutaneous formulation in rabbits. These preclinical toxicology data support chronic spesolimab dosing in humans. In addition, a characterisation of individuals with homozygous [redacted] loss-of-function mutations revealed that normal immune function was broadly preserved, and that the medical history of these individuals showed no increased risk of infections or malignancies. These data suggest that [redacted] signalling pathway inhibition may not substantially compromise host defences (R17-3632).

1.2.3 Clinical experience

In the first-in-human (FIH) study (1368.1), spesolimab or placebo were administered to 78 healthy adult volunteers, with 58 subjects assigned to single ascending [redacted] subjects assigned to placebo. Safety and tolerability of all tested i.v. doses was good. There were no SAEs. AEs categorised as related to treatment were observed in [redacted] subjects in the placebo group and in [redacted] subjects treated with spesolimab. The most frequent treatment-emergent AEs were [redacted] here were two AEs of moderate intensity [redacted], all remaining AEs were of mild intensity. There were no serious AEs, no AEs that led to discontinuation of trial drug, no protocol-specified AEs of special interest and no other significant AEs according to ICH E3. No relevant changes were observed in safety laboratory tests, vital signs, and electrocardiograms (ECGs). Importantly, there were no relevant differences in frequencies of subjects with treatment-emergent AEs between the treatment groups, and no dose dependency was observed.

PK analysis showed that exposure ($AUC_{0\text{-}tz}$ and C_{max}) to spesolimab increased with increasing dose in an approximately dose-proportional manner from [redacted] The effective half-life of spesolimab is approximately 4 weeks in the linear dose range. Overall, PK data so far suggests TMDD kinetics for spesolimab. Anti-drug antibodies (ADA) were detected in nine subjects (eight subjects receiving spesolimab and one subject receiving placebo), three of whom had preexisting levels. Pharmacodynamic effects in this FIH single rising dose trial were assessed by indirect target engagement (ITE) of [redacted] by spesolimab using an ex-vivo whole blood stimulation assay (c09985235-01). The analyses indicate for doses of [redacted] and above, the percent inhibition of [redacted]

[redacted] was at least [redacted] compared with baseline during the entire time course up to [redacted].

In a multiple rising dose trial (1368.2), spesolimab or placebo have been administered to healthy adult volunteers at multiple ascending i.v. doses of [redacted] given weekly for [redacted] or a [redacted]. Overall, multiple [redacted], as well as single and multiple doses of [redacted] were found to be safe and well tolerated by the healthy male subjects in this trial. The incidence and intensity of drug-related AEs appeared to be [redacted] dose spesolimab treatment group than in [redacted], mainly driven [redacted]. No dose-dependent AEs or other clinically relevant changes in safety laboratory tests, vital signs, or ECG were observed (c03320877).

The open-label, single group phase I study trial (1368.11) was conducted to investigate the safety, tolerability, PK and efficacy of a [redacted] with a GPP flare. The [redacted] in GPP was achieved in these patients who showed rapid clinical responses to single administrations of spesolimab. Five of these seven patients became clear or almost clear of GPP [redacted] after the infusion, and all of them reached this status [redacted] after treatment. Within [redacted] of treatment, pustules were completely cleared in [redacted] patients. The early response in the skin was also accompanied by an early response in systemic components, with [redacted] approaching normalization within [redacted]. A major improvement in GPPASI was observed in all patients very early with a mean (SD) percent change from baseline of [redacted], all of which were also sustained through [redacted]. All patients reported at least one AE, but none was severe, serious, led to discontinuation, or considered significant. AEs in four patients were considered drug-related. The most frequently reported treatment-emergent AE was [redacted]. There were no clinically relevant laboratory or vital sign abnormalities (c03320877, P19-01888).

The multicenter, randomized, placebo-controlled, double-blind Phase II Effisayil-1 study (1368-0013, ClinicalTrials.gov identifier: NCT03782792) was conducted to evaluate the efficacy and safety of a [redacted] spesolimab compared with placebo in [redacted] with GPP presenting with a flare. Baseline demographic and disease characteristics were generally balanced between arms. At randomization, [redacted], and most patients had a [redacted], and highly impaired quality of life and clinical burden as indicated by DLQI, pain VAS, FACIT-Fatigue and PSS.

[redacted] GPPGA total score of 0 or [redacted] was achieved in [redacted] randomized to

spesolimab versu [redacted] Clinical responses were observed regardless of [redacted] mutation status. At week [redacted] Additionally, significantly higher reductions in pain [redacted] and improvement in [redacted] at [redacted] were achieved by patients receiving spesolimab versus those receiving placebo.

At day [redacted] randomized to spesolimab received an open-label [redacted] spesolimab. Beyond [redacted], response rates in patients in the spesolimab arm who received one or two doses continued to increase. A total o [redacted] These were sustained in at least [redacted]. The median percent improvement in the GPPASI score from baseline was [redacted]. A GPPASI 75 was achieved in [redacted] Rapid reductions in pain VAS score and improvements in DLQI scores were achieved through [redacted] and sustained through [redacted] in patients with elevated baseline [redacted], who received one or two doses of spesolimab.

At [redacted], respectively, had an AE. The most common AE was [redacted], respectively. [redacted] was reported in [redacted] of the patients receiving spesolimab or placebo, respectively. [redacted] were reported in [redacted] of patients in the spesolimab and placebo groups, respectively. SAE were reported in [redacted] of patients in the spesolimab and placebo groups, respectively.

At week [redacted], including those who received [redacted] at day [redacted]. Symptoms observed in two patients receiving spesolimab were reported [redacted] and in close [redacted], which was two days after treatment in one case. Both patients received concomitant [redacted] in one patient, and [redacted] in the other.

Anti-drug antibodies (ADAs) were [redacted], with cumulative rate of [redacted]. Formation of ADAs did not affect the primary and secondary efficacy endpoints [redacted]. If ADAs developed, re-treatment of recurring flares with spesolimab i.v. was still efficacious even in the presence of high ADA titers. For safety, no association between immunogenicity and safety was observed, i.e. there was no indication for an association of ADA titers and hypersensitivity events, even against a high ADA titer background. Of note, it was shown that additional i.v. administration can be made without induction of systemic hypersensitivity reactions while achieving complete pustular clearance.

From Effisayil-1, [redacted] continued treatment with spesolimab as part of the ongoing longer-term follow-up study 1368-0025 (ClinicalTrials.gov identifier NCT03886246).

Spesolimab has also been assessed in multiple additional phase I and II studies, supporting the PK and safety data. Safety, tolerability and pharmacokinetics using single rising intravenous dose and single subcutaneous dose of spesolimab was assessed in healthy Japanese male volunteers (double-blind, randomised, placebo-controlled design) (1368.9) and included 24 patients who received spesolimab; two bioavailability trials (1368.3 and 1368.29) enrolled 82 patients to receive spesolimab; and four trials (1368.15, 1368.32, 1368.4 and 1368.5) enrolled patients with active disease (palmoplantar pustulosis, atopic dermatitis, and ulcerative colitis), in which 145 patients (across all four trials) received spesolimab. In all trials, spesolimab was generally well tolerated and no safety signals were identified. Most reported AEs were of mild or moderate intensity, although there have also been a small number of patients experiencing severe or serious AEs in clinical trials. It is unknown whether these AEs were caused by spesolimab. Overall AEs observed in subjects who received spesolimab were comparable to AEs observed in those who received placebo and no dose-limiting adverse effects were observed.

Chronic administration of spesolimab is being evaluated with a subcutaneous formulation in an ongoing 5-year open-label extension and the prevention of flares trial Effisayil 2 (ClinicalTrials.gov identifiers: NCT03886246 and NCT04399837).

Please refer to the current version of the Investigator's Brochure (c03320877) for complete and updated information on spesolimab in GPP and other diseases under study.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Current treatment options for controlling flare of GPP, complete resolution of symptoms and prevention of reoccurrence of flares are limited and often do not provide sustained efficacy. Moreover, as the current treatment options have no reports of randomised double-blind trials, evidence supporting those is limited.
Some of standard of care therapies are not suitable for life-long treatment due to their side effect profile and existing contraindications.

The Effisayil-1 trial demonstrated that treatment of GPP flares with spesolimab was associated with unprecedented rapid pustular and skin clearance, as well as improvements in systemic symptoms and quality of life, with a favourable benefit–risk profile.

Spesolimab has the potential to provide rapid and effective treatment to patients with GPP presenting with a flare; therefore, this EAP will provide access to the investigational product spesolimab to patients suffering from this serious and potentially life-threatening condition without alternative satisfactory treatment options and not able to be enrolled in a clinical trial.

1.4 BENEFIT - RISK ASSESSMENT/ MEDICAL NEEDS STATEMENT

Spesolimab is an anti-IL-36R antibody with high clinical activity to block IL-36R signaling as shown in patients with GPP, a severe inflammatory skin disease driven by uncontrolled IL-

36 activity. The results from the pivotal phase II Effisayil-1 trial suggest that treatment of flare in patients with GPP with spesolimab is associated with rapid and sustained pustular and skin clearance. Improvement in systemic markers supports the beneficial effect of spesolimab on both skin and systemic components of the disease. The overall treatment effect was sustained over time and correlated with improvement in PROs (e.g. pain, fatigue) and quality-of-life measures.

No other IL-36 receptor antagonist is currently approved to provide information on identified risks in molecules of this class.

The risks shown in the table below (Table 1.4: 1) are derived from general safety considerations of immunomodulatory drugs in clinical development and data generated for spesolimab to date.

Table 1.4: 1 Risks associated with spesolimab administration

Risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Drug-induced liver injury (DILI)	Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, DILI is considered as a standard risk in all BI development trials.	Patients with hepatic impairment will be excluded from the trial. In case of suspicion of DILI during the trial (refer to Section 5.2.4.1.4) patients need to be followed according to a detailed checklist to ensure adequate follow-up and patient safety. DILI is defined as an AESI.
Systemic hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of immediate (such as anaphylaxis) or delayed (such as drug reaction with eosinophilia and systemic symptoms) adverse immune reactions.	Patients with a history of allergy/hypersensitivity to spesolimab or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of spesolimab, the investigator should consider, in accordance with severity of the reaction and local standard of care, interruption of therapy and treatment of the condition. Systemic hypersensitivity reaction is defined as an AESI. It is subject to close monitoring and investigators are requested to assess these conditions using the criteria discussed in the statement paper from Sampson et al. [R11-4890].

Table 1.4: 1 Risks associated with spesolimab administration (cont.)

Risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections. In clinical trials with spesolimab, a higher proportion of patients with mild to moderate infections was seen in the spesolimab treatment group than in the placebo treatment group. Nevertheless, there was no indication of an increased frequency of patients with severe, serious, and opportunistic infections in association with spesolimab treatment. A recent characterisation of individuals with homozygous *IL36R* KO mutations revealed that normal immune function was broadly preserved, suggesting that IL36 signalling pathway inhibition may not substantially compromise host defenses [R17-3632].	Patients with any relevant chronic or acute infections including HIV, viral hepatitis or active tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standard of care. Severe infections and opportunistic infections are considered AESI for this trial. These conditions and serious infections are subject to close monitoring.

Table 1.4: 1 Risks associated with spesolimab administration (cont.)

Risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Malignancies	Inhibition of the immune response with an immunomodulatory drug may potentially impair immune defences and thus theoretically decrease immune defence against malignancies. A recent characterisation of individuals with homozygous *IL36R* KO mutations revealed that normal immune function was broadly preserved, suggesting that IL36 signalling pathway inhibition does not compromise host defences [R17-3632].	Patients with a recent (within 5 years) history of malignancy will be excluded from participation in this trial except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix. In case of occurrence of malignant neoplasm, other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with spesolimab. Diagnostics and treatment will be initiated according to local standard of care. Malignancies always represent SAEs and are subject to close monitoring.

Table 1.4: 1 Risks associated with spesolimab administration (cont.)

Risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Peripheral Neuropathy	Three cases reported by the investigator as Guillain-Barré syndrome (GBS) were received in ongoing clinical trials with spesolimab. A panel of independent neurologists and experts in the study of neuropathies assessed the 3 cases. Only 1 met level 4 diagnostic certainty for the diagnosis of GBS (lowest level on Brighton scale of 1 to 4). In that case, there was a coincident infection with SARS-CoV-2. The other 2 cases were assessed as not GBS. Observed cases showed a heterogenous pattern. A causal association to spesolimab to any of the reported cases was assessed to be unlikely. As per assessment by the panel of external neurologists the nonspecific symptoms and findings in all three cases may best be referred to as peripheral neuropathy.	Timely detection, evaluation, and follow-up of suspected peripheral neuropathies to ensure patients´ safety. Use of dedicated questions to elicit neurologic history during screening and exclusion criteria to avoid selection of patients with acute demyelinating neuropathy. Targeted Follow up questions to gather detailed information in case of any event during trial to ensure proper decision making. Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.

Other risks related to trial-specific procedures include blood sampling and i.v. infusion of study medication, which can cause local bruising, inflammation, nerve damage and pain.

Based on the findings in nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of Women of Child Bearing Potential (WOCBP) in this trial is justified. To minimize the risk of unintentional exposure of an embryo or foetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing and contraceptive methods described in the protocol.

Benefit–risk assessment in context of COVID-19 pandemic for patients receiving the investigational product spesolimab
A thorough assessment based on the data available as of 29 April 2021 has been conducted to evaluate whether spesolimab may pose a higher risk associated with COVID-19 infection. Additionally, the general risk of COVID-19 infection in context of the trial population's underlying disease and common co-morbidities was assessed. The key aspects of the assessment are summarized below.

Spesolimab is an immune-modulating humanized monoclonal antibody that blocks the human IL-36 receptor and thereby the pro-inflammatory IL-36 pathway. As reflected in table 1.4:1 above and the patient informed consent form, similar to other immune modulating biological treatments, spesolimab may potentially increase the risk of infections. Available non-clinical and clinical data (see Spesolimab Investigators Brochure Version 9) have not shown an increased frequency of patients with severe, serious and opportunistic infections with spesolimab treatment. However, a higher proportion of patients with mild to moderate infections was seen in the spesolimab treatment group than in the placebo treatment group. Therefore, risk mitigation measures, such as exclusion of patients with increased risk of infections, close monitoring of adverse events, as well as guidance on treatment and handling of acute infections occurring during the trial have been included within this EAP protocol.

As with any other acute infection, a suspected or diagnosed COVID-19 infection should be treated according to the standard of care and interruption of study medication should be considered.

Currently, information about the immune response in patients with COVID-19 is sparse and inconclusive. There are some reports suggesting high levels of pro-inflammatory cytokines in severe cases, with much of the morbidity associated with coronavirus infection potentially related to immune activation and inflammation. To date, there is no reliable evidence suggesting a link between SARS-CoV-2 infections and the IL-36 pathway targeted by spesolimab. Considering the current knowledge of COVID-19 and the implemented risk mitigation measures addressing the potential risk of infections, patients receiving the investigational product spesolimab are not believed to be at higher risk of COVID-19 owing to their background or concomitant diseases. Protocol-defined procedures do not impose undue risk to trial participants.

The benefit–risk assessment of spesolimab remains favourable in the context of the COVID-19 pandemic. Patients receiving the investigational product spesolimab are expected to benefit from treatment and interruption of treatment may worsen their disease. Published guidance for the use of biologics during the COVID-19 pandemic recommends to continue treatment with biologics (e.g. NICE COVID-19 rapid guideline: severe asthma (R20-2257), American College of Allergy, Asthma & Immunology (R20-2258), and National Psoriasis Foundation (R20-2256)). In line with this guidance no systematic testing for SARS-CoV-2 is required to be performed in this trial. However, the investigator may choose to perform the testing as per his or her discretion if useful based on individual medical consideration and in the case of suspected COVID-19 infection.

To address potential risks associated with operational aspects related to the participation in this EAP in context of COVID-19 pandemic, the following risk mitigation measures are to be considered based on local requirements and development of pandemic.

Every subject or patient will be assessed thoroughly, and individual benefit–risk assessments are made prior to trial enrolment and during the trial by the investigator with respect to SARS-CoV-2 infection. As with any other acute infection, a suspected or diagnosed COVID-19 infection should be treated according to the standard of care and interruption of spesolimab should be considered. In case of a confirmed infection, spesolimab should not be administered and appropriate measures for monitoring, treatment and quarantine will be implemented. The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all such aspects, the investigator will determine each patient's (continued) participation in the planned trials. BI as the sponsor, where required, will support the investigator in their decision making. It is acknowledged that the investigator may decide to implement protocol deviations to protect the safety, wellbeing, and/or best interest of the patient. The patient may be eligible for spesolimab treatment following recovery from a SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.

BI is supportive of allowing approved COVID-19 virus vaccines in patients/subjects enrolled in BI clinical trials, in line with local recommendations/guidance and approved labels. Immunocompromised individuals may still receive COVID-19 vaccination if they have no contraindications to vaccination. However, they should be counseled (note: by the investigators) about the unknown vaccine safety profile and effectiveness in immunocompromised populations, as well as the potential for reduced immune responses and the need to continue to follow all current guidance to protect themselves against COVID-19.

Considering that GPP flares constitute a serious and potentially life-threatening condition, and the fact that currently used treatments have limited evidence supporting efficacy and safety, the potential benefit of spesolimab for the treatment of flares in adult patients with GPP is considered to outweigh the potential risks, therefore justifying providing expanded access to patients suffering from this condition.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The aim of this trial is to provide early access to the investigational drug spesolimab for patients with GPP presenting with a flare. A secondary aim of this trial is to collect additional data on the safety and tolerability of spesolimab.

2.1.2 Primary endpoint

Occurrence of treatment emergent adverse events (TEAEs)

2.1.3 Secondary endpoint

Occurrence of:

- Treatment emergent serious adverse events (SAEs)
- Treatment emergent adverse events of special interest (AESIs).

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is an open-label, multi-centre, single-arm trial, designed to provide early access to spesolimab, for patients with GPP presenting with a flare and for whom no satisfactory authorised alternative therapy exists and who are unable to participate in a clinical trial, as assessed by the investigator.

After signing informed consent and if all eligibility criteria are met, patients will receive a single dose of 900 mg spesolimab. If deemed necessary by the investigator (i.e. if the flare symptoms persist), a second dose of 900 mg spesolimab may be administered one week after the initial infusion.

If only one single dose is administered, then patients will visit the investigator approximately at week 1, week 4 and week 16. If a second dose may be given, then the dates that patients will visit the investigator is changed to approximately at week 1, week 2, week 5 and week17 after initial dose of spesolimab. Please refer to section 6.1 for details on the trial visit procedures. Patient's participation in the trial will end after conclusion of the 16-week follow-up period after the last infusion / drug administration.

If a patient experiences a new GPP flare (following the resolution of a previous flare with spesolimab treatment) after the 16-week follow-up period the patient may re-enter in the trial and be treated again with spesolimab, providing eligibility criteria are still met and the overall trial is still running. The same dosing and follow-up requirements apply as for the previous flare.

In the situation that a patient experiences a new GPP flare within the 16-week follow-up period and the physician wishes to treat this new flare with spesolimab, eligibility needs to be assessed and agreed upon with the BI clinical team.

Sponsor will inform clinial sites of the deadline of patient enrolment for the trial when spesolimab receives marketing authorization for GPP treatment.

3.2 SELECTION OF TRIAL POPULATION

3.2.1 Main diagnosis for trial entry

At screening, the diagnosis of GPP is based on the criteria of the JDA guidelines for the management and treatment of GPP. (R19-1562). These diagnosis criteria include:

- Systemic symptoms such as fever and fatigue;
- Systemic or extensive flush accompanied by multiple sterile pustules that sometimes merge to form lakes of pustule;
- Neutrophilic subcorneal pustules histopathologically characterized by Kogoj's spongiform pustules;

- The above clinical and histological features recur repeatedly. However, the diseases mentioned below can be excluded from initial-onset cases.
  Subcorneal pustular dermatosis or pustular drug eruptions (including AGEP)
- For a GPP patient with first episode, skin biopsy is to be taken prior to receving IMP treatment and histopathological result (findings of Kogoj's spongiform pustules) will be confirmed retrospectively.

Participation in this trial will be available to patients with GPP who meet the eligibility requirements specified in section 3.2.2 and section 3.2.3. Owing to the nature and objectives of this trial, no recruitment goals or limits apply.

Patients previously enrolled in this trial presenting again with a new episode of a GPP flare must be re-evaluated and meet eligibility criteria to receive new treatment with spesolimab.

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

A log of all patients enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with investigational drug or not.

If retrospectively it is found that a patient has been entered in error (=did not meet all inclusion criteria or met one or more exclusion criteria), the sponsor or delegate should be contacted immediately. Based on an individual benefit-risk assessment a decision will be made whether continued trial participation is possible or not.

3.2.2 Inclusion criteria

1. Diagnosis of GPP confirmed based on the JDA guidelines for the management and treatment of GPP.
2. Patient is experiencing a flare, defined as new or worsening of widespread eruption of sterile macroscopically visible pustules, with or without systemic inflammation, as assessed by the investigator.
3. Male or female patients, aged 18 to 75 years at time of enrollment. Women of childbearing potential (WOCBP)[1] must be willing and able to use a highly effective method 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 list of contraception methods meeting these criteria is provided in the patient information.
4. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial.
5. No satisfactory authorised alternative therapy exists, as assessed by the investigator.

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal 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.

3.2.3 Exclusion criteria

1. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
   a) Women who stop nursing before study drug administration do not need to be excluded from participating; they should refrain from breastfeeding for 16 weeks after the last spesolimab infusion.
2. Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold ULN elevation in AST or ALT or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin.
3. Active systemic infections (fungal and bacterial disease) during the last 2 weeks prior to drug administration, as assessed by the investigator.
4. Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency (e.g. HIV), past organ or stem cell transplantation), as assessed by the investigator.
5. Relevant chronic or acute infections, including active tuberculosis (TB), HIV infection or viral hepatitis at the time of drug administration.
   a) Patients should be evaluated for TB infection prior to initiating treatment with spesolimab.
   b) Anti-TB therapy should be considered, in accordance with local guidelines, prior to initiating spesolimab in patients with latent TB or a history of TB.
6. History of allergy / hypersensitivity to systemically administered spesolimab or its excipients.
7. 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.
8. Immediate life-threatening flare of GPP requiring intensive care treatment according to the investigator's judgement. Life-threatening complications include cardiovascular / cytokine driven shock, pulmonary distress syndrome, or renal failure.
9. Patients who must or wish to continue the intake of restricted medications (other IL-36R inhibitors, live vaccinations, or IL-1R/IL-1 inhibitors, see section 4.2.2.1) or any drug considered, in the judgement of the investigator, likely to interfere with the safe conduct of the study.
10. 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), or eligible to participate or participating in an ongoing actively accruing clinical trial with spesolimab in the treatment of GPP.
11. A disease or condition that in the opinion of investigator may put the patient at risk because of participation in this trial or limit the patient's ability to participate in this trial.
12. Presence of acute demyelinating neuropathy.

3.2.4 Discontinuation / withdrawal of patients from trial

Patients may discontinue trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.2.4.1 and 3.2.4.2 below.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Section 5.2.4.2).

3.2.4.1 Discontinuation of trial medication and assessment

An individual patient will discontinue treatment if:

- The patient wants to discontinue trial treatment. The patient will be asked to explain the reasons but has the right to refuse to answer.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, the safety of the patient cannot be guaranteed as he / she is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the safety of the investigational medicinal product.
- The patient can no longer receive treatment for medical reasons such as surgery, adverse events, other diseases, or pregnancy.
- If a DILI alert (as defined in Section 5.2.4.1.4) is detected without identification of an alternative cause in the work-up according to the "DILI checklist", the patient should not receive subsequent doses of investigational medication. (If alternative cause is identified and patient has recovered according to investigator assessment, treatment can be restarted after consultation with the sponsor.)
- If peripheral neuropathy is suspected, treatment with spesolimab should be temporarily discontinued until a full neurological investigation has been conducted. After completion of the neurological investigation, treatment can be restarted based on medical judgement of the investigator.
- For individual stopping rules related to specific adverse events, please see Section 4.2.1 "Other treatments and emergency procedures."

If new efficacy / safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the infusion/treatment for all patients or take any other appropriate action to guarantee the safety of the patients participating in the trial.

If a patient wants to discontinue the trial participation, the investigator should request that the patient consent to be contacted, at least by phone, for a final follow-up assessment at 16 weeks after last drug intake. Where possible, any new or changes in previously reported AEs and concomitant therapies should be recorded at this assessment, as indicated in section 6.1.3. Specific information to be collected at the 16-week assessment in patients who have discontinued trial medication or assessment is detailed in section 5.2.4.2.1.

3.2.4.2 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.2.4.1 above. This discussion, as well as the patient's decision, should be well documented in the source.

3.2.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular site at any time for the following reasons:

1. New efficacy or safety information invalidating the earlier positive benefit–risk assessment.
2. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.
3. Marketing authorization of spesolimab i.v.

Trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the second reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Product

All patients will be treated with spesolimab in this trial. There is no active comparator or placebo.

Table 4.1.1: 1 Spesolimab

Substance:	Spesolimab (BI 655130)
Pharmaceutical formulation:	Solution for infusion
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	Spesolimab 450 mg/vial (60 mg/mL), 7.5 mL fill volume
Posology:	900 mg single i.v dose
Method and route of administration:	i.v infusion

4.1.2 Drug assignment and administration of doses for each patient

Trial medication kits will be assigned to patients via Interactive Response Technology (IRT) system after verification of all inclusion and exclusion criteria, and patient will receive spesolimab 900 mg i.v at Visit 2 (Day 1). If flare symptoms persist after a single infusion of study medication, a second infusion (900 mg i.v. spesolimab) is allowed at Visit 3 (Day 8) per investigator's discretion and the medication number of the second dose will be also assigned via IRT system.

An Interactive Response Technology (IRT) will be used to screen eligible patients, assign medication kits and manage initial/re-supply ordering of drug supplies. The investigator will receive all necessary instructions to access the IRT from the Sponsor. Detailed IRT functions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the IRT vendor.

Site personnel will enter the medication numbers in the eCRF. Note that the patient number is different from the medication number (the former is generated during screening via the IRT System). Each medication kit (containing 2 vials) will have a unique medication number.

Detailed instructions for administration of spesolimab i.v. are provided in the ISF.

4.1.3 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). The investigational product consists of a carton holding 2 vials of the trial medication. Each carton will have a unique medication number.

Shipment and re-supply of trial medication to the local depots and/or sites will be managed via an IRT system, which will also monitor expiry dates of available supplies.

For details of packaging and the description of the label, refer to the ISF.

4.1.4 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation. Trial medication must be securely stored, e.g. in a locked refrigerator or at a pharmacy. If the storage conditions are found to be outside the specified range, the Cinical Research Associate (CRA) (as provided in the list of contacts) must be contacted immediately. Refer to the ISF for additional information.

The trial medication must be administered in the manner specified in the trial protocol and instructions for IMP preparation handling and administration of spesolimab.

4.1.5 Drug accountability

The primary investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / ethics committee.
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site.
- Approval/notification of the regulatory authority, e.g. competent authority.
- Availability of the curriculum vitae of the Principal Investigator.
- Availability of a signed and dated clinical trial protocol.

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.

All unused trial medication must be returned to the sponsor. All used and partially used medication must be destroyed locally by the trial site. Receipt, usage and return or disposal must be documented on the respective forms. Account must be given for any discrepancies.

The primary investigator or designee must maintain records of the product’s delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers assigned to the investigational medicinal product and patients participating in the trial. The primary investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the trial protocol and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed CRO, the primary investigator or designee must verify that all unused drug supplies have been returned by the clinical trial staff and all used or partially used supplies have been destroyed by the trial site, and that no remaining supplies are in the primary investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

All concomitant therapies will be recorded on the appropriate pages of the electronic CRF (eCRF).

4.2.1.1 Emergency procedures

Systemic hypersensitivity including infusion reactions and anaphylactic reaction

In case of systemic hypersensitivity, including infusion reactions and anaphylactic reaction, emerging during or after infusion of investigational medication, the investigator should consider, in accordance with severity of the reaction and local standard of care, to:

- Immediately interrupt the infusion
- Treat with systemic antihistamines, i.v. steroids, and in case of a severe allergic reaction (e.g., anaphylactic reaction) epinephrine
- Refer the patient to an emergency unit

In case of systemic hypersensitivity including infusion reactions, based on the patient's clinical course and the physician's medical judgment, the infusion may be re-initiated in case of mild or moderate systemic hypersensitivity, including infusion reactions (according to NCI grading, grade 1 or 2), at a slower speed with a gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of spesolimab in the ISF. In all cases, the total duration of infusion should not exceed 180 minutes (3 hours).

In case of anaphylactic reactions based on published criteria (Appendix 10.1; R11-4890), the investigator should discontinue treatment with spesolimab.

When a delayed hypersensitivity reaction is suspected, in addition to drawing a blood sample for laboratory assessment (complete blood count with differential, comprehensive metabolic panel (includes liver enzymes), LDH, immune complexes profile), please evaluate for signs of extra-cutaneous organ involvement. The decision to discontinue treatment and/or restart treatment after resolution of the reaction should be based on reaction type and severity.

In case of potential systemic allergic reaction: where possible, blood samples for determination of serum tryptase, as well as histamine, IgE and serum complement component assay, should be collected 0.5 h, 2 h, 6 h, 24 h after onset of the event.

Any clinically meaningful changes in laboratory values should be reported as an AE, SAE or AESI (as appropriate).

Severe infections (according to RCTC grading the ISF), serious infections, opportunistic or mycobacterium tuberculosis infections
Treatment of the infection should be initiated promptly according to local standard of care.

Active/Latent TB:
A suitable TB test, according to local regulations will be performed at screening. If the result is positive, the patient may participate in the trial if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. Active TB patients must be excluded. If the presence of latent tuberculosis is established, then treatment should have been initiated and maintained according to local country guidelines. If the TB test results are not available at the time of infusion, these patients may receive 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 infusion.

Malignancies

In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, treatment discontinuation is to be a consideration if deemed clinically appropriate by the investigator. In addition, diagnostics and treatment are to be initiated according to local standard of care.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medications (or classes of medications) listed in Table 4.2.2.1: 1 must not have been taken before infusion for the time periods as specified

Table 4.2.2.1: 1 Restricted medications

Medication or class of medications	Restriction duration
IL-36R inhibitors (other than spesolimab provided in the trial)	4 weeks prior to any infusion and not until after 16 weeks after last infusion of spesolimab
Live vaccinations	
Anakinra (or other IL-1/IL-1R inhibitors)	Not to be administered concurrently with spesolimab

4.2.2.2 Restrictions on diet and lifestyle

No specific restrictions on diet or lifestyle of the patients are required.

4.2.2.3 Contraception requirements

Women of childbearing potential must 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 list of contraception methods meeting these criteria is provided in the Patient Information.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

This is an open-label trial with no active or placebo control. Efficacy will not be evaluated.

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on the occurrence of:

- Treatment emergent adverse events (TEAEs)
- Treatment emergent serious adverse events (SAEs)
- Treatment emergent adverse events of special interest (AESIs).

No confirmatory safety analysis is planned.

5.2.1 Physical examination

A complete physical examination will be performed before first drug administration at the time points specified in the FLOW CHART. Examination includes, at a minimum, general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Measurement of height and body weight should also be performed.

Physical examination will be performed at follow-up visits according to standard clinical practice and when deemed appropriate by the investigator.

The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated before first drug administration at the time points specified in the Flow Chart. This includes measuring temperature, pulse rate and systolic/diastolic blood pressure. Pulse rate and blood pressure will be measured after patients have been sitting comfortably for at least 5 minutes.

Vital signs will be evaluated at follow-up visits according to standard clinical practice and when deemed appropriate by the investigator.

The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

The laboratory tests listed in Table 5.2.3:1 are to be collected at the trial sites and assessed by the investigators prior to study drug infusion for eligibility confirmation.

Any additional laboratory testing during the trial is optional and should be performed at the discretion of the investigator in accordance with the current standard of care, which may yield useful information for the management and safety evaluation of the patient.

Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to section 5.2.4).

In case the criteria for DILI are fulfilled, a number of additional measures will be performed (please see section 5.2.4.1.4 and the DILI Checklist provided in the ISF).

Table 5.2.3:1 Laboratory tests to be assessed at V1 prior to i.v. administration (Local Labs)

Category	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) White blood cell count (WBC) Platelet count
WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase
Substrates	Total bilirubin
Infection testing	Hepatitis B Surface Antigen Hepatitis B Surface Antibody Hepatitis B core Antibody HBV-DNA (quantitative)[1] QuantiFERON® TB or T-Spot® [2] Hepatitis C Antibodies HIV-1, and HIV-2 Antibody
Serum Pregnancy test (only for female patients of childbearing potential)	Human Serum Chorionic Gonadotropin

[1] An HBV-DNA test should be conducted if Hepatitis B core Antibody and/or Hepatitis B Surface Antibody is positive and Hepatitis B Surface Antigen is negative. If HBV DNA level is undetectable (<2.1 log copies/mL) at screening, the patient can participate in this trial.

[2] If the 1st QuantiFERON® TB or T-Spot® test result is indeterminate, a retest should be performed.

5.2.4 Assessment of adverse events

5.2.4.1 Definitions of AEs

5.2.4.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether related or not.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.4.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.
- An event that possibly leads to disability will be handled as ‘deemed serious for any other reason’ and, therefore, reported as an SAE.

5.2.4.1.3 AEs considered “Always Serious”

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above.

The latest list of “Always Serious AEs” can be found in the eDC system. A copy of the latest list of “Always Serious AEs” will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.4.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.2.4.2, subsections “AE Collection” and “**AE reporting to sponsor and timelines”.**

5.2.4.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.4.2.2.

The following are considered as AESIs:

Potential Severe Drug Induced Liver Injury (DILI)

A potential severe Drug Induced Liver Injury (DILI) that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST and/or ALT≥3-fold ULN,
  combined with an elevation of total bilirubin ≥2-fold ULN measured in the same blood sample, or in samples drawn within 30 days of each other, or
- ALT, and/or AST elevations ≥ 10-fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, alkaline phosphatase, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Systemic hypersensitivity reactions including infusion reactions and anaphylactic reaction
Any suspicion of severe systemic hypersensitivity including infusion reactions and any anaphylactic reaction should be defined and assessed using the criteria discussed in the statement paper from Sampson et al. (Section 4.2.1.1 and Appendix 10.1, R11-4890).

Severe infections (according to RCTC grading in the ISF)

Opportunistic and mycobacterium tuberculosis infections
These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, posttransplant lymphoproliferative disorder (EBV), progressive multifocal leucoencephalopathy, bartonellosis (disseminated only), blastomycosis, toxoplasmosis, coccidioidomycosis, histoplasmosis, aspergillosis (invasive only), candidiasis (invasive or pharyngeal), cryptococcosis, other invasive fungi (mucormycosis (zygomycosis, rhizopus, mucor, lichtheimia), scedosporium/pseudallescheria boydii, fusarium), legionellosis, listeria monocytogenes (invasive only), tuberculosis, nocardiosis, non-tuberculous mycobacterium, salmonellosis (invasive only), HBV reactivation, herpes simplex (invasive only), herpes zoster, strongyloides (hyperinfection syndrome and disseminated forms only),

paracoccidioides, penicillium marneffei, sporothrix schenckii, cryptosporidium species (chronic only), microsporidiosis, leishmaniasis (visceral only), trypanosoma cruzi infection (Chagas' disease) (disseminated only), campylobacteriosis (invasive only), shigellosis (invasive only), vibriosis (invasive due to vibrio vulnificus), HCV progression (R17-2617).

Peripheral neuropathy
Any event suspected or diagnosed as Peripheral Neuropathy is considered as an AESI.
For the treatment interruption rules, please see section 3.2.4.1

5.2.4.1.5 Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the CRF according to the RCTC version 2.0 (refer to ISF for details).

5.2.4.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse event and the BI investigational compound, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, considering the pharmacological properties of the compound (e.g. after 5 half-lives).
  Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- There is an alternative explanation, e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned.

- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.4.2 Adverse event collection and reporting

5.2.4.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files. The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of study (16 weeks after last dose of spesolimab, or at the time of withdrawal of participation): all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of study: the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and trial drug-related SAEs and trial drug-related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however not be reported in the CRF.
- Upon patient re-entry into the trial, the patient should be re-evaluated to ensure that eligibility criteria are still met and the overall trial is still running in order to assess AEs (serious and non-serious) and AESIs.

Vital Status Data Collection
Patients who discontinue trial medication or participation prematurely, who agree to be contacted further but do not agree to physical visits, should be followed up as described in section 3.2.4.1, discontinuation of trial medication and assessment. Thus, for patients who discontinue trial medication or participation prematurely but agree to be contacted by phone for a last follow-up assessment at 16 weeks after last drug intake, the investigator must report any occurrence of cancer, all deaths / fatal AEs regardless of relationship, and trial drug-related SAEs and and trial drug-related AESIs the investigator becomes aware of.

5.2.4.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form to the sponsor's unique entry point within 24 hours of becoming aware of the event. The country-specific process will be specified in the ISF. The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information related to these events, a follow-up SAE form must be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.4.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

6. INVESTIGATIONAL PLAN

6.1 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.1.1 Screening period

After informed consent, patients considered for this trial will undergo an eligibility evaluation. Laboratory tests, must be conducted locally to ensure patients meet the inclusion and exclusion criteria described in sections 3.2.2 and 3.2.3, which include:

- Liver function tests (AST, ALT and alkaline phosphatase)
- Complete blood count, with differential
- Pregnancy (blood) test in women of childbearing potential
- TB test, to rule out active disease
    - In accordance with details in section 4.2.1.1, if TB test results are not available at the time of infusion, patients may receive 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 infusion.
- Possible HIV and viral hepatitis tests, to rule out active disease in presence of clinical signs or suspicion
    - If HIV and viral hepatitis test results are not available at the time of infusion, patients may receive 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 HIV and viral hepatitis) within 3 months prior to infusion.

Once consent is obtained, the patient is considered to have started the screening process and is assigned a unique patient number in the IRT system. The patient is to be recorded on the enrolment log and registered in the IRT system as a screened patient. All patients who are screened must be registered in the IRT system.

Demographics, baseline conditions (including any findings of the physicial examination and vital signs evaluation) and concomitant therapies will be recorded in the eCRF.

If the patient meets all eligibility criteria, infusion of spesolimab may proceed immediately.

6.1.2 Treatment period(s)

Spesolimab will be administered as a single dose i.v. infusion in the clinic.

If deemed necessary by the investigator (i.e. if the flare symptoms persist), a second dose of 900 mg spesolimab may be administered one week after the initial infusion.

IRT transactions are required to obtain all medication kit number assignments. Dates and times of infusions will be recorded in the patient's records and eCRF.

6.1.3 Follow up period and trial completion

Patients will visit the investigator at approximately week 1, week 4 and week 16 after only one single drug administration. If the patient requires a second dose of spesolimab, visits will be re-scheduled based on the date of the last infusion, i.e, patients will visit the investigator at approximately week 1, week 2, week 5, and week 17 after initial dose of spesolimab. Additional visits within the 16-week follow-up period can be planned according to standard clinical practice. Visits may also be conducted by phone or video if judged appropriate by the investigator. At all visits any new or changes in previously reported AEs and concomitant therapies will be recorded in the patient's chart and eCRF.

Patient's participation in the trial will end after conclusion of the 16-week follow-up period after the last infusion / drug administration. The Trial Completion eCRF page will be completed at this time.

A patient will be considered lost to follow-up if the investigator is not able to contact the patient despite multiple attempts. Every effort must be made to contact the patient: at least two telephone contacts plus one mailing should be documented in the patient's chart.

If a patient experiences a new GPP flare (following the resolution of a previous flare with spesolimab treatment) after the 16-week follow-up period, the patient may re-enter in the trial with the same patient number and be treated again with spesolimab, providing eligibility criteria are still met and the overall trial is still running. The same dosing and follow-up requirements apply as for the previous flare.

In the situation that a patient experiences a new GPP flare within the 16-week follow-up period and the physician wishes to treat this new flare with spesolimab, eligibility needs to be re-assessed and agreed upon with the BI clinical team.

Then, in case of re-entry due to a new GPP flare within the 16-wks follow-up period, the patient will end the current follow-up period, and restart the trial from the screening for eligibility. If eligibility criteria is met, and permission from BI is granted (see above), the patient can be treated again to receive a new dose of spesolimab. After infusion, the patient is followed-up for 16-weeks after the latest dose of spesolimab. Also for this scenario, after one week, a second dose of spesolimab can be administered, if deemed necessary by the treating physician.

7. STATISTICAL METHODS

Exploratory descriptive statistics of demographic and safety data will be presented.

7.1 PLANNED ANALYSES

Analyses will be based on the treated set (TS) which includes all patients who have been administered spesolimab.

7.1.1 Safety analyses

In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the REP, a period of 16 weeks after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’. All adverse events with an onset between start of treatment and end of the REP, a period of 16 weeks after the last dose of trial medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term. after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".

In addition, the trial also will be carried out in compliance with Good Post-Marketing Study Practice (GPSP) upon commencement of the post marketing clinical trial.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the investigator.

The investigator will inform the sponsor or delegate immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regards to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments. Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

The investigator or delegate must give a full explanation to patients in the trial based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient

time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan or alternative plan, in line with the guidance provided by ICH Q9 and ICH-GCP E6, for fully outsourced trials, documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches. A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to section 4.1.5.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).
Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

If the patient is not compliant with the protocol, any corrective action e.g. re-training must be documented in the patient file.

For the CRF, data must be derived from source documents, for example:

- Patient identification: gender, year of birth (in accordance with local laws and regulations).
- Patient participation in the trial (substance, trial number, patient number, date patient was informed).
- Dates of patient's visits, including dispensing of trial medication.
- Medical history (including trial indication and concomitant diseases, if applicable).
- Medication history.
- Adverse events and outcome events (onset date (mandatory), and end date (if available)).
- Serious adverse events (onset date (mandatory), and end date (if available)).
- Concomitant therapy (start date, changes).
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available).
- Completion of patient's participation in the trial (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor or deligate will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).
Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

To ensure confidentiality of records and personal data, only pseudonymised data will be transferred to the sponsor by using a patient identification number instead of the patient's name. the code is only available at the site and must not be forwarded to the sponsor. I case patient's records will be forwarded e.g. for SAE processing or adjudication committees, personal data that can identify the patient will be redacted by the site prior to forwarding. Access to the patient files and clinical data is strictly limited: personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

A potential data security breach will be assessed regarding the implications for rights and privacy of the affected person(s). Immediate action as well as corrective and preventive action will be implemented. Respective regulatory authorities, IRBs / IECs and patients will be informed as appropriate.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "Last Patient Last Treatment" (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of the treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the treatment medication until 30 days after LPLT at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CTL), responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CTM), CRAs, and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. On-site monitoring will be performed by BI or a contract research organization appointed by BI.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs or by a CRO with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

An IRT vendor will be used in this trial. The physician will receive all necessary instructions to access the IRT system from the Sponsor. Detailed IRT functions and procedures will be documented in the IRT Manual available in the ISF.

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10. APPENDICES

10.1 CLINICAL CRITERIA FOR DIAGNOSING ANAPHYLAXIS

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalised hives, pruritus or flushing, swollen lips /tongue / uvula)

AND AT LEAST ONE OF THE FOLLOWING

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips / tongue / uvula)
   b. Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg +[2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Reference: R11-4890

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		06 Jul 2022
EudraCT number **EU number**		NA
BI Trial number		1368-0073
BI Investigational Medicinal Product(s)		Spesolimab, BI 655130
Title of protocol		Multi-centre, open-label, expanded access trial of spesolimab i.v. in patients with generalized pustular psoriasis (GPP) presenting with a flare
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Clinical Trial Protocol Synopsis Table: Main in and exclusion criteria 3.2.2 Inclusion Criteria #3
Description of change		Minimum age of inclusion criteria was changed from 20 to 18 years.
Rationale for change		The legal age of adulthood was changed per revision of local regulation.
Section to be changed		Flow Chart
Description of change		Foot note #8, 9 and 10 in Flow Chart were corrected to #7, 8 and 9.
Rationale for change		Correction
Section to be changed		Table 1.4: 1, Risk associated with spesolimab administration
Description of change		Added to inform about the newly added potential risk “peripheral neuropathy” deriving from the three cases reported as Guillain-Barré syndrome by the investigator in Spesolimab trials. The cases were considered as peripheral neuropathy by the external neurologist expert panel’s assessment.
Rationale for change		Added to inform about the newly identified risk “peripheral neuropathy”
Section to be changed		Section 3.2.3 Exclusion Criteria #9 Table 4.2.2.1: 1 Restricted Medications
Description of change		Live virus vaccinations was corrected to live vaccinations
Rationale for change		Correction

Section to be changed		Clinical Trial Protocol Synopsis Table: Main in and exclusion criteria Section 3.2.3 Exclusion Criteria #12
Description of change		The following Exclusion criterion was added: "Presence of acute demyelinating neuropathy
Rationale for change		Added as mitigation strategy to account for the three cases reported as Guillain-Barré syndrome by the investigator in Spesolimab trials. The cases were considered as peripheral neuropathy by the external neurologist expert panel's assessment. This way the selection of patients with acute demyelinating neuropathy would be avoided.
Section to be changed		Section 3.2.4.1 Discontinuation of trial medication and assessment.
Description of change		Following information was added. • If peripheral neuropathy is suspected, treatment with spesolimab should be temporarily discontinued until a full neurological investigation has been conducted. After completion of the neurological investigation, treatment can be restarted based on medical judgement of the investigator.
Rationale for change		Added as mitigation strategy to account for the three cases reported as Guillain-Barré syndrome in Spesolimab trials. The cases were considered as peripheral neuropathy by the external neurologist expert panel's assessment.
Section to be changed		Table 5.2.3:1 Laboratory tests to be assessed at V1 prior to i.v. administration
Description of change		Category "automatic WBC differential" was corrected to "WBC differential". Category "manual differential WBC" was removed "Qualitative" was removed from Hepatitis B Surface Antigen, Hepatis B Surface Antibody, Hepatitis C Antibodies and HIV-1 and HIV-2 Antibody.
Rationale for change		Correction to remove unnecessary requirement.

Section to be changed		Section 5.2.4.1.4 Adverse events of special interest
Description of change		Following information was added. Peripheral neuropathy Any event suspected or diagnosed as Peripheral Neuropathy is considered as an AESI. For the treatment interruption rules, please see section 3.2.4.1
Rationale for change		To update reporting requirements to ensure all cases of suspected peripheral neuropathy including the non-serious ones are analyzed quickly.
Section to be changed		Section 6.1.3 Follow up period and trial completion
Description of change		The information to keep the same patient number for the case of re-entry was added.
Rationale for change		Clarification
Section to be changed		Section 6.1.3 Follow up period and trial completion
Description of change		The following information was added Then, in case of re-entry due to a new GPP flare within the 16-wks follow-up period, the patient will end the current follow-up period, and restart the trial from the screening for eligibility. If eligibility criteria is met, and permission from BI is granted (see above), the patient can be treated again to receive a new dose of spesolimab. After infusion, the patient is followed-up for 16-weeks after the latest dose of spesolimab. Also for this scenario, after one week, a second dose of spesolimab can be administered, if deemed necessary by the treating physician.
Rationale for change		Clarification for the case of re-entry due to a new GPP flare within the 16-weeks follow-up period
Section to be changed		Section 8.1 Trial approval, patient information, informed consent
Description of change		“trial patients” was corrected to “patients in the trial”
Rationale for change		Correction

Section to be changed		9.2 Unpublished references
Description of change		Release date of IB was removed
Rationale for change		To avoid the old release date is kept in the protocol

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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Approval-Biostatistics		07 Jul 2022 10:03 CEST
Approval-Team Member Medical Affairs		08 Jul 2022 13:35 CEST
Verification-Paper Signature Completion		08 Jul 2022 13:40 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed