EXPANDED Access Program (EAP) Protocol

	Document Number:	c39436286-01
BI Trial No.	1368-0077	
BI Investigational Medicinal Product(s)	Spesolimab, BI 655130	
Title	Multi-centre, open-label, expanded access program of [redacted] spesolimab in patients with generalized pustular psoriasis (GPP) presenting with a flare	
Lay Title	An Expanded Access Program in China to provide spesolimab to people with a flare-up in Generalized Pustular Psoriasis who have no other treatment options	
Clinal Trial Leader	[redacted] TEL: Email:	
Coordinating Investigator	[redacted] TEL: Email:	
Status	FinalProtocol	
Current Version and Date	**Version:**	**Date:**
	V2.0	12 May 2022

EXPANDED ACCESS PROGRAM/EXPANDED ACCESS CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	12 May 2022
Revision date	Not applicable
BI trial number	1368-0077
Title of study/trial	Multi-centre, open-label, expanded access program of [redacted] spesolimab in patients with generalized pustular psoriasis (GPP) presenting with a flare
Coordinating Investigator	[redacted] TEL: [redacted] Email: [redacted]
Trial site(s)	Multi-centre trial
EAP rationale	GPP flares are associated with considerable morbidity and mortality, and existing treatment options for GPP may provide little-to-no benefit for many patients. The Effisayil-1 trial demonstrated that treatment of GPP flares with spesolimab was associated with rapid pustular and skin clearance, as well as improvements in systemic symptoms and quality of life, with a favourable benefit–risk profile. Therefore, this expanded access program (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.
EAP objective(s)	The aim of this program is to provide early access to the investigational drug spesolimab for patients with GPP presenting with a flare. A secondary aim of this program is to collect additional data on the safety and tolerability of spesolimab.
EAP endpoints	Primary endpoint: • Occurrence of Treatment Emergent Adverse Events (AEs) Secondary endpoints: • Occurrence of Treatment Emergent Serious Adverse Events (SAEs) • Occurrence of Treatment Emergent Adverse Events of Special Interest (AESIs) [redacted]
Trial design	Single-arm, open-label, active treatment
Number of patients	There is no recruitment goal for this expanded access program

entered	
Diagnosis	Patients with GPP presenting with a flare
Main in- and exclusion criteria	Main inclusion criteria: 1. Diagnosis of GPP, consistent with ERASPEN criteria 2. Patient is experiencing a flare 3. Male or female patients aged 18 to 75 years 4. Written informed consent 5. No available satisfactory authorized alternative therapy Main exclusion criteria: 1. Severe, progressive, or uncontrolled hepatic disease, active systemic, relevant chronic or acute infections, including active TB, HIV infection or viral hepatitis at the time of drug administration, or history of allergy / hypersensitivity to systemically administered spesolimab or its excipients 2. Women who are pregnant, nursing, or who plan to become pregnant while in the program. 3. 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. 4. Immediate life-threatening flare of GPP requiring intensive care treatment 5. Patients who must or wish to continue the intake of medications which are likely to interfere with the safe conduct of the program. 6. Currently enrolled in another investigational device or drug program
BI Medicinal product(s)	Spesolimab
dose	[redacted] dose
method and route of administration	[redacted]
Duration of treatment	[redacted], with the potential for a [redacted] after initial [redacted], if deemed necessary by the treating physician
Statistical methods	Exploratory descriptive statistics of demographic and safety data will be presented as appropriate. [redacted]

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

AD	Atopic Dermatitis
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
AUC	Area Under the Curve
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
C_{max}	Maximum Plasma Concentration
C_{min}	Minimum Plasma Concentration
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CRO	Contract Research Organization
CRP	C-Reactive Protein
CTL	Clinical Trial Leader
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DEDP	Drug exposure during pregnancy
EACT	Expanded Access Clinical Trial
EAP	Expanded Access Program
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
ERASPEN	European Rare and Severe Psoriasis Expert Network
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue

FDA	Food and Drug Administration
FIH	First in human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPP	Generalized Pustular Psoriasis
GPPGA	Generalized Pustular Psoriasis Physician Global Assessment
GPPASI	Generalized Pustular Psoriasis Area and Severity Index
GOT	Glutamic-Oxaloacetic Transaminase
GPT	Glutamic-Pyruvic Transaminase
HA	Health Authority
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
IgG	Immunoglobulin G
IL	Interleukin
IMP	Investigational Medicinal Product
INN	International Non-Proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITE	Indirect Target Engagement
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
KO	Knock Out
LPLT	Last Patient Last Treatment
MedDRA	Medical Dictionary for Drug Regulatory Activities
MIP	Macrophage Inflammatory Protein

NOAEL	No-Observed Adverse Effect Level
OPU	Operative Unit
PK	Pharmacokinetics
PSS	Psoriasis Symptom Scale
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
TNF	Tumour necrosis factor
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
UC	Ulcerative Colitis
ULN	Upper Level of Normal
VAS	Visual Analogue Scale
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 aseptic 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 [redacted] or Week [redacted]). 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 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.

IL-36R signalling in GPP

IL-36 is a member of the IL-1 family of cytokines and includes the isoforms IL-36α, IL-36β and IL-36γ and the IL-36 receptor antagonist (IL-36Ra) (R20-2760), which are expressed at high levels in epithelial cells (R18-2717, R20-1386, R16-2297). Dysregulated IL-36R signalling promotes the infiltration of neutrophilic granulocytes into the epidermis, leading to the formation of sterile pustules.

The overexpression of IL-36 or a loss-of-function mutation in the gene encoding IL-36Ra (*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 IL-36 pathway, including *CARD14* (R14-5158, R16-0929, R16-0928, R20-2761). Notably, mutations in *IL36RN* 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 IL-36 isoforms versus non-lesional skin ((R18-2717).

In summary, there is strong genetic link between the IL-36 signaling pathway and GPP, with experimental data identifying IL-36 as the dominant cytokine driving GPP (R17-3602).

Therefore, there is a strong scientific rationale to support that inhibition of IL-36R signaling with the humanized anti-IL-36R 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 IL-36R signaling. Binding of spesolimab to IL-36R is anticipated to prevent the subsequent activation of IL-36R by cognate ligands (IL-36 α, β and γ) 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.

1.2.2 Nonclinical pharmacology

Preclinical studies
Spesolimab binds to human IL-36R with a binding avidity of less than 1 pM. Spesolimab inhibits IL-36 ligand-stimulated NF-κB 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 does not bind to IL-36R 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 IL-36R 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 IL-36R 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 IL-36 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 i.v. doses from 0.001 mg/kg to 10 mg/kg body weight and 20 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 3/20 (15.0%) subjects in the placebo group and in 8/58 (13.8%) subjects treated with spesolimab. The most frequent treatment-emergent AEs were nasopharyngitis (spesolimab: 20.7%; placebo: 15.0%), headache (spesolimab: 8.6%; placebo: 15.0%), influenza-like illness (spesolimab: 6.9%; placebo: 10.0%), and diarrhoea (spesolimab: 3.4%; placebo: 10.0%). There were two AEs of moderate intensity (injection site haematoma, headache), 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.

[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 3, 6,10 and 20 mg/kg given weekly for 4 weeks (i.e. 4 administrations) or a single dose of 20mg/kg (eight subjects each, 3:1 receiving spesolimab or placebo). Overall, multiple i.v. doses of 3 mg/kg, 6 mg/kg, and 10 mg/kg, as well as single and multiple doses of 20 mg/kg spesolimab 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 higher in the 20 mg/kg multiple dose spesolimab treatment group than in the other treatment groups, mainly driven by headache. 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 single i.v. dose of spesolimab (10 mg/kg) in seven patients with a GPP flare. The proof-of-concept for IL-36R inhibition 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 1 week after the infusion, and all of them reached this status 4 weeks after treatment. Within 48 hours of treatment, pustules were completely cleared in three patients; pustules were cleared by Week 1 in five patients, and by Week 2 in six patients. The early response in the skin was also accompanied by an early response in systemic components, with C-reactive protein (CRP) approaching normalization within 4 weeks. A major improvement in GPPASI was observed in all patients very early with a mean (SD) percent change from baseline of 73.2% (16.2) at Week 2; by Week 4, this was further reduced (82.0% from baseline), and was maintained to Week 20 (83.6%). Additional improvements (mean [SD]) from baseline to Week 2 were observed in FACIT-F, 12.3 (10.1); Pain-VAS, –45.9 (32.3); and PSS, –5.14 (3.18), all of which were also sustained through Week 4. 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 arthralgia (42.9%). 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 single i.v. dose of 900 mg spesolimab compared with placebo in 53 patients with GPP presenting with a flare. Baseline demographic and disease characteristics were generally balanced between arms. At randomization, 18.9% of patients had a GPPGA total score of 4 (severe), and most patients had a GPPGA pustulation subscore 3 or 4 (high or very high-density of pustules), and highly impaired quality of life and clinical burden as indicated by DLQI, pain VAS, FACIT-Fatigue and PSS.

At week 1, 19 patients (54.3%) randomized to spesolimab versus one patient (5.6%) randomized to placebo achieved a GPPGA pustulation subscore of 0 (no visible pustules; risk difference, 48.7; 95% CI, 21.5–67.2; one-sided P<0.001). A GPPGA total score of 0 or 1 (clear or almost clear skin) at week 1 was achieved in 15 patients (42.9%) randomized to spesolimab versus two patients (11.1%) randomized to placebo (risk difference, 31.7; 95% CI,

2.2–52.7; one-sided P=0.012). Clinical responses were observed regardless of *IL36RN* mutation status. At week 4, 16 patients (45.7%) receiving a single spesolimab dose at day 1 achieved a GPPASI 75 versus two patients (11.1%) receiving placebo (risk difference, 34.6; 95% CI, 5.8–55.4; one-sided P=0.008). Additionally, significantly higher reductions in pain VAS (P=0.001) and PSS (P=0.004), and improvement in FACIT-Fatigue scores (P=0.001) at week 4 were achieved by patients receiving spesolimab versus those receiving placebo.

At day 8, 12 patients randomized to spesolimab received an open-label (second) dose of 900 mg spesolimab. Beyond day 8, response rates in patients in the spesolimab arm who received one or two doses continued to increase. A total of 23 patients (65.7%) achieved a GPPGA pustulation subscore of 0 by week 2, and the same proportion achieved a GPPGA total score of 0 or 1 by week 4. These were sustained in at least 60% of patients up to week 12. The median percent improvement in the GPPASI score from baseline was 42.8% at week 1 and progressively increased up to 81.8% at week 12. A GPPASI 75 was achieved in 13 patients (37.1%) at week 2, in 18 patients (51.4%) at week 4, and in 21 patients (60.0%) at week 8, and was sustained up to week 12. Rapid reductions in pain VAS score and improvements in DLQI scores were achieved through week 4 and sustained through week 12. CRP normalized within 4 weeks in patients with elevated baseline CRP (≥ 10mg/L), who received one or two doses of spesolimab.

At week 1, 77.1% and 66.7% of patients receiving spesolimab and placebo, respectively, had an AE. The most common AE was pustular psoriasis, reported in 37.1% and 38.9% of patients randomized to spesolimab or placebo, respectively. Pyrexia was reported in 5.7% and 22.2% of the patients receiving spesolimab or placebo, respectively. Infections were reported in 17.1% and 5.6% of patients in the spesolimab and placebo groups, respectively. SAE were reported in 14.3% and 16.7% of patients in the spesolimab and placebo groups, respectively.

At week 12, 91.4% of patients randomized to spesolimab, including those who received a second spesolimab dose at day 8, had an AE, and 25.7% had a SAE. Symptoms observed in two patients receiving spesolimab were reported as drug reactions with eosinophilia and systemic symptoms (DRESS) with RegiSCAR scores ≤3 (P14-06207) and in close temporal relationship to the reported GPP flares, which was two days after treatment in one case. Both patients received concomitant paracetamol and antibiotics, cefuroxime and cefepime in one patient, and spiramycin in the other.

Anti-drug antibodies (ADAs) were detected as early as week 2, with cumulative rate of 46.7% (25 of 45 patients) by week 12. Formation of ADAs did not affect the primary and secondary efficacy endpoints at week 1. 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, 39 patients 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.

[redacted]

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 PROGRAM

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

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 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 program	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 programs.	Patients with hepatic impairment will be excluded from the program. In case of suspicion of hepatic injury during the program (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. Hepatic injury 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 program. 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 program. 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 program 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.
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	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.

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
	showed a heterogenous pattern. 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.	Trial treatment discontinuation criteria as well as criteria for trial treatment restart are implemented for relevant cases.

Other risks related to program-specific procedures include blood sampling and [redacted] 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 program 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. 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 program 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 program. However, the treating physician 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 program enrolment and during the program by the treating physician 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 treating physicians 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. 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 treating physician and sponsor.

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. PROGRAM OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

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

2.1.2 Primary endpoint

- Occurrence of Treatment Emergent Adverse Events (AEs)

2.1.3 Secondary endpoints

- Occurrence of Treatment Emergent Serious Adverse Events (SAEs)
- Occurrence of Treatment Emergent Adverse Events of Special Interest (AESIs)

3. DESCRIPTION OF DESIGN AND PROGRAM POPULATION

3.1 OVERALL PROGRAM DESIGN AND PLAN

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 treating physician.

After signing informed consent and if all eligibility criteria are met, patients will receive a [redacted] spesolimab. If deemed necessary by the treating physician (i.e. if the flare symptoms persist), a [redacted] spesolimab may be administered [redacted] after the initial [redacted].

If [redacted] is administered, then patients will visit the treating physician approximately at week [redacted], week [redacted] and week [redacted]. If a [redacted] may be given, then the dates that patients will visit the treating physician is changed to approximately at [redacted] after initial dose of spesolimab. Please refer to section 6.1 for details on the program visit procedures. Patient's participation in the program will end after conclusion of the [redacted]-week follow-up period after the last [redacted] / drug administration.

If a patient experiences a new GPP flare (following the resolution of a previous flare with spesolimab treatment) after the [redacted]-week follow-up period the patient may re-enter in the program and be treated again with spesolimab, providing eligibility criteria are still met and the overall program 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 [redacted]-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.

The enrolment of patients for the program will stop at the time spesolimab becomes commercially available or 6 months after marketing authorization for treatment of GPP in China (whichever is earlier). The overall program will close when the last patient completes the follow up period after the last [redacted] of spesolimab or if any other reason listed in section 3.2.4.3 is met.
Below is suggested flow chart for patient visit.

Flow Chart

Trial Period	**Screening**	**Treatment**		**Follow-up Period**		
Visit	**V1[1]**	**V2[1]**	**V3[2]**	**V4**	**V5**	**V6/EoS[3]**
Week ([redacted])[2]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week ([redacted])[2]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Window			±1d	±1d	±7d	±7d
Informed consent	X					
Demographics	X					
Medical history	X					

Trial Period	Screening	Treatment		Follow-up Period		
Visit	**V1[1]**	**V2[1]**	**V3[2]**	**V4**	**V5**	**V6/EoS[3]**
Week ( )[2]**						
Week ( )[2]**						
Window			±1d	±1d	±7d	±7d
Baseline condition	X					
Physical examination	X	X	(X)[5]	(X)[5]	(X)[5]	(X)[5]
Vital signs	X	X	(X)[5]	(X)[5]	(X)[5]	(X)[5]
Pregnancy test[4]	X					
Infection testing[6]	X					
Safety laboratory tests (Local lab)[7]	X		(X)[5]	(X)[5]	(X)[5]	(X)[5]
Nucleic acid testing	X					
COVID-19 symptoms		(X)	(X)	(X)	(X)	(X)
Review of in-/exclusion criteria	X	X				
IRT transaction	X	X	X			
Dispense/administration study drug		X	X			
Adverse events	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X
Study Completion						X

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

1: Visit 1 and Visit 2 can be on the same day. If V1 and V2 is performed on the same day, the procedures do not need to be repeated.
2: V3 is an additional visit. There's a possibility that patient will receive of spesolimab at V3 (if his flare symptoms persist after the dose. If in that case, the visit schedule will be changed to approximately at after initial dose of spesolimab.
3: 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 6) should be conducted at 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 weeks after the last spesolimab administration.
4: Only applicable for women of childbearing potential.
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, viral hepatitis tests (at least to include anti-hepatitis B core antibody, hepatitis B surface antigen, hepatitis C virus antibody) and HIV assessments.
7: Safety laboratory tests at screening visit (Visit 1) include liver function test (at least to include AST/GOT, ALT/GPT, alkaline phosphatase, and total bilirubin), haematology test (at least to include complete blood count with differential).

3.2 SELECTION OF PROGRAM POPULATION

3.2.1 Main diagnosis for program entry

Participation in this program 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 program, no recruitment goals or limits apply.

Patients previously enrolled in this program presenting 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.

3.2.2 Inclusion criteria

1. Diagnosis of GPP, consistent with ERASPEN criteria, defined as primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques). GPP can occur with or without systemic inflammation, with or without plaque-type psoriasis, and be either relapsing (>1 episode) or persistent (>3 months).
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 treating physician.
3. Male or female patients, aged 18 to 75 years at time of enrolment. 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 program.
5. No satisfactory authorized alternative therapy exists, as assessed by the treating physician.

3.2.3 Exclusion criteria

1. Women who are pregnant, nursing, or who plan to become pregnant while in the program.
   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 [redacted].
2. Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (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 treating physician.
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 treating physician.
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.

[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.

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 treating physician, likely to interfere with the safe conduct of the program.
10. Currently enrolled in another investigational device or drug program, or less than 30 days since ending another investigational device or drug program(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 treating physician may put the patient at risk because of participation in this program or limit the patient's ability to participate in this program.
12. Presence of acute demyelinating neuropathy.

3.2.4 Discontinuation / withdrawal of patients from program

Patients may discontinue program treatment or withdraw consent to program participation for any reason. The decision to withdraw consent to program participation and the reason must be documented in the patient files and CRF. If the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

3.2.4.1 Discontinuation of trial medication and assessment

An individual patient will discontinue treatment if:

- The patient wants to discontinue 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 program 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 program 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 hepatic injury 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 [redacted]/treatment for all patients or take any other appropriate action to guarantee the safety of the patients participating in the program.

If a patient wants to discontinue the participation in the program, 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 [redacted]-week assessment in patients who have discontinued triam medication or assessment is detailed in section 5.2.4.2.1.

3.2.4.2 Withdrawal of consent to program participation

Patients may withdraw their consent to program 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 treatment discontinuation and withdrawal of consent to program participation, as well as explain the options for continued follow-up after 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 program by the sponsor

Boehringer Ingelheim reserves the right to discontinue the program 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 program protocol, or the contract impairing the appropriate conduct of the program.
3. Commercial availability of spesolimab i.v. or 6 months after marketing authorization in China, whichever is earlier.

The investigator / the program site will be reimbursed for reasonable expenses incurred in case of program 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 program. There is no active comparator or placebo.

Table 4.1.1: 1 Spesolimab

Substance:	Spesolimab (BI 655130)
Pharmaceutical formulation:	Solution [redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	Spesolimab [redacted]
Posology:	[redacted]
Method and route of administration:	[redacted]

4.1.2 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). Shipment of material to the local depots and/or sites will be managed via an IRT system, which will also monitor expiry dates of available supplies.

An Interactive Response Technology (IRT) system will be used to screen eligible patients, assign medication kits, and manage re-supply ordering of medication kits. At program entry, as well as subsequent medication administration visits (if applicable), and IRT system will assign medication numbers. 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.

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

4.1.3 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. Program 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 program medication must be administered in the manner specified in the EAP Protocol and instructions for IMP preparation handling and administration of spesolimab.

4.1.4 Drug accountability

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

- Approval of the clinical program protocol by the IRB / ethics committee.
- Availability of a signed and dated clinical program 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 program protocol.
- Availability of the proof of a medical licence for the Principal Investigator.

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

The investigator or designee must maintain records of the product's delivery to the participating 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 program. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the EAP Protocol and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator or designee must verify that all unused drug supplies have been returned by the clinical staff and all used or partially used supplies have been destroyed by the participating site, and that no remaining supplies are in the 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 [redacted] reactions and anaphylactic reaction

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

- Immediately interrupt the [redacted]
- 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 [redacted] reactions, based on the patient's clinical course and the physician's medical judgment, the [redacted] may be re-initiated in case of mild or moderate systemic hypersensitivity, including [redacted] reactions (according to NCI grading, grade 1 or 2), at a slower speed with a gradual increase to complete the [redacted] as detailed in the Instructions for Preparation and Handling of spesolimab in the ISF. [redacted]

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 program 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 [redacted], 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 [redacted].

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 must not have been taken before [redacted] 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 program)	4 weeks prior to any [redacted] and not until after 16 weeks after last [redacted] 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

Female patients:
WOCBP (for the definition please refer to section 3.2.3) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year

when used consistently and correctly during the study, and for a period of at least 16 weeks after the last dose of study drug.
Acceptable methods of birth control for this program are:

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

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on the incidence of:

- Treatment emergent Adverse events (AEs)
- 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. 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 treating physician.

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.

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

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

5.2.3 Safety laboratory parameters

Safety laboratory examinations include liver function tests for elibility check: aspartate transaminase (AST/GOT), alanine transaminase (ALT/GPT), alkaline phosphatase, and total bilirubin.

Any additional laboratory testing during the program is optional and should be performed at the discretion of the treating physician 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 hepatic injury 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).

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 or not considered related to the medicinal product.

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 program 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 that 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,
- requires 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.

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 further 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 above.

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 program, 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 DILI
A potential severe DILI that requires follow-up is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (aspartate transaminase) and/or ALT (alanine aminotransferase) ≥ 3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw 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. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Systemic hypersensitivity reactions including [redacted] reactions and anaphylactic reaction
Any suspicion of severe systemic hypersensitivity including [redacted] 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 1.4 and 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 ICF for details).

5.2.4.1.6 Causal relationship of AEs

Medical judgement should be used to determine the relationship between the adverse envent 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, taking into account 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 program 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 program (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 program: the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and program drug-related SAEs and program 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 program, the patient should be re-evaluated to ensure that eligibility criteria are still met and the overall program is still running in order to assess AEs (serious and non-serious) and AESIs.

Vital Status Data Collection
Patients who withdraw their consent to program participation, who agree to be contacted further but do not agree to physical visits, should be followed up as described in section 3.2.4.2, withdrawal from program treatment. Thus, for patients who withdraw their consent

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 program drug-related SAEs and and program 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 instances, 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 to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

5.2.4.2.3 Information required

All (S)AEs, including those persisting after individual patient's end of program, must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.4.2.4 Pregnancy

In rare cases, pregnancy might occur in a clinical program. Once a patient has been enrolled in the clinical program and has taken program medication, the investigator must report any drug exposure during pregnancy (DEDP) in a program 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 PROGRAM PROCEDURES AT SELECTED VISITS

6.1.1 Screening period

After informed consent, patients considered for this program 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 (urine or 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 [redacted], 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 [redacted].
- 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 [redacted], 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 [redacted].

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, [redacted] of spesolimab may proceed immediately.

6.1.2 Treatment period(s)

Spesolimab will be administered [redacted] in the clinic.

If deemed necessary by the treating physician (i.e. if the flare symptoms persist), [redacted] spesolimab may be administered [redacted] after the initial [redacted].

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

6.1.3 Follow up period and program completion

Patients will visit the treating physician at approximately week [redacted], week [redacted] and week [redacted] after [redacted] drug administration. If the patient requires [redacted] of spesolimab, visits will be re-scheduled based on the date of the last [redacted], i.e, patients will visit the treating physician at approximately week [redacted], week [redacted], week [redacted], and week [redacted] after initial dose of spesolimab. Additional visits within the [redacted]-week follow-up period can be planned according to standard clinical practice. Visits not including the mandatory presential visits at screening (baseline) and [redacted] week after (any) administration of spesolimab, may also be conducted by phone or video if judged appropriate by the treating physician. 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 program will end after conclusion of the [redacted]-week follow-up period after the last [redacted] / drug administration. The Trial (Program) Completion eCRF page will be completed at this time.

A patient will be considered lost to follow-up if the treating physician is not able to contact the patient despite multiple attempts. Every effort must be made to contact the patient and 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 [redacted]-week follow-up period, the patient may re-enter in the program with the same patient number and be treated again with spesolimab, providing eligibility criteria are still met and the overall program 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 [redacted]-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.

Then, in case of re-entry due to a new GPP flare within the [redacted]-wks follow-up period, the patient will end the current follow-up period, and restart the program from the screening for eligibility. If eligibility criteria are met, and permission from BI is granted (see above), the patient can be treated again to receive a new dose of spesolimab. After [redacted], the patient is followed-up for [redacted]-weeks after the latest dose of spesolimab. Also for this scenario, after [redacted] week, a [redacted] 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.

[redacted]

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 program 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 program 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.

7.1.2 Efficacy analyses

[redacted]

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

The program 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 EU directive 2001/20/EC / EU regulation 536/2014, 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.

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

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the program 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 program are described in the investigator contract. As a rule, no program results should be published prior to finalization of the Clinical Trial Report of the program.

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

8.1 PROGRAM APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This program will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments. Prior to patient participation in the program, 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 program 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 program patients 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 program. 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 program collaborator has given a supplementary explanation, the program 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 program quality management. It is initiated by the assessment of critical data and processes for program 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 program 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 program conduct, program design or monitoring approaches. A quality assurance audit/inspection of this program 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 program-related files and correspondence, and the informed consent documentation of this clinical program.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to section 4.1.4.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and program records that include all observations and other data pertinent to the investigation on each program 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 program and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make 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 program (substance, program number, patient number, date patient was informed).
- Dates of patient's visits, including dispensing of program medication.
- Medical history (including program 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 program (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical program, there must be documented evidence in the source data (e.g. medical records) that the program 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 program.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site program-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 will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Program site(s):
The program 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 program (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

Individual patient data obtained as a result of this program is considered confidential and disclosure to third parties is prohibited with the exceptions noted in section 8.7.

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.

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 program need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6 PROGRAM MILESTONES

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

The end of the program is defined as the date when the last patient completes the follow up period after the last [redacted] of spesolimab in the whole program ("Last Patient Completed").

The "Last Patient Last Treatment" (LPLT) date is defined as the date on which the last patient in the whole program 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 program is defined as the premature termination of the program due to any reason before the end of the program as specified in this protocol.

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE PROGRAM

The program is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this program. 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 program in accordance with applicable regulations and internal SOPs,
- direct the clinical program team in the preparation, conduct, and reporting of the program,
- ensure appropriate training and information of Clinical Trial Managers (CTM), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the program 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 Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical program. 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 program.

Tasks and functions assigned in order to organise, manage, and evaluate the program 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 program. 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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c09985235-01 [redacted]

10. APPENDICES

10.1 APPENDIX 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)

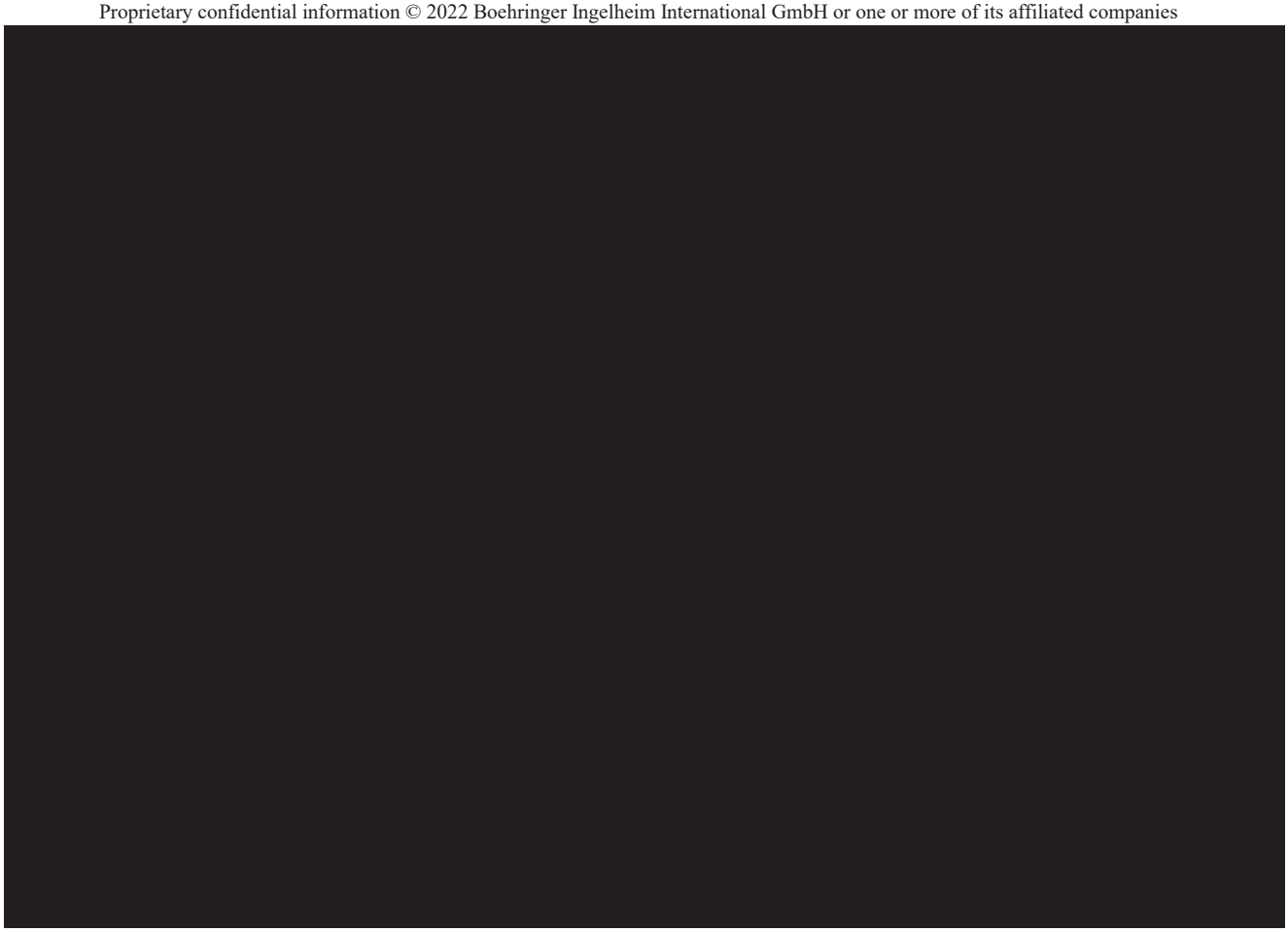
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalised hives, itch-flush, swollen lips / tongue / uvula)
   b. Respiratory compromise (e.g., dyspnoea, wheeze-bronchospasm, 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 PROTOCOL AMENDMENT(S)

Version 1.0 update to version 2.0

Section number	Description of change
Table 1.4:1 Risks associated with spesolimab administration	Peripheral neuropathy added. Update made according to updated IB.
3.2.3 Exclusion criteria	New exclusion criteria added: 7. Presence of acute myelinating neuropathy. Update made according to updated IB.
3.2.4.1 Discontinuation of trial medication and assessment	New stopping rule added for myelinating neuropathy. Update made according to updated IB.
5.2.4.1.4. Adverse evenst of special interest	Event suspected or diagnosed as peripheral neuropathy added. Update made according to updated IB.
[redacted]	[redacted]
3.1 Overrall program design and plan	New flow chart added
[redacted]	[redacted]