Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	c29867818-04
EudraCT No. **EU Trial No.**	2020-000189-41	
BI Trial No.	1368-0024	
BI Investigational Medicinal Product(s)	Spesolimab, BI 655130	
Title	An open-label, single arm, long term trial of Spesolimab treatment in patients with Palmoplantar Pustulosis (PPP) who have completed previous BI Spesolimab trials	
Lay Title	A study to test long-term treatment with Spesolimab in people with Palmoplantar Pustulosis (PPP) who took part in previous studies with Spesolimab	
Clinical Phase	II	
Clinical Trial Leader	[redacted] Tel.: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Tel.: [redacted] Fax: [redacted]	
Version and Date	**Version: 4.0**	**Date: 23 Jun 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	31 Mar 2020
Revision date	23 Jun 2022
BI trial number	1368-0024
Title of trial	An open-label, single arm, long term trial of Spesolimab treatment in patients with Palmoplantar Pustulosis (PPP) who have completed previous BI Spesolimab trials
Coordinating Investigator	[redacted] Tel.: [redacted] Fax: [redacted]
Trial site(s)	Multi-centre trial
Clinical phase	II
Trial rationale	Evaluate long term safety and efficacy in patients with Palmoplantar Pustulosis; Offer patients with a health benefit in the parent trials to continue Spesolimab (BI 655130) treatment with the aim to maintain their health benefit;
Trial objective(s)	1) To evaluate the long-term safety of Spesolimab (BI 655130) in patients with PPP, who have completed previous Spesolimab (BI 655130) trials and are qualified for entry in this trial. 2) To evaluate the long-term efficacy of Spesolimab (BI 655130) in patients with PPP, who have completed treatment in previous Spesolimab trials and are qualified for entry in this trial.
Trial endpoints	Primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) up to week 260 of maintenance treatment Secondary endpoints are - Percent change in PPP ASI from baseline in parent trial at week 48, 96, 144, 192, 240 and 260 - Proportion of patients with PPP ASI50 compared to baseline in parent trial at week 48, 96, 144, 192, 240 and 260 - Proportion of patients with PPP PGA of 0 (clear) or 1 (almost clear) at week 48, 96, 144, 192, 240 and 260
Trial design	Open label (OL), 5 years treatment, single arm, long-term extension trial
Total number of patients randomised	No randomisation, 500 patients from parent trial expected

Number of patients on each treatment	Only one open label dose, 500 patients from parent trials expected
Diagnosis	Palmoplantar Pustulosis
Main in- and exclusion criteria	• Willing male or female patients who have completed treatment in one of the parent trials without premature discontinuation • Patients who have obtained an individual health benefit, per investigator judgement (such as PPP PGA of 0 (clear) or 1 (almost clear) or other clinical improvement), from treatment in the parent trial. • Women of childbearing potential (WOCBP) must be ready to use highly effective methods of birth control • Patients who experienced study treatment-limiting adverse events during their pre-ceding trial are to be excluded.
Test product(s)	Spesolimab, BI 655130
dose	600 mg every 4 weeks
mode of administration	subcutaneous (s.c.)
Comparator product(s)	Not applicable
dose	Not applicable
mode of administration	Not applicable
Duration of treatment	260 weeks
Statistical methods	Descriptive statistics only

FLOW CHART VISIT 1-15

Please see also footnotes at the very end of the Flow Chart table.

Trial Periods	**Screening**	**Maintenance Treatment**													
Visit	**1**[1]	**2**[2]	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Week	N/A	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Day	-28 to -1	1	29	57	85	113	141	169	197	225	253	281	309	337	365
Visit Window (days)	N/A	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed consent	X[4]														
Review of in-/exclusion criteria	X														
Demographics	X														
Baseline conditions, Medical History	X														
Infection Testing[5]	X[1]													X	
Physical examination[6]	X[C,1]					X[T]				X[T]				X[C]	
Vital signs[7]	X[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking status / history[20]	X													X	
12 lead-ECG[8]	X[1]													X	
Pregnancy test[9]	X[1,U,(S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]	X[U, (S)]
Safety laboratory tests[10]	X[1]					X				X				X	
[redacted]		[redacted]				[redacted]				[redacted]				[redacted]	
[redacted]		[redacted]				[redacted]				[redacted]				[redacted]	
[redacted]		[redacted]				[redacted]				[redacted]				[redacted]	
[redacted]	[redacted]					[redacted]				[redacted]				[redacted]	
PPP PGA, [redacted]	X[1]					X				X				X	
PPP ASL [redacted]	X[1]					X				X				X	
[redacted]	[redacted]					[redacted]				[redacted]				[redacted]	
[redacted]	[redacted]					[redacted]				[redacted]				[redacted]	
[redacted]	[redacted]									[redacted]				[redacted]	
[redacted]	[redacted]									[redacted]				[redacted]	
IRT Call	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administer trial drugs[15]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Local tolerability[16]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[17,18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion															

FLOW CHART VISIT 16-EOS

Trial Periods	**Maintenance Treatment**													**Follow-up**
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**	**27-66**	**67/ EoT**	**68/EoS[3]**
Week	56	60	64	68	72	76	80	84	88	92	96	Repeat every 4 weeks until EoT	260	16wks after the last trial drug administration
Day	393	421	449	477	505	533	561	589	617	645	673		1821	
Visit Window (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Informed consent														
Review of in-/exclusion criteria														
Demographics														
Baseline conditions, Medical History														
Infection Testing[5]											X	X^{5}	X	
Physical examination[6]			X^{T}				X^{T}				X^{C}	$X^{T,19}$	X^{C}	X^{C}
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking history/status											X	X^{20}	X	X
12 lead-ECG[8]											X	X^{8}	X	X
Pregnancy test[9]	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$	$X^{U,(S)}$
Safety laboratory tests[10]			X				X				X	X^{19}	X	X
[redacted]														
PPP PGA, [redacted]			X				X				X	X^{19}	X	X
PPP ASL [redacted]			X				X				X	X^{19}	X	X
[redacted]														
IRT Call	X	X	X	X	X	X	X	X	X	X	X	X	X	
Administer trial drug[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	
Local tolerability[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events[17, 18]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion														X

[1]Visit V1 of this long-term extension study should be performed during the last treatment visit (EoT) of the preceding parent trial of Spesolimab (BI 655130). This is strongly recommended.

Assessments done at the EoT-visit in the parent trial do not have to be repeated for Visit V1 in this extension trial. In case it is not possible to perform V1 of the extension trial at the EoT visit of the parent trial, the maximum days allowed between EoT parent trial and V1 of this trial will be 28 days. The time window for Visit 1 may be extended at the discretion of the Clinical Trial Leader on a case by case basis.

Even in this case the procedures of V1 that were already performed at EoT of the parent trial will not be repeated if there are no clinically significant changes in PPP and clinical status of the patient.
Important: results of lab or any other assessment that needs to be repeated in the opinion of the investigator must be available prior to V2 (1st IMP administration in the extenstion trial

See Section 6.2.1 for detailed instructions.

[2]V2 (= 1st IMP administration in extension trial) must be performed on Day 28 (±7) from EoT of parent trial (last IMP administration). The time window between last IMP administration in the parent trial and the first IMP administration in the extension trial may be extended in exceptional cases at the discretion of the Clinical Trial Leader on a case by case basis.

[3]For patients who discontinue study medication in the extension trial before their scheduled end of treatment, an early EoT visit has to be scheduled. Subsequently EoS visit 16 weeks after the last dose of study medication has to be performed.

[4]The written informed consent (IC) must be obtained prior to performing any study related procedures. Date of IC will be reported in the eCRF.

[5]Infection testing at screening includes tuberculosis (TB), hepatitis B (HBV), hepatitis C (HCV), and HIV assessments. In patients with negative TB result, repeat the test approx. once a year at visits in Wk48, 96, 144, 192, 240 and at EoT, as long as the TB result is negative. HBV (not HCV and HIV) to be repeated at EoT.
For details on infection testing please see Section 5.2.3 **incl. table and important footnotes**. See Section 3.3.4.3 for newly occurring infections during the trial.

[6]Physical examination: C=complete incl. weight, T=targeted (focus on evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities). For details please see Section 5.2.1

[7]Measurement of vital signs should precede blood sampling and will be assessed pre-dose at all dosing visits and at approx. 10 minutes after study drug administration. For details please see Section 5.2.2

[8]ECG measurements should always precede blood sampling and drug administration. ECGs are taken approximately once a year: at screening (not to be repeated if done at EoT in parent trial) and at visits in Wk 48, 96, 144, 192, 240, EoT and EoS; For details please see Section 5.2.4

[9]Pregnancy testing is applicable only for women of childbearing potential (WOCBP).
U - urine pregnancy tests will be performed at all visits. Urine pregnancy testing should be done locally on-site prior to administration of study drug by using the urine-dipstick test provided by central lab. Study drug should only be administered in case of a negative test result. In case of a positive urine test result, the visit will be re-scheduled, IMP administration postponed and serum pregnancy test performed.
(S) - in case of a positive urine pregnancy test, a serum pregnancy test will be done and evaluated by the central lab. In case of a positive serum test, the patient must be discontinued from the trial. In case

of a negative serum test the trial team should be contacted to discuss if the previous visit can still be re-scheduled or must be skipped.

[10]Includes clinical chemistry, hematology, coagulation and urinalysis assessments. Patient is not required to be fasting prior to blood collection but information on food before blood collection must be collected. At visits with study drug administration blood sampling should be done prior to the study drug administration. **TSH and HbA1c to be done at screening (not done at EoT in parent trial) and approximately yearly thereafter** in Wk48, 96, 144, 192, 240 and at EoT . Please see Section 5.2.3 for details.

[redacted]

[15]First study drug administration will be administered at V2 after eligibility criteria are confirmed. Administration of the study drug must be performed by a healthcare professional. Drug will be administered after PPP assessments. For the sequence of procedures please see Section 6.2.

[16]Local tolerability will be assessed during the study drug administration on site and retrospectively by asking the patient if local tolerability related AEs occurred. Please see Section 6.2.2 for details.

[17]After a patient´s EoS-visit in the extension trial the investigator does not need to actively monitor the patient for new AEs but should only report new malignancies or the exacerbation of existing malignancies, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication. See Section 5.2.6.2.2 for details.

[18] Please see Section 5.2.6.2.1 for important instructions regarding AE collection in parent and extension trial.

[19]Repeat every 16 weeks, at EoT and EoS

[20]Current smoking status needs to be completely re-assessed at V1 of extension trial. Afterwards changes in smoking should be evaluated approximately once per year at visits in Wk 48, 96, 144, 192, 240, EoT and EoS;

[redacted]

[redacted]

[redacted]

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[redacted]

ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
CA	Competent Authority
C_{max}	Maximum Concentration
CMV	Cytomegalovirus
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EoS	End of Study
EoT	End of Treatment
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FUP	Follow-up
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
HA	Health Authority
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
i.v.	intravenous
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRD	Multiple Rising Dose
Nab	Neutralizing Antibody
OPU	Operative Unit
PFS	Pre-filled syringe
PK	Pharmacokinetics
PRO	Patient Reported Outcome
PVAN	Polyomavirus nephropathy
RA	Regulatory Authority
REP	Residual Effect Period
s.c.	subcutaneous
SAE	Serious Adverse Event
(S)AE	(Serious) Adverse Event – refers to both serious and non-serious AE
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SUSAR	Suspected Unexpected Serious Adverse Reactions

TB	Tuberculosis
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
WHO	World Health Organisation
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

The target indication is Palmoplantar Pustulosis (PPP), a disease with a high unmet medical need. PPP is a chronic disease and a form of pustular psoriasis (as is Generalized Pustular Psoriasis, GPP). Recent evidence suggests that PPP and GPP are genetically distinct from chronic plaque psoriasis as the major genetic determinant PSORS1 for plaque psoriasis has not been found in PPP and GPP patients [R16-3560; R16-3546]. Gene expression [R16-3543] and human genetic [R16-3553, R15-1421, R16-0950, R16-3544] and clinical data imply that the IL36 pathway (targeted by Spesolimab, BI 655130) drives the pustular psoriasis diseases of PPP and GPP [P19-01888, R16-0950, R16-3561, R16-3544].

Genetic human studies have established a link between IL36R signalling and PPP: The same hypomorphic missense mutation in IL36RN reported for GPP [R16-0950; R16-3561] has also been observed in PPP, albeit to a lesser extent as compared to GPP [R16-3544].

Further genetic linkage between PPP and the IL36 pathway has been recently disclosed. For example, mutations in other genes linked to the IL36 pathway such as CARD14 [R16-3544] and AP1S3 [R16-0928] have been linked to the pathogenesis of all forms of pustular psoriasis including PPP. CARD14 is specifically and predominantly expressed in keratinocytes in the skin. It acts downstream of the IL36 pathway and is a known activator of NF-kB signalling. Mutations in the coding sequence (c.11T>G and c.97C>T) in AP1S3 have been linked to the pathogenesis of all forms of pustular psoriasis including PPP. The gene encodes a subunit of the AP-1 complex. Functionally the occurrence of these rare mutations causes a destabilizing of the AP-1 complex and could be linked to impaired Toll-like receptor 3 signalling and subsequent expression of the anti-inflammatory mediator IFN-β [R16-0928].

Currently there is no standard of care available for the treatment of PPP, i.e., no approved therapy except for Guselkumab in Japan. PPP is notorisouly difficult to treat. Patients usually end up being treated with the currently available systemic treatment options for plaque Psoriasis including retinoids, PUVA, methotrexate, cyclosporine and topical corticosteroids. Unfortunately, these options are usually not effective in reducing duration and severity of PPP. Thus, there is a high unment medical need for patients with PPP.

Spesolimab (BI 655130) will target as a first in class compound the IL36 pathway which is genetically linked to PPP disease pathogenesis and will be investigated in the clinical program for treatment of PPP, a disease with significant unmet medical need.

1.2 DRUG PROFILE

Please see current IB [c03320877] for all details of non-clinical and clinical studies conducted so far. Below a summary of important aspects regarding drug profile is given.

Mode of action
Spesolimab (BI 655130) is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signalling. Binding of Spesolimab (BI 655130) to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways with the aim to reduce epithelial cell/ fibroblast/ immune cell-mediated inflammation and interrupt the inflammatory response that drives pathogenic cytokine production in inflammatory skin diseases including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP) and atopic dermatitis, and inflammatory bowel disease (IBD).

Key pharmacokinetic characteristics
PK analysis showed that exposure (AUC0-tz and Cmax) to Spesolimab (BI 655130) increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. Overall, PK data so far suggests target-mediated drug disposition (TMDD) kinetics for Spesolimab (BI 655130). The effective half-life of Spesolimab (BI 655130) is approximately 4 weeks in the linear dose range in healthy volunteers and approximately 3 weeks in GPP patients. For details please see the IB.

Drug interactions
Drug interaction studies have not been conducted to date. A drug interaction study is planned in a different indication.

Residual Effect Period
The Residual Effect Period (REP) of Spesolimab (BI 655130) is 16 weeks. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.
The median half-life for Spesolimab (BI 655130) observed in the healthy volunteer SRD study, 1368.1, was ~4 weeks.
However, in the patient trial 1368.11 where Spesolimab (BI 655130) was tested in GPP patients, the effective half-life was 23.9 days, ~3.4 weeks. Therefore 16 weeks would correspond to approximately 4 to 5 half-lives in patients, corresponding to 3% -5% of steady state Spesolimab (BI 655130) serum levels.

Data from non-clinical studies

Toxicology studies
Spesolimab (BI 655130) does not bind to IL-36R from common toxicology species. Therefore, meaningful toxicity studies of the molecule cannot be performed in any animal species with Spesolimab (BI 655130). However, hazard identification studies of the mode-of-action (MoA) of IL-36R inhibition were performed in mice using a mouse specific anti-IL-36R monoclonal antibody (BI 674304), which is a mouse IgG2a monoclonal antibody with rat variable regions. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL-36R antagonism were seen at a dose (50 mg/kg, twice weekly) 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 BI 674304 twice weekly for 26 weeks by intravenous injection via the caudal vein. There were no BI 674304-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 (BI 655130) 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 (BI 655130) dosing in humans.

Data from clinical studies

Studies in Healthy Volunteers
Spesolimab (BI 655130) or placebo (PBO) was administered to 78 healthy volunteers (59 on Spesolimab (BI 655130) and 19 on PBO at single ascending i.v. doses from 0.001 mg/kg to 10 mg/kg body weight (1368.1). Safety and tolerability of all tested i.v. doses was good. There were no drug-related Serious Adverse Events (SAEs). There was no apparent relationship between the frequency of AEs and the dose. There were no relevant changes compared to placebo for laboratory safety, including clinical chemistry, haematology, coagulation parameters, and urinalysis. No clinically relevant changes were observed in 12-lead ECGs, vital signs, and cardio-monitoring.

In a multiple rising dose (MRD) trial (1368.2), Spesolimab (BI 655130) or placebo have been administered to healthy volunteers at multiple ascending i.v. doses of 3, 6, 10 and 20 mg/kg given once weekly (qw) for 4 weeks (i.e. 4 administrations) or a single dose of 20 mg/kg (8 subjects each, 3:1 on active or PBO). Overall, Spesolimab (BI 655130) was well tolerated. There were no dose dependent AEs, AEs considered to be dose limiting and no SAEs. In all cases the AEs were of mild or moderate intensity. Furthermore, there were no clinically relevant abnormalities on treatment with Spesolimab (BI 655130) with respect to safety laboratory, vital signs, or ECGs as assessed by a central reader. Importantly, based on the analysis of the ITE studies, more than 90% of peripheral IL36R was engaged for at least 22 weeks after the last application of four weekly doses. For further details and most recent results refer to the current Investigator`s Brochure [c03320877].

Study 1368.3 explored pharmacokinetics as well as safety and tolerability of a subcutaneous formulation of Spesolimab (BI 655130) at two different dose strengths of 150 mg (1 mL) and 300 mg (2 mL) using an open-label, single dose, parallel group, matched pair design to determine the relative bioavailability of the 300 mg s.c. compared to one single 300 mg i.v. dose of Spesolimab (BI 655130). In this study, 36 healthy male and female subjects have been treated with Spesolimab (BI 655130), with 12 subjects per dose group. 35 subjects completed the study per protocol, one subject discontinued for logistical reasons (work-related issues).
The local tolerability of the s.c. formulation can be considered as well tolerated.
The type, intensity and duration of systemic adverse events were similar to what has been observed in the preceding SRD/MRD studies 1368.1 and 1368.2. Most of the AEs were of mild intensity, there were no AEs considered to be dose limiting, and no SAEs.

In 1368.9 trial, 32 healthy Japanese male subjects were enrolled in 4 dose groups comprising 8 subjects per group. The study consisted of three dose groups receiving single rising intravenous doses of Spesolimab (BI 655130) (300 mg, 600 mg, and 1200 mg) and one dose group receiving single subcutaneous doses of Spesolimab (BI 655130) (300 mg). In each dose group, 6 subjects received Spesolimab (BI 655130) and 2 subjects placebo.
The overall AE frequency following administration of single doses of 300 to 1200 mg i.v. or 300 mg s.c. Spesolimab (BI 655130) was comparable with placebo. None of the observed AEs were judged by the investigator as related to the trial medication.

Study 1368-0029 investigated the relative bioavailability, safety, and tolerability of subcutaneous injections (SC) of different doses of Spesolimab (BI 655130) and of different injection sites in healthy male and female subjects using a single dose, mono-centric, open-label, matched-group (gender and weight) design.
A total of 48 subjects entered the trial and completed the planned observation time according to the clinical trial protocol. In total, 43 of the 48 treated subjects (89.6%) reported at least 1 treatment-emergent AE. The frequency of subjects with treatment-emergent AEs was comparable between each treatment group.
Investigator-assessed drug-related AEs were reported for 35 subjects (72.9%) and were reported with similar frequency in each treatment group.
No ‘other significant AEs’ (according to ICH E3), AEs leading to discontinuation of trial medication, AEs of severe intensity, adverse events of special interest, deaths, or other SAEs were reported.
Safety laboratory tests, physical examination, and the evaluation of vital signs, local tolerability, and electrocardiogram recordings revealed no clinically relevant findings.

To sum up, Spesolimab (BI 655130) was safe and well tolerated by the healthy subjects and no safety signal was identified in trial 1368.29.

Studies in Patients
In a multi-center, open-label single arm phase I study (1368.11) to investigate safety, tolerability, pharmacokinetics, pharmacogenomics, and efficacy of a single intravenous dose of Spesolimab (BI 655130) (10 mg/kg) in patients with an acute flare of Generalized Pustular Psoriasis (GPP), 7 patients were treated. This trial could demonstrate that Spesolimab (BI 655130) treatment rapidly stops the flare and clears pustules, the primary lesions in GPP, a disease closely linked to loss-of-function mutations in the natural IL36R antagonist. Spesolimab (BI 655130) was well tolerated and no safety signal was identified in trial 1368.11.

1368.15 was a double-blind, randomised and placebo-controlled trial with 59 patients that was intended to explore safety, tolerance, PK and efficacy in PPP patients. Patients were enrolled in Europe and Canada and randomised in a 1:1:1 allocation ratio and received either 900 mg Spesolimab (BI 655130), 300 mg Spesolimab (BI 655130) or placebo intravenously every 4 weeks over a period of 12 weeks and were monitored for up to 32 weeks.
As there are currently no established nor validated endpoints available to specifically assess clinician- or patient reported outcomes in PPP, several endpoints were explored in this proof of concept trial. The endpoints included a PPP-specific PASI (ppPASI = PPP ASI in the nomenclature of trial 1368-0016) where induration was replaced with pustulation, as the

sterile pustule is the primary component of PPP (as it is in GPP), while the scaling and erythema components remained unchanged. The primary efficacy endpoint was PPP ASI50 at Week 16.
As PPP is a neutrophilic dermatosis characterised by sterile pustules on palms and soles and in light of the rapid response observed on pustule clearance in trial 1368.11 (GPP), change from baseline in pustule severity was also included in the efficacy assessment. The focus on pustules allows to specifically address the impact and benefit of Spesolimab (BI 655130) treatment on PPP disease.
Overall, the baseline disease severity within the trial population was lower than expected because few patients with severe disease were enrolled in the trial. More specifically, half of the patients had a PPP ASI total score at baseline ≤16.70, which was close to the minimum required PPP ASI score of 12 for inclusion. The proportion of patients who achieved PPP ASI50 at Week 16 in the total population was similar in all treatment groups (6 of 19 in 900 mg Spesolimab (BI 655130) arm, 6 of 19 in 300 mg Spesolimab (BI 655130) arm, and 5 of 21 in placebo arm), the primary endpoint was not met. However, post-hoc subgroup analyses indicated efficacy of both doses of Spesolimab (BI 655130) in patients with more severe PPP disease at baseline (above the median baseline PPP ASI value of 16.7). In particular, the results on pustule severity were pronounced with a rapid reduction in pustule severity with evidence of a dose response relationship. In the same subgroup, a mean percent reduction from baseline in PPP ASI has been observed. For details please see the current Investigator´s Brochure [c03320877].
There were no clinically relevant abnormalities on treatment with Spesolimab (BI 655130) with respect to safety laboratory and vital signs. Spesolimab (BI 655130) was well tolerated and no safety signal was identified in trial 1368.15.

Summary
Spesolimab (BI 655130) is an anti IL36R antibody with a high clinical activity to block IL36R signalling, as demonstrated in patients with GPP and PPP. IL36R inhibition shows a favorable nonclinical safety profile in healthy volunteers and in patients tested.
Spesolimab (BI 655130) has been tested in healthy volunteers with single or multiple dosing up to 4 weeks of 20 mg/kg i.v. qw, in GPP patients (1368.11 trial, N=7 in a single i.v. dose of 10 mg/kg) and in PPP patients (1368.15 trial, N=59, i.v. doses 300 mg and 900 mg every 4 weeks) which were all safe and well tolerated.

1.3 RATIONALE FOR PERFORMING THE TRIAL

The target indication is Palmoplantar Pustulosis (PPP), a disease with a high unmet medical need. PPP is a chronic disease and a form of pustular psoriasis (as is Generalized Pustular Psoriasis, GPP). Recent evidence suggests that PPP and GPP are genetically distinct from chronic plaque psoriasis as the major genetic determinant PSORS1 for plaque psoriasis has not been found in PPP and GPP patients. Gene expression and human genetic and clinical data imply that the IL36 pathway (targeted by Spesolimab (BI 655130)) drives the pustular psoriasis diseases of PPP and GPP. PPP may be considered a rare disease. PPP is characterised by the presence of sterile pustules on palms and/or soles, in some cases evolve from vesicles. Despite the limited area of skin involvement in PPP, the disease is very debilitating with a large impact on quality of life including ability to work. PPP symptoms

include pruritus, burning sensations, and pain. In severe cases, the skin affliction makes walking or other activities of daily living challenging if not impossible.

Spesolimab (BI 655130) is currently in development for the treatment of Palmoplantar Pustulosis (PPP). The main rationale of this extension trial is to collect additional longterm safety and efficacy data of Spesolimab (BI 655130) in PPP patients who have previously been treated with Spesolimab (BI 655130)

Additional appreciable benefit for the patients of this extension study is the possibility to receive Spesolimab (BI 655130) as s.c. maintenance treatment with the aim to maintain their positive clinical response reached in one of the preceding Spesolimab (BI 655130) PPP trials, if they are eligible to receive further Speesolimab (BI 655130) treatment in this extension study. If patients lose their benefit during the course of the extension trial in their personal opinion or in the opinion of the investigator, or a preferred treatment option becomes available patients can discontinue trial participation after a discussion with the investigator. As in any other clinical trial patients can also revoke their consent at any time without the need to justify the decision. For all details please see Section 3.3.4.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

Preclinical profiles of Spesolimab (BI 655130) and clinical data from healthy volunteer and patient trials suggest that Spesolimab (BI 655130) is safe, tolerable and may address an unmet medical need in PPP patients by an anti-inflammatory mechanism of action. The data from the completed PoC trial 1368.11, in patients with an acute flare of generalized pustular psoriasis (GPP), demonstrate that Spesolimab (BI 655130) treatment rapidly stops the flare and clears pustules, the primary lesions in GPP, a disease closely linked to loss-of-function mutations in the natural IL36R antagonist. This and the data from 1368.15 indicates that Spesolimab (BI 655130) inhibits IL36R signalling also in human disease and thus has the potential to be further investigated also in PPP patients.

No relevant animal species is available for toxicology testing of the highly human specific antibody Spesolimab (BI 655130). However, preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of IL-36R inhibition in mice, please refer to the IB.

An estimated number of 378 subjects have been exposed to single or multiple i.v. doses of Spesolimab (BI 655130) in ongoing or completed clinical trials as of Sep 2019. Spesolimab (BI 655130) was safe and well tolerated in five healthy volunteer trials evaluating the i.v. and s.c. formulation.
In trial 1368.15 for patients with PPP there were no clinically relevant abnormalities on treatment with Spesolimab (BI 655130) with respect to safety laboratory and vital signs. Spesolimab (BI 655130) was well tolerated and no safety signal was identified. For details refer to IB [c03320877].

1.4.2 Risks

There are no identified or potential risks for Spesolimab (BI 655130), based on the toxicology program or any clinical trials conducted for this product to date. No other IL-36 receptor antagonist is currently approved, providing information on identified risks in molecules of this class.

The risks shown in the table below are hypothetical in nature; these are derived from general safety considerations of immunomodulatory drugs.

In order to protect the patient's safety during conduct of this trial, an independent Data Monitoring Committee has been established for the periodic review of clinical trial safety data.

Table 1.4.2: 1 Risks

Hypothetical risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product		
Drug-induced liver injury (DILI)	Rare but severe event, thus under constant surveillance by sponsors and regulators.	Timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety. See also Section 5.2.6, adverse events of special interest
Systemic hypersensitivity reaction	After administration of any biologic agent or protein, there is a possibility of occurrence of adverse immune reactions which can be local (e.g. redness, pruritus, and or swelling at the injection site) or systemic (e.g. anaphylactic reactions, see also Appendix 10.2).	Patients with a history of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients are excluded from the trial. In case of systemic hypersensitivity reactions including anaphylactic reaction emerging during or after administration of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to interrupt and treat the condition. Systemic hypersensitivity reaction is defined as 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 HA [R11-4890].

Table 1.4.2: 1 Risks (cont.)

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

Table 1.4.2: 1 Risks (cont.)

Hypothetical risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product		
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections. 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].	Screening procedures for infections will be established for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Severe infections and opportunistic infections are considered AESIs for this trial. These conditions and serious infections are subject to close monitoring.
Malignancies	Inhibition of the immune response with an immune-modulating biologic may increase the risk of a decreased immune defense 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 history of malignancy other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix will be excluded from participation in this trial. 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 (BI 655130). Diagnostics and treatment have to be initiated according to local standard of care. Malignancies represent always serious adverse events and are subject to close monitoring

Table 1.4.2: 1 Risks (cont.)

Hypothetical risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Trial procedures		
Blood Sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	These risks will be addressed by careful safety monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs; (b) selection of experienced sites and site staff; (c) training.

Based on the findings in the nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of Women of Child Bearing Potential (WOCBP) in this study is justified. To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing and contraceptive methods as described in Section 4.2.3.

Patients rolling over into the current open label extension study completed their treatment with the study drug in previous Spesolimab (BI 655130) trials. Even if the balance between safety and efficacy from the parent trials is still unknown at the timepoint the patients are rolled over into this open label extension trial, a long-term treatment is considered justifiable as there is currently no other suitable standard treatment that reliably controls PPP symptoms and is safe and tolerable for a long-term treatment.

Benefit-Risk Assessment in context of COVID-19 pandemic for patients participating in clinical trials investigating Spesolimab:

A thorough assessment based on the data available as of 18 May 2020 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. Available non-clinical and clinical data in 378 subjects (see current Investigators Brochure [c03320877]) have not

shown an increased risk of infections with spesolimab. However, as reflected in Table 1.4.2:1 above and the patient informed consent form, similar to other immune modulating biological treatments, spesolimab may hypothetically 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 clinical trial protocol.

As 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 the 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 studied in trials with spesolimab are not believed to be at higher risk of COVID-19 due to their background or concomitant diseases. Protocol-defined procedures do not impose undue risk to study participants.

The benefit-risk assessment of spesolimab remains favourable in the context of the COVID-19 pandemic. Patients participating in trials with spesolimab are expected to benefit from trial 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 on the trial. However, the investigator may choose to perform the testing as per his/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 clinical trial 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 study entrance and during the study by the investigator in respect of SARS-CoV-2 infection. A suspected or diagnosed, non-severe and non-serious COVID-19 infection should be treated according to the standard of care and interruption of study medication should be considered by the investigator. In case of a confirmed severe (according to RCTC grading in Appendix 10.3), and/or serious COVID-19 infection, trial treatment will be interrupted immediately and appropriate measures for monitoring, treatment and quarantine will be implemented. No further trial medication will be administered until the active infection has resolved. Treatment with study drug may be restarted when the patient has recovered according to investigator's assessment.

The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis.

1.4.3 Discussion

Due to the lack of mechanism- or compound-related safety signals and the antagonistic mode of action of Spesolimab (BI 655130) it is considered likely that PPP patients will not be exposed to undue risks and adverse events in relation to the information that is expected to be gained from this trial. Considering the medical need of the development of an effective and well tolerated drug specifically and directly treating PPP, the benefit of this trial is considered to outweigh the potential risks and justifies the administration of Spesolimab (BI 655130) to patients with PPP. The benefit-risk profile is thus considered appropriate for an experimental therapy at this stage of clinical development.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

To evaluate the long-term safety and efficacy of Spesolimab (BI 655130) in patients with PPP, who have completed previous Spesolimab (BI 655130) trials and are qualified for entry in this trial.

2.1.2 Primary endpoint(s)

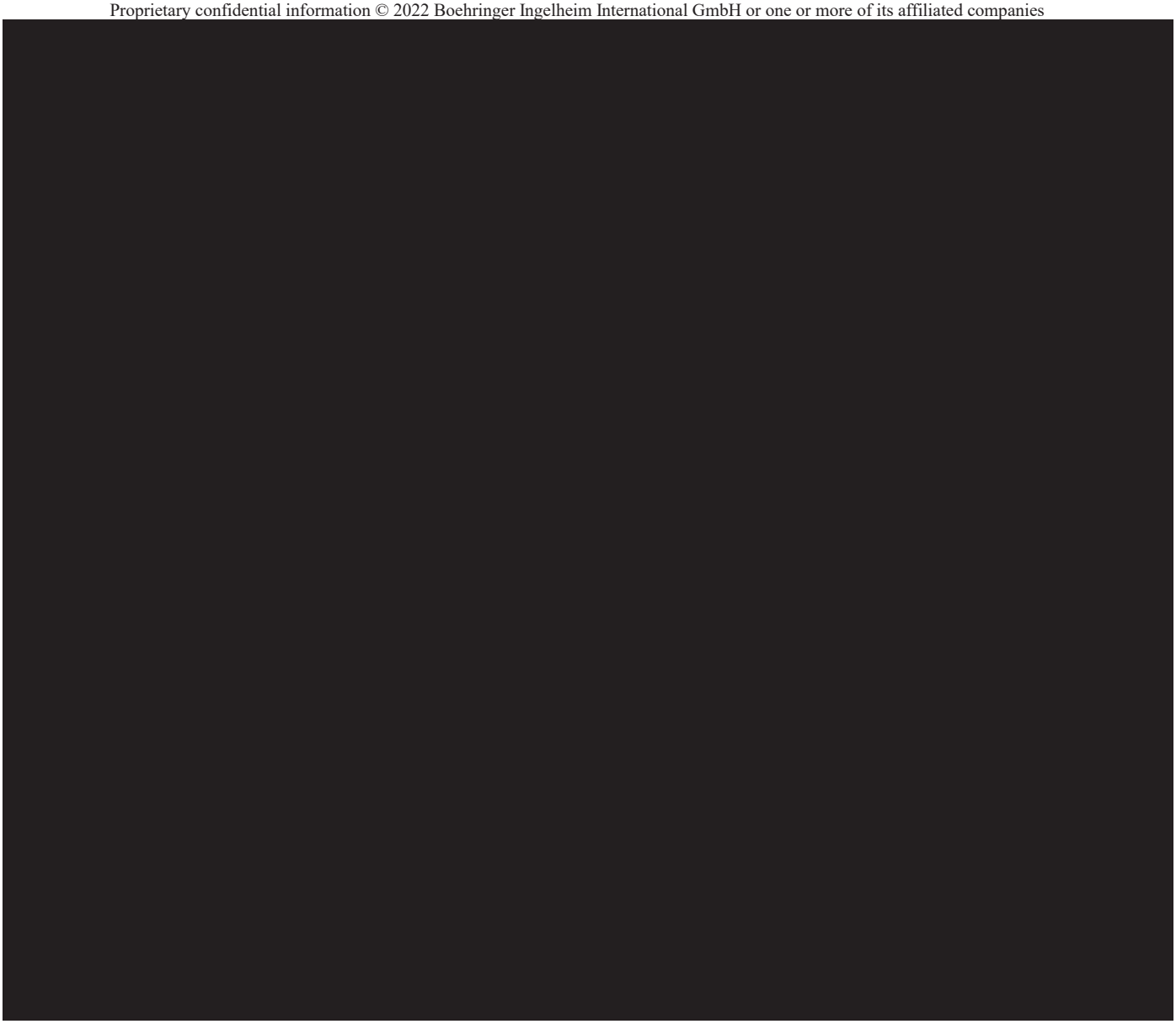
The primary endpoint is the occurrence of treatment emergent adverse events (TEAEs) up to week 260 of maintenance treatment.

Note: TEAEs are defined as all adverse events occurring between start of treatment in the extension trial and the end of its residual effect period. Adverse events that start before first drug intake in the extension trial and deteriorate under treatment during the extension trial will also be considered as 'treatment-emergent'.

2.1.3 Secondary endpoint(s)

The following secondary endpoints are defined as described below. Note that for the secondary endpoints, any data collected after use of any rescue therapy or after 6 weeks following discontinuation of treatment (to allow for incorporation of the continuing maximum treatment effect period) in current trial are censored for the purpose of the primary estimand.

- Percent change in PPP ASI from baseline in parent trial at week 48, 96, 144, 192, 240 and 260
- Proportion of patients with PPP ASI50 compared to baseline in parent trial at week 48, 96, 144, 192, 240 and 260
- Proportion of patients with PPP PGA of 0 (clear) or 1 (almost clear) at week 48, 96, 144, 192, 240 and 260



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This open label, single-arm, multi-regimen, 5-year extension study investigates the long-term safety and efficacy of Spesolimab (BI 655130) in patients with PPP who have completed their treatment in previous Spesolimab (BI 655130) trials (´the parent/preceding/previous trial´). BI trial 1368-0016 is the first trial from which patients will roll over into this extension trial. At a later stage further patients may roll over from planned Phase III trials with Spesolimab (BI 655130).

Approximately 500 patients from the parent trials are expected to meet the entry criteria and are planned to be rolled over into this open-label extension study. Enrollment period will not be expanded in case less than 500 patients can roll over. Patients rolling over into 1368-0024 trial must have completed the treatment period as required in the parent trial. Ideally, the EoT visit of the preceding trial is the Screening visit (V1) of the extension trial. Procedures performed at the last visit of the preceding trial should not be repeated in 1368-0024 (see Section 6.2.1 for details).

If patients lose their benefit during the course of the extension trial in their personal opinion or in the opinion of the investigator, or a preferred treatment option becomes available patients can discontinue trial participation aftter a discussion with the investigator. As in any other clinical trial patients can also revoke their consent at any time without the need to justify the decision. For all details please see Section 3.3.4.

The extension study consists of a screening period lasting up to 28 days for patients rolling over from parent trials, followed by a 260 weeks treatment period and a 16 weeks safety follow-up period. 1st IMP administration in the extension trial should be done 28 days (±7 days visit window) after last IMP administration in preceding trial. The time window between last IMP administration in the parent trial and the first IMP administration in the extension trial may be extended in exceptional cases at the discretion of the Clinical Trial Leader on a case by case basis. Patients will receive open label Spesolimab (BI 655130) 600mg every 4 weeks subcutaneously during the treatment period. This is the highest maintenance dose from the first preceding trial 1368-0016 as this is assumed to provide the optimal treatment effect. At the same time the dose is safe and well tolerated based on the available data so far (see Figure 3.1: 1).

Trial Design

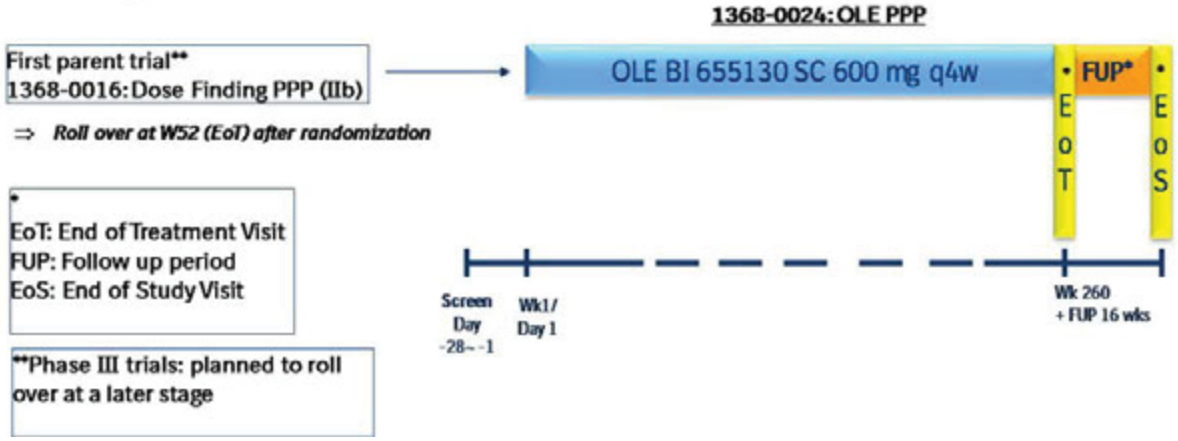


Figure 3.1: 1 One single arm: Spesolimab (BI 655130) 600mg s.c. q4w over 260 weeks

For patients who terminate study drug prematurely in this extension study the subsequent visit will be replaced by an early EoT visit followed by an EoS visit 16 weeks after the last study drug administration (see Figure 3.1: 1).

Interim analyses of [redacted] and clinical data may be performed throughout the conduct phase of this 5-year study to support future trial applications, investigator brochures, regulatory documents and scientific publications. The final analysis of the entire trial data will be performed once all patients have completed the last scheduled trial visit. Individual patient participation is concluded when the patient has completed the last scheduled visit. The end of whole study is defined as “last patient out”; i.e. last scheduled visit completed by the last patient in the study.

An independent Data Monitoring Committee will evaluate safety and efficacy data on a continuous basis.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This open label extension study aims to offer active long-term treatment to patients having benefited from treatment with Spesolimab (BI 655130) in the previous Spesolimab (BI 655130) trials, and to characterize the safety of Spesolimab (BI 655130) long-term treatment. It will also characterize the clinical outcome over a long period of Spesolimab (BI 655130) treatment. Spesolimab (BI 655130) as s.c. treatment is to be offered to maintain the clinical response in PPP that was reached in the parent trials. A control group is not planned in this extension study because there is no established standard of care for PPP and active treatment should be offered for this high unmet needs patient population.

It is acknowledged that the reporting of data for this open-label trial will likely be biased due to, among others, selection and reporting bias. This is, however, deemed acceptable given that all patients who respond to previous treatment and who continue into this extension trial will be able to receive an active treatment with Spesolimab (BI 655130) for their ongoing disease.

3.3 SELECTION OF TRIAL POPULATION

Patients in this long-term open label extension trial will be rolled-over from previous trials with BI 651330. Patients must have completed the treatment of the previous trial and must meet the eligibility criteria for this open label extension trial. Patients must be willing and eligible to continue a long-term treatment with Spesolimab (BI 655130) for up to 5 years.

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

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Patients with PPP who have completed and clinically responded to the treatment with study drug (Spesolimab) in previous trials with Spesolimab (BI 655130).

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

3.3.2 Inclusion criteria

Each patient must meet all of the following inclusion criteria to be included into the trial:

1. Signed and dated written informed consent for the current trial 1368-0024, in accordance with ICH-GCP and local legislation prior to admission to the current trial
2. Male or female patients who have completed the treatment period in one of the parent trials without premature discontinuation
3. Patients who have obtained an individual health benefit, per investigator judgement (**e.g.** PPP PGA of 0 (clear) or 1 (almost clear) or other clinical improvement), from treatment in the parent trial.
4. Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in Section 4.2.3 and in the patient information. *Note: A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.*

3.3.3 Exclusion criteria

Patients meeting any of these exclusion criteria must not be enrolled into the trial:

1. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
2. Patients who experienced study treatment-limiting adverse events during the parent trial.
3. Severe, progressive, or uncontrolled condition such as renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof.
4. Patients with congestive heart disease, as assessed by the investigator.
5. Patient with a transplanted organ (with exception of a corneal transplant >12 weeks prior to screening in parent trial) or who have ever received stem cell therapy (e.g., Prochymal).
6. Known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease (e.g. splenomegaly).
7. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening in parent trial, except appropriately treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
8. Patients who have developed active or severe infective disease and opportunistic infections/infective diseases.

- Patients with **latent** TB during preceding trial are allowed to be included in study 1368-0024, provided they have received and/or receive currently appropriate treatment according to local guidelines. See Section 5.2.3 for more details.

9. Use of any restricted medication as specified in Section 4.2.1 or any drug considered by the investigator likely to interfere with the safe conduct of the study since the last visit of the previous Spesolimab (BI 655130) trial and during screening period for the current trial.
10. Plans for administration of live vaccines during the study period or since parent trial.
11. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
12. Major surgery (major according to the investigator's assessment) performed since the last visit of previous Spesolimab (BI 655130) trial or planned during the current trial (e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator.
13. Patient has received surgical treatment of focal infection (e.g. tonsillectomy or dental therapy) since the last visit of previous Spesolimab (BI 655130) trial or planned during the current trial.
14. Total white blood count (WBC) <3,000/µL (SI unit <3.00 GI/L), or platelets <100,000/µL (SI unit <100 GI/L) or neutrophils <1,500/µL (SI unit <1.5 GI/L), or hemoglobin <8.5 g/dL (SI unit <85 g/L) at screening.
15. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2x the upper limit of normal, or total bilirubin >1.5x the upper limit of normal (patients with Gilbert's syndrome are not excluded) at screening.
16. Any condition which in the opinion of the investigator affects the safety of the patients, the patients´ ability to participate in this trial or could compromise the quality of data.
17. Previous participation in this trial.
18. Presence of acute demyelinating neuropathy

3.3.4 Withdrawal of patients from the trial

Patients may discontinue the trial or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

The decision to discontinue the trial or withdraw consent to trial participation and the reason (if known) must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see Section 5.2.6)

Patients withdrawn form the trial, independent of the underlying reason, should complete an early EoT-visit and the 16 week FUP period for safety reasons (please see Flow Chart and Section 6.2.3.1). This should also be proposed to patients who withdraw their informed consent.

3.3.4.1 Wish to discontinue trial treatment, non-compleance of patient, medical reason and intake of restricted medication

An individual patient will be withdrawn from the trial if:

- The patient wants to discontinue trial treatment, without the need to justify the decision. This includes patients losing individual perceived health benefit or becoming aware of a preferred treatment option.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events – see also Section 3.3.4.3, other diseases, or pregnancy).The patient took restricted medication which is not allowed acc. to Section 4.2.1 and Table 4.2.1: 1.

3.3.4.2 Implications due to loss of treatment response

- Patients who need to take rescue medication must be discontinued from the trial. Rescue therapy is defined as the use of topical corticosteroids or other topical treatment, systemic immunomodulating treatments or biologics and therapy such as tonsillectomy, for the treatment of worsening of PPP. For the complete list and all details of restricted medication see Section 4.2.1 and Table 4.2.1: 1.
- The following additional trial treatment discontinuation criteria apply from Visit 2 onwards:
  - Increase of pustulation severity compared to baseline (baseline (V1) of extension trial)

    AND
  - Loss of PPP ASI by ≥ 5 points compared to baseline (baseline (V1) of extension trial)

A patient who meets the trial treatment discontinuation criteria at 2 consecutive visits must be discontinued from the trial treatment and administered standard of care therapy.

3.3.4.3 Implications of specific adverse events

Systemic hypersensitivity including anaphylactic reaction
In case of systemic hypersensitivity including anaphylactic reaction emerging during or after injection(s) of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to

- Stop further injection(s)
- Treat with systemic anti-histamines, i.v. steroids, and in case of a severe allergic reaction (e.g., anaphylactic reaction) epinephrine

Also draw a plasma sample for IgE and ADA as detailed in the laboratory manual (ISF) and consider the evaluation of histamine and complement components.

In case of systemic hypersensitivity, based on patient's clinical course and medical judgment, injections may be cautiously re-initiated or continued in case of mild or moderate systemic hypersensitivity (according to RCTC grading, provided in the ISF).
In case of anaphylactic reaction based on the criteria discussed in the statement paper from Sampson HA (Appendix 10.2, R11-4890) suspected to be caused by the trial medication, the investigator should discontinue treatment with study drug.
When a non-acute hypersensitivity reaction related to immune complexes (i.e., serum sickness) is suspected, please draw a sample for the laboratory assessment for circulating immune complexes.

Severe infections (according to RCTC grading in Appendix 10.3), serious infections, opportunistic or mycobacterium tuberculosis infection
Treatment of the infection should be initiated promptly according to local standard of care. No further trial medication should be administered until the active infection has resolved. Treatment with study drug may be restarted when the patient has recovered according to investigator's assessment.

- Latent TB must be treated according to local guidelines. Patient can continue the IMP treatment based on the discretion of the investigator.

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, the investigator should discontinue treatment with study drug and withdraw the patient from the trial. Diagnostics and treatment have to be initiated according to local standard of care.
- In case of basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, diagnostics and treatment have to be initiated according to local standard of care. The treatment with study drug should be interrupted until confirmation that the event was treated successfully. Re-scheduling of any missed visit needs to be discussed with the Sponsor.

Peripheral Neuropathy

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.

3.3.4.4 Withdrawal of consent to trial participation

Patients may withdraw their consent to trial participation at any time without the need to justify the decision.
If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the importance to perform still the early EoT (eEoT) visit and to complete the 16 week FUP period to ensure patient´s safety.

3.3.4.5 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time **including but not limited to the following**:
1. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment;
2. Potentially better treatment option becomes available;
3. Deviations from GCP, the trial protocol, or the contract that impairs conduct of the study, patient safety, or data integrity;

Further follow up of patients affected will occur as described in Section 3.3.4.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product has been manufactured by BI Pharma GmbH & Co. KG, Biberach, Germany. The Spesolimab (BI 655130) molecule is an anti-human IL-36 receptor monocloncal antibody heterodimer with a molecular weight of approximately 146 kDa.

4.1.1 Identity of the Investigational Medicinal Products

The investigational product is provided in prefilled syringes of either 1 mL or 2 mL (PFS-1 or PFS-2) volume. The patients rolling over from the first parent trial 1368-0016 will all start with the PFS-2. However, depending on the availability of timely re-supply, there might be the need to switch to the PFS-1 at a later stage of the trial. Therefore, both PFS options are listed in the Table 4.1.1: 1 below and will also be covered in the Patient Information and Informed Consent Form.

Table 4.1.1: 1 Test product Spesolimab (BI 655130)

Substance:	Spesolimab, BI 655130
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co KG
Unit strength:	150 mg in 1 mL solution ⇨ 300 mg/pre-filled syringe, 2 mL fill volume ⇨ 150 mg/ pre-filled syringe, 1 mL fill volume
Posology:	600 mg every 4 weeks
Mode of administration:	Subcutanous injections

4.1.2 Selection of doses in the trial and dose modifications

Patients will receive open label Spesolimab (BI 655130) 600mg every 4 weeks subcutaneously for up to 5 years. This is the highest maintenance dose from the first preceding trial 1368-0016 as this is assumed to provide the optimal treatment effect based on the data from the PoCC trial 1368-0015. Based on the available data so far this dose is also safe and well tolerated. Dose selection data from the parent trials will not be available prior to the 1st patient rolling over to this open label extension trial. As soon as new data from other Spesolimab (BI 655130) trials will become available the impact for this extension trial will be evaluated and if needed the dose would then be adjusted by amendening this protocol (1368-0024).

4.1.3 Method of assigning patients to treatment groups

Not applicable, as all patients in this trial will receive the same treatment.

4.1.4 Drug assignment and administration of doses for each patient

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

Visit 1 of this extension trials is ideally the EoT visit of the parent trial. During this visit no medication assignment for the patients in this open label extension trial is assigned as they receive the last dose of the parent trial during this visit.

At Visit 2 and at all subsequent medication administration visits, IRT will assign medication numbers. Each syringe will have an individual medication number for dispensation. The last dose of medication will be assigned at the EoT-Visit.
Site personnel will enter the medication numbers in the eCRF. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System).

Spesolimab (BI 655130) must be administered as a subcutaneous injection in thighs or abdomen by the investigator or authorized study personnel. The date and time of the administration of each syringe needs to be documentedby the investigator. Details are described in the drug administration manual located in ISF. If a dose was missed or trial treatment was temporary discontinued due to any reason, it must be discussed with the Clinical Trial Leader if the dose can be given later or if the treatment can be re-started.

The injection sites should avoid sites of psoriasis involvement as well as sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is an open label, single arm trial; therefore, no blinding will be necessary. In this open-label trial, treatment allocation will not be concealed throughout the trial.

4.1.5.2 Unblinding and breaking the code

Not applicable.

4.1.6 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). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 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.
If the storage conditions are found to be outside the specified range, the Clinical Trial Manager, identified in the list of contacts, must be contacted immediately.

4.1.8 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 trial protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.
The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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

4.2 RESTRICTIONS

4.2.1 Restrictions on previous and concomitant medications

Restrictions regarding previous and concomitant treatment are summarized in Table 4.2.1: 1

Table 4.2.1: 1 Restrictions regarding previous and concomitant treatment

Medication or class of medications	**Restriction duration**
IL36R inhibitors other than the study drug	not allowed from screening (V1) until the EoS-visit;*
Biologic treatment, e.g. Secukinumab (Cosentyx®), ustekinumab (Stelara®), guselkumab (Tremfya®), ixekizumab, tildrakizumab, brodalumab Adalimumab, infliximab Etanercept Anakinra Natalizumab or agents that deplete B or T cells (e.g. rituximab, alemtuzumab or visilizumab)	not allowed from screening (V1) until the EoS-visit;*
Investigational products for psoriasis	not allowed from screening (V1) until the EoS-visit;*
Live virus vaccinations	not allowed from screening (V1) until the EoS-visit;*
Other systemic immunomodulating treatments (e.g. corticosteroids, methotrexate, fumaric acid esters, acitretin, ciclosporin, apremilast) for the treatment of PPP Any investigational device or product	not allowed from screening (V1) until the EoS-visit;*

Table 4.2.1: 1 Restrictions regarding previous and concomitant treatment (cont.)

Medication or class of medications	**Restriction duration**
Any topical treatment for ***PPP*** (e.g. corticosteroids, vitamin D analogues, salicylic acid, urea, tar, anthralin, keratolytic properties), Phototherapy (e.g. UVA, UVB). This includes all areas affected by PPP, even if extended beyond palms and /or soles (e.g. ankle).	not allowed from screening (V1) until the EoS-visit* Emollients are allowed but must not be used within 24hrs prior to visits with PPP assessments. For details see the skin care instructions in the ISF.
Conditions other than PPP: Topical corticosteroids on palms and/or soles and all other regions also affected by PPP Topical treatments other than topical corticosteroids that may affect the assessment of PPP	not allowed from screening (V1) until the EoS-visit* ***Note:*** *Patients should avoid applying topical treatments with bare hands on allowed body parts (e.g. use gloves).* *Topical corticosteroids on allowed body parts not to be used within 24 hours prior to trial visits in which PPP ASI is assessed.*
Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen/paracetamol	Allowed but recommended that a stable dose is maintained and the medication is not changed.

*if taken, the patient must be discontinued from the trial (see Section 3.3.4) and an early EoT- and regular EoS-visit need to be performed. If taken after an EoT-visit, the regular EoS-visit needs still to be performed.

In the event a patient with prior use of biologic treatment, systemic steroids or immunomodulating treatments is enrolled, past medical records are required to document when these treatments were stopped. All concomitant or rescue therapies will be recorded on the appropriate pages of the CRF.

4.2.2 Restrictions on diet and life style

No specific restrictions on diet or life style of the patients are required.
Emollients will be provided by the sponsor upon request for the patient´s use during the trial. However, emollients must not be used within 24hrs prior to the PPP assessments. Further details will be provided in ISF.

4.2.3 Contraception requirements

Women of childbearing potential (for the definition of WOCBP, please refer to Section 3.3.3) must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during the trial, and for a period of at least 16 weeks after the last study drug administration. A double barrier method of contraception is not required. A list of contraception methods meeting these criteria is also provided in the patient information.

Female Patients:
Acceptable methods of birth control for this trial are:

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal)
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable)
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised sexual partner with documented absence of sperm

Or

Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence, e.g. calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of exposure to study drug and withdrawal are not acceptable.

Male Patients:
Contraception of male trial participants and female partners of male trial participants are not required.

4.3 TREATMENT COMPLIANCE

Treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the Clinical Research Associate (CRA) authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of actual injections} \times 100}{\text{Number of per protocol planned injections}}$$

The measured plasma concentrations will provide additional information about compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

5.1.1 Palmoplantar Pustulosis Area and Severity Index (PPP ASI)

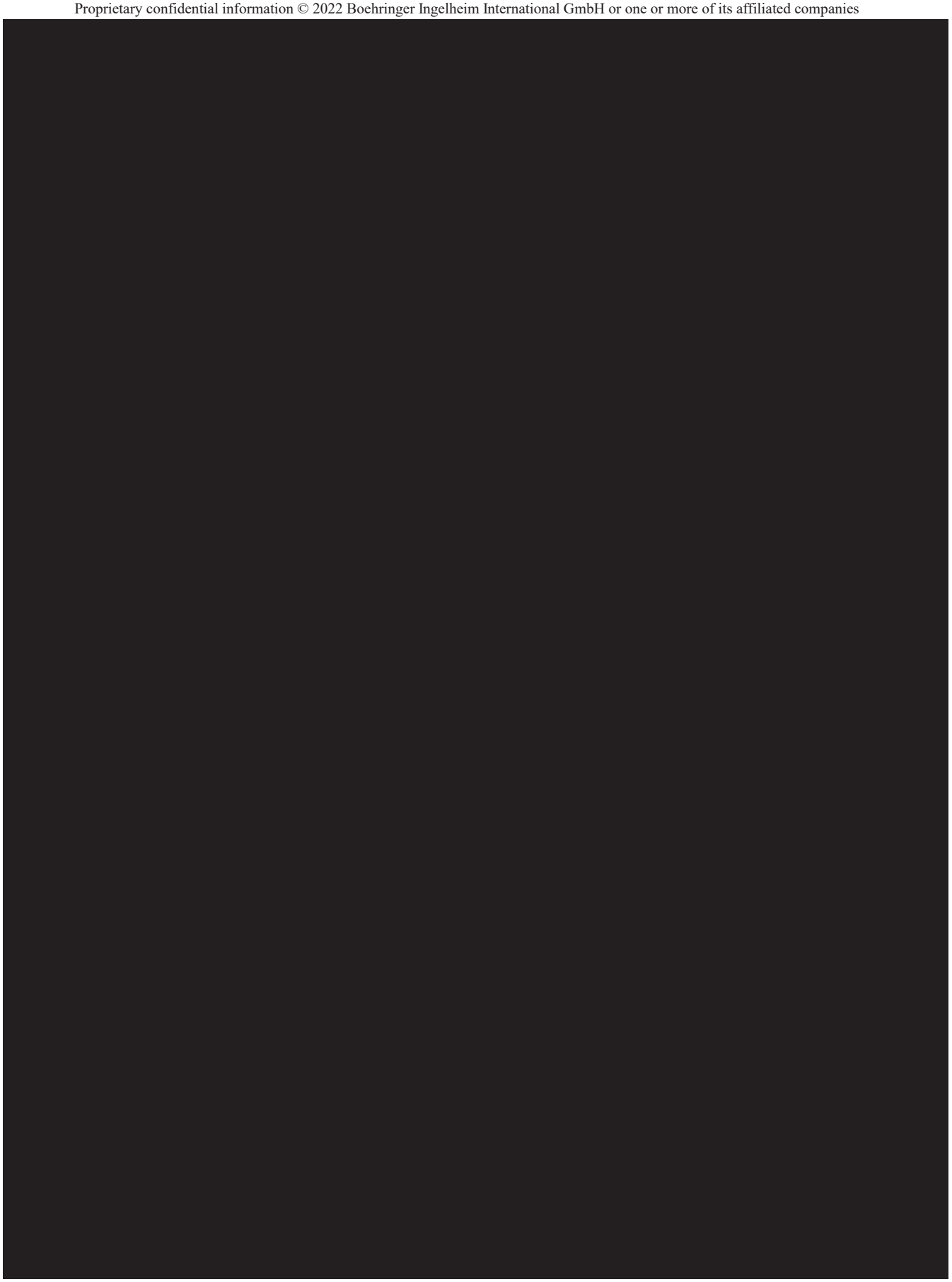
The Palmoplantar Pustulosis Area and Severity Index (PPP ASI) is an investigator assessment of the extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP patients. The adaptation from PASI, an established measure of severity and area of psoriatic lesions in patients with psoriasis, by Bhushan et.al [R16-5334] will be used in this trial.
This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 to 72. It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation).
The PPP ASI will be measured at the timepoints noted in the Flow Chart. The PPP ASI is provided in Appendix 10.1.1.

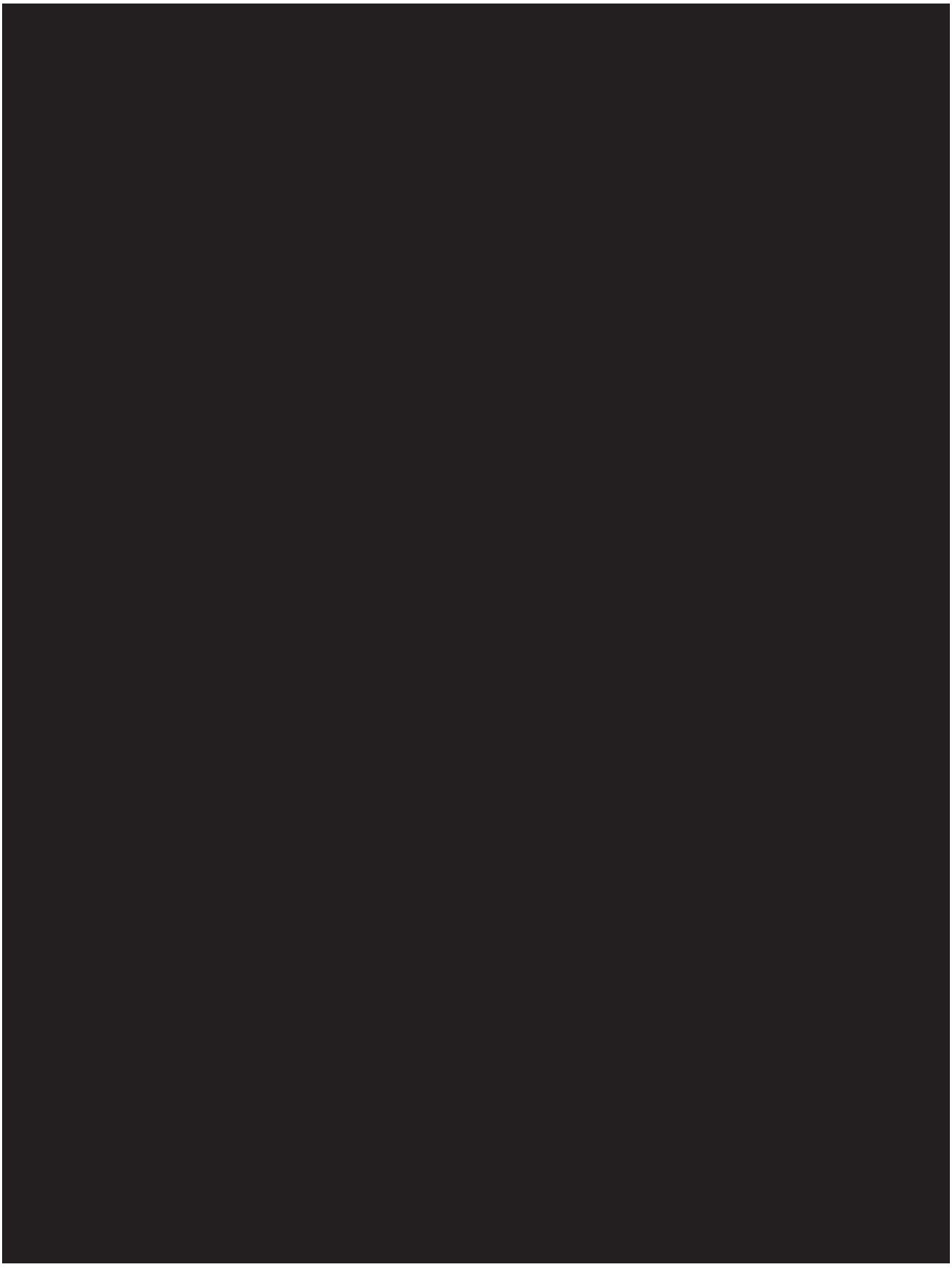
5.1.2 Palmoplantar Pustulosis Physician Global Assessment (PPP PGA)

The Palmoplantar Pustulosis Physician Global Assessment (PPP PGA) relies on clinical assessment of the patient's skin presentation on the palms and soles. The investigator scores the individual components (erythema, pustules and scaling/crusting) from 0 to 4 as clear, almost clear, mild, moderate or severe.
PPP PGA is using severity scores for erythema, pustules, and scaling. The PPP PGA will be analyzed as PPP PGA total score including erythema, pustules and scaling, and as PPP PGA pustules score for pustules only. Further details and practical guidance will be available in the ISF.

The PPP PGA will be measured at the timepoints noted in the Flow Chart. The PPP PGA is provided in Appendix 10.1.2.

[redacted]





5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events (including drug-related AEs and AEs leading to discontinuation)
- Adverse events of special interest (AESIs)
- Serious adverse events (SAEs)
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to Appendix 10.3 and ISF for details)
- Safety laboratory tests
- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature, respiratory rate)
- 12-lead Electrocardiogram (ECG)
- Local tolerability
- Immunogenicity (ADA/Nab)

5.2.1 Physical examination

A complete physical examination incl. weight measurement will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin.
Targeted physical examination without weight measurement will include vital sign assessment and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.
The results must be included in the source documents available at the site.

5.2.2 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Chart, prior to blood sampling. At dosing visits, vital signs evaluations will be performed pre-dose and additional evaluation will be taken at approx. 10 minutes post-dose.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest, and additionally temperature and respiratory rate. The results must be included in the source documents available at the site.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. For the sampling timepoints please see the Flow Chart.

All analyses (except for the urine pregnancy dipstick tests which are done locally at the investigational site) will be performed by a central laboratory, the respective reference ranges will be provided in the ISF.
Patients do not have to be fasted for the blood sampling for the safety laboratory but information of food intake before blood sampling must be collected in the source data of the patient.

Instructions regarding blood and urine sample collection, sample handling/ processing and sample shipping are provided in the laboratory manual in the ISF.
The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4 and the DILI Checklist provided in the ISF). The amount of blood taken from the patient concerned will be increased due to this additional sampling.
The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3: 1 Safety laboratory tests

Category	**Test name**
Haematology	Haematocrit (Hct) Haemoglobin (Hb) Glycosylated Hbc (HbA1c) (**at screening**, and yearly from week 48 onwards) Red Blood Cell Count Reticulocyte Count White Blood Cells / Leukocytes Platelet Count / Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute) Eosinophils (relative and absolute) Basophils (relative and absolute) Monocytes (relative and absolute) Lymphocytes (relative and absolute)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes

Table 5.2.3: 1 Safety laboratory tests (cont.)

Category	**Test name**
Coagulation	Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (Reflex, in case of elevated CK) Protein, Total Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol
Specific gamma-globulin quantification	IgE[2]
Urine Pregnancy test[1] (only for female patients of childbearing potential). At the drug administration visits, the test will be performed and checked at the investigational site prior to the administration of study drug	Human Chorionic Gonadotropin in urine
Serum Pregnancy test[1] (only for female patients of childbearing potential)	Human Serum Chorionic Gonadotropin
Hormones	TSH (free T3 and free T4 in case of abnormal TSH result) (**at screening**, and yearly from week48 onwards)

Table 5.2.3: 1 Safety laboratory tests (cont.)

Category	Test name
Urinalysis	Dipstick (qualitative), test and analysis done by central lab: • Urine Nitrite • Urine Protein • Urine Glucose • Urine Ketone • Urobilinogen • Urine Bilirubin • Urine Blood • Urine Leukocytes Esterase • Urine pH • Urine Creatinine
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC / Erythrocytes Urine Sediment WBC / Leukocytes
Infections testing	Hepatitis B Surface Antigen (qualitative) [3] Hepatitis B core Antibody[3] HBV-DNA (quantitative)[3] Hepatitis C Antibodies (qualitative)[4] HIV-1, and HIV-2 Antibody (qualitative)[4] QuantiFERON®-TB[5,6]

[1] Urine and serum pregnancy testing will be performed as indicated in the Flow Chart.

[2] IgE will be taken in case of systemic hypersensitivity reaction together with ADA (anti-drug antibodies) sample.

[3] HBV at screening and EoT. A HBV-DNA should be conducted if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative.

[4] HCV and HIV at screening only; not to be repeated if done at EoT in parent trial;

[5] If the 1st QuantiFERON®-TB test result is indeterminate, a retest should be performed. If the restest QuantiFERON-TB test result is undetermined, a tuberculin skin test should be performed

[6] In patients with a previously (i.e. in parent trial or in ongoing extension trial) negative QuantiFERON®-TB test, the test should be repeated approx.once a year at visits in Wk48, 96, 144, 192, 240 and at EoT, as long as the results are negative. In case the QuantiFERON®-TB test result changes to indeterminate/positive further work up as a tuberculin-skin-test and x-ray should be inititated to exclude or confirm active TB.

5.2.4 Electrocardiogram

The 12-lead ECGs must be administered by a qualified technologist and results will be recorded as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and assess clinical relevance. ECGs may be repeated for quality reasons and a repeated recording used for analysis. Additional ECGs may be recorded for safety reasons. Dated and signed printouts of ECG with findings should be documented in patient's medical record.
For AE reporting of clinically relevant abnormal findings please refer to Section 5.2.6.2.

5.2.5 Other safety parameters

All cases of malignancies that are detected during the trial will be reported as SAEs. Patients with a history of malignancy (except for specific cancers) will be excluded from this trial per the exclusion criteria (Section 3.3.3). For correct AE reporting in this extension trial refer to Section 5.2.6.2.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 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.

For AE reporting of abnormalities refer to Section 5.2.6.2.

5.2.6.1.2 Serious adverse event

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

For Japan only: the following events will be handled as “deemed serious for any other reason”. AEs which possibly lead to disability will be reported as SAEs.

5.2.6.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.
The latest list of "Always Serious AEs" can be found in the EDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see Section 5.2.6.2.2.

The following are considered as AESIs:

Systemic hypersensitivity reactions including anaphylactic reaction
Any suspicion of severe systemic hypersensitivity reaction and of any potential cases of anaphylaxis should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Appendix 10.2, R11-4890).

Severe infections (according to RCTC grading in Appendix 10.3)

Opportunistic and mycobacterium tuberculosis infections
These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, post-transplant 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].

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST (Aspartate Aminotransferase) 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
- aminotransferase (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, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Peripheral Neuropathy

Any event suspected or diagnosed as Peripheral Neuropathy would be considered as an AESI. For the treatment interruption rules, please see Section 3.3.4.3 Implications of specific adverse events.

5.2.6.1.5 Intensity (severity) of AEs

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by [redacted] [R13-3515]. Refer to the ISF for intensity/severity classification. Intensity options are:

Grade 1	mild
Grade 2	moderate
Grade 3	severe
Grade 4	includes life-threatening

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, 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.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 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 (special notes on SAE form reporting where needed):

- From the time of first dose of trial drug administration in the extension trial until the EoS-visit:

  all AEs (serious and non-serious) and all AESIs

- All AEs that started in the parent trial (onset date in parent trial) and are still ongoing after 1st IMP administration in the extension trial:

  - Re-record the AE in the extension trial eCRF with the same information as it was recorded in the parent trial.
  - Should the AE end during the course of the extension trial (after 1st IMP administration in the extension trial), update only the extension trial eCRF;However, concerning reporting on the SAE form (if applicable), the follow-up report will still be sent on the parent trial SAE form, no new SAE form is to be completed for the extension trial.

- If the intensity of an ongoing AE changes after 1st IMP administration in the extension trial:

  ⇨ update only the extension trial eCRF;

  - ➢ The AE with the new intensity will be handled as new event with the onset of the new intensity as start date; Example: If the intensity increased then the new AE name/term should contain "Worsening of…." or "Exacerbation of….".

  Considerations for reporting on the SAE form, when intensity change qualifies as worsening/exacerbation of an event that had already been reported on the SAE form:
  - corresponding follow up report to be sent on the parent trial SAE form with date of worsening as event end date.
  - extension trial SAE form to be sent as initial report for the extension trial for new event "worsening/exacerbation of…." with date of worsening as onset date.

  Considerations for reporting on the SAE form, when intensity change qualifies as worsening/exacerbation of an event and requires for the first time reporting on the SAE form (meeting for the first time seriousness/AESI criteria):
  - only extension trial SAE form to be sent - as initial report for the extension trial for new event "worsening/exacerbation of…." with date of worsening as onset date.

- All AEs with an end date **before** the 1st IMP administration in the extension trial, even if Informed Consent of the extension trial was already signed:

  - Record only in the eCRF of the parent trial.
  - In case of an AE reportable on the SAE form, send the update only on the SAE form of the parent trial.
  - Do not re-record in the extension trial eCRF, do not complete a new SAE form for the extension trial.

After the EoS visit in the extension trial:

After a patient´s EoS-visit in the extension trial the investigator does not need to actively monitor the patient for new AEs but should only report new malignancies or the exacerbation of existing malignancies, trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see Section 5.2.6.2.2) for the extension trial, but not on the CRF (neither on CRF for extension nor for parent trial).

5.2.6.2.2 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 immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information 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. All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.
For further details specific to the AE reporting of this extension trial see Section 5.2.6.2.1.

5.2.6.2.3 Pregnancy

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

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

[redacted]

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

[redacted]

[redacted]

5.4.3 Methods of sample collection

Sampling of whole blood and serum is described in the laboratory manual in the ISF.

[redacted]

5.5 BIOBANKING

Not applicable

[redacted]

5.7 APPROPRIATENESS OF MEASUREMENTS

The measurements performed during this trial are standard measurements in PPP treatment trials and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way. The [redacted] included in this trial have been used and described in other diseases, including dermatologic conditions, where they have demonstrated adequate

measurement properties. They were included because they explore concepts of PPP that patients and physicians have highlighted as relevant and important.

Therefore, the appropriateness of all measurements applied in this trial is given.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. Each visit date (with its window) up to EoT is to be counted from Day 1 (V2 date = visit with first IMP administration). If any of these visits has to be rescheduled, the date of the subsequent visit should be calculated again from Day 1. EoT of the extension trial refers to the last dose administration of Spesolimab (BI 655130) at week 260. Additional visits (unscheduled visits) for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator. If a visit was missed due to any reason, the Clinical Trial Leader must be contacted to discuss if the visit must be skipped.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and respective protocol sections.

[redacted]

The following sequence of procedures at each visit (where applicable) is recommended; please note: not at all visits all below assessments are needed (please follow Flow Chart).

1. [redacted]
2. AE and concomitant therapy collection; smoking status
3. Physical examinations (including predose vital signs)
4. PPP PGA, PPP ASI, [redacted]
7. ECG
8. Urine pregnancy testing (if applicable)
9. Blood and [redacted] sampling, [redacted]
10. Assign (IRT call) /Administer study drug
11. Local tolerability
12. Post-dose vital signs

6.2.1 Screening period

Study requirements, including the procedure for the follow-up of prematurely withdrawn patients must be fully explained to the patient and written informed consent obtained prior to initiating any study-related evaluation. The importance of staying in the trial until completion of all study requirements will be emphasized. No trial procedures should be done unless the patient has consented to taking part in the trial.

Once consented, the patient is considered to be enrolled in the trial and has started screening. The patient should be recorded on the enrolment log and be registered in IRT as a screened patient. Patients will be assigned a patient number (different from the patient number in the parent trial) generated via the IRT system.

Screening Visit (Visit 1):

Visit 1 of the extension trial should be performed in one visit and in combination with the EoT visit of the preceding parent trial.

The aim of V1 is 1) to evaluate the willingness and eligibility of the patient to take part in this open label extension trial and 2) to collect the baseline data for the extension trial (1368-0024). Note: the endpoints of the extension trial refer to different baselines (either baseline from parent trial or baseline from extension trial); please see Section 2 for details.

This means most of the procedures performed at the EoT visit of the previous trial should not be repeated for V1 of 1368-0024 as the data collected at EoT of the parent trial serve at the same time as screening information for V1 of the extension trial. Please see below a complete list of V1 assessments and how data are handled.

In exceptional cases visit 1 could be performed up to 28 days after EoT of preceding trial. Also in this case procedures of V1 will not need to be repeated if investigator considers that patient does not have any clinical significant change from EoT visit of parent trial. The time between last IMP dose in parent trial (EoT visit) and the first IMP dose in the extension trial should not exceed 28 days (±7 days). The time window for Visit 2 may be extended at the discretion of the Clinical Trial Leader on a case by case basis.
If the investigator considers the patient to have any clinical significant change, re-testing/re-evaluation should be done to determine eligibility. Important: results of lab or any other assessment that needs to be repeated in the opinion of the investigator must be available prior to V2 (1st IMP administration in the extension trial).

Re-screening is not allowed.

Informed Consent
A separate Informed Consent must be obtained for the extension trial before performing any other trial procedure.

Review of In/Exclusion criteria
All in/exclusion criteria must be evaluated/re-considered for the extension trial and documented in the corresponding source data; see Section 3.3 for the in/exclusion criteria of the extension trial.

Baseline Conditions
This refers to chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy (excluding PPP).

- Baseline conditions from the parent trials need to be re-considered and those which are still ongoing after Informed Consent of the extension trial was signed, need to be re-recorded with the same information in the eCRF of the extension trial.
- (S)AEs that ended with sequelae in the parent trial need to be included as baseline condition in the eCRF of the extension trial
- Any new baseline condition needs to be recorded in the eCRF of the extension trial (for example, a missed baseline condition from the parent trial)

Concomitant Medications and Concomitant Non-Drug Therapies (CT)

- Ongoing CTs from the parent trial which are still ongoing after the Informed Consent of the extension trial was signed, need to be re-recorded with the same information in the eCRF of the extension trial.
- CTs which ended in the parent trial, will not be re-recorded in the eCRF of the extension trial.

Demography
Informed consent date, gender, age, race and ethnic origin will be collected/re-recorded in the eCRF page of the extension trial.
Note: information concerning race/ethnicity will be collected, as it has been suggested that there may be race/ethnicity variations in the incidence, phenotypic manifestations and outcome of PPP. However, in some countries, race may not be collected.

Smoking history
The patient's smoking history based on the calculation of pack years will be re-assessed for the extension trial and newly recorded to the extension trial eCRF. See Appendix 10.4 for details.

Medical History:
Past medical history reported in the parent trial eCRF is not re-recorded in the extension trial eCRF.
If some historical information was missed in the parent trial, it should be recorded to the parent trial if it is not yet locked. If the parent trial is already locked, the missed information can be entered in the extension trial eCRF.
If a new condition developped but recovered during the parent trial this can be recorded in the extension trial if considered relevant information by the investigator.

The following assessments will not to be repeated for the extension trial at screening if V1 of the extension trial is done at the same time as the EoT visit of the parent trial unless the assessment was not done at EoT in parent trial due to any reason. The same is true if the V1

of the extension trial is done later than the EoT visit of the parent trial but there is no significant change in the opinion of the investigator.
The data is recorded only in the parent trial eCRF, not to be re-recored in eCRF of extension trial:

- Infection Testing
- Physical examination, weight
- Vital signs
- 12 lead-ECG
- Pregnancy test
- Safety laboratory tests (except for TSH and HbA1c, as this is not done at EoT in parent trial)
- [redacted]
- PPP PGA,
- PPP ASI
- [redacted]

IRT Contact
IRT system to be contacted at Screening Visit, see Flow Chart;

6.2.2 Treatment period

The treatment period lasts from Visit 2 (Day 1) until the End of Treatment Visit inclusively (EoT/Day 1821).

Study related procedures during treatment period will be performed as specified in the Flow Chart. Review also the notes at the end of the Flow Chart, they include important information regarding time points and important aspect to consider.

The following assessments are done at every visit (every 4 weeks) during treatment period (V2 – EoT inclusively):

Vital signs, plus EoS
Measurement of vital signs should precede blood sampling and will be assessed pre-dose at all dosing visits and at approx. 10 minutes after study drug administration.

Pregnancy test, plus EoS
Urine pregnancy testing for all women of child-bearing potential will be conducted on-site every 4 weeks and must be negative to continue treatment. More frequent testing should be done if required by the local regulation and / or authority or per investigator judgment.
The urine pregnancy testing should be done **prior to** study drug administration. Study drug should only be administered in case of a negative test result. In case of a positive urine test result, the visit will be re-scheduled, IMP administration postponed and serum pregnancy test performed. In case of a positive serum test, the patient must be discontinued from the trial. In case of a negative serum test the Sponsor trial team should be contacted to discuss if the previous visit can still be re-scheduled or must be skipped.

See also Flow Chart.

Concomitant therapy, plus EoS
Data concerning concomitant medications and procedures will be collected throughout the trial. These data will be obtained at scheduled or unscheduled trial visits based on information provided spontaneously by the patient or as a result of questioning the patient.

Adverse Event review/discussion, plus EoS
To be done at every visit, see Section 5.2.6 for more details;

IRT Contact
IRT system to be contacted at each visit until EoT (incl.), see Flow Chart;

IMP administration
IMP is administered at each visit from V2 to EoT (incl.), see Flow Chart;

Local tolerability, plus EoS
Local tolerability at the administration site of the subcutaneous injection will be assessed during the study drug administration on site and retrospectively by asking the patient if local tolerability related AEs occurred. Any observed local tolerability reaction, e.g. "swelling", "induration", "heat", "redness", "pain", and other findings should be reported as an adverse event.

The following assessments are done every 16 weeks during treatment period (EoT inclusively), 1st assessment after screening at week 16 (V6):

Physical examination, plus EoS
See Flow Chart and Section 5.2.1 for details;

Safety laboratory tests, plus EoS
(except: TSH and HbA1c only to be done once per year)
See Flow Chart and Section 5.2.3 for details;

[redacted]

PPP PGA, [redacted], plus EoS
See Flow Chart and Section 5.1.2 for details;

PPP ASI[redacted], plus EoS
See Flow Chart and Sections 5.1.1 and 5.1.5 for details;

[redacted]

[redacted]

The following assessments are done with less frequency during treatment period:

[redacted]

[redacted]

Change in smoking status
Once per year, plus EoT and EoS;
See Flow Chart;

Infection testing (HBV)
At EoT only during treatment period;
See Flow Chart and Section 5.2.3 for details;

Infection testing (TB)
TB testing once per year as long as result is negative, plus EoT;
See Flow Chart and Section 5.2.3 for details;

12 Lead ECG
Once per year, plus EoT and EoS;
See Flow Chart and Section 5.2.4 for details;

[redacted]

[redacted]

[redacted]

Unscheduled visits
The patient may be asked for additional unscheduled visits due to safety reason at the discretion of the investigator or the sponsor, unless the patient has withdrawn his/her consent. The patient may also contact the site due to safety reason for an unscheduled visit. The unscheduled visit may include additional collection of blood samples for safety reasons. The unscheduled visit may also include additional assessments deemed necessary by the investigator such as laboratory samples, ECGs, or other procedures which were missed at a previous visit. All unscheduled visits should be described and documented in the medical/source record, and in the eCRF.

For early discontinuation and withdrawal of patients see Section 3.3.4.

6.2.3 Follow-up period and trial completion

For all patients, termination of trial medication and trial completion must be recorded on the corresponding eCRF.

For patients completing the safety FU period, the EoS visit is scheduled at 16 weeks after the last dose of study drug. For more details please follow Flow Chart.

6.2.3.1 Early treatment discontinuation

Patient who discontinue treatment prior to the planned EoT visit have to be invited for an early EoT visit as soon as possible. These patients should be registered as withdrawn from treatment in IRT and return to the site for the End of Study (EoS) visit 16 weeks after last study drug intake. For more details please the Flow Chart and Section 3.3.4.

No further follow-up on vital status is performed in the extension trial.

6.2.3.2 Trial completion

Patients who finish the treatment period will return to the site for the EoS visit 16 weeks after the EoT visit. Completion is defined as a patient having reached the EoS visit.

6.2.3.3 Further treatment after the end of the trial

At the end of the trial, patients will be treated for their PPP at the discretion of the investigator, according to local PPP guidelines. Ongoing Aes must be followed up sufficiently at the discretion of the investigator.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 NULL AND ALTERNATIVE HYPOTHESES

Given the single arm and open-label nature of this trial, all statistical assessments will be performed in a descriptive manner only. No hypothesis testing is intended to be performed.

7.2 PLANNED ANALYSES

7.2.1 General considerations

This trial is designed as a single arm, open-label trial in patients with Palmoplantar Pustulosis who have completed the planned treatment period in previous (parent) trials with Spesolimab (BI 655130).

The patients eligible for roll over from parent trials receive subcutaneous Spesolimab (BI 655130) 600 mg q4w as maintenance treatment for up to 5 years.

Thus, there will be only one patient population in this trial for analyses: the treated set for maintenance treatment (TS-MT).

There is no confirmatory statistical testing planned during the analysis of this extension trial; only descriptive analyses are intended.

Treated Set for Maintenance Treatment (TS-MT)
This patient set includes all patients who were on the maintenance treatment of 600 mg s.c. q4w.

Further analysis sets will be defined in the TSAP if necessary.

Important violations of the protocol will include deviations of the key inclusion and exclusion criteria, concomitant use of restricted medications, and any other deviations of the protocol deemed important by the study team. All decisions concerning important protocol deviations will be made prior to final database lock for this extension trial.

Standard statistical parameters (number of non-missing values, mean, standard deviation (SD), median, quartiles, minimum and maximum) or frequency tables (including patient frequencies and percentages) will be calculated where appropriate.

A Clinical Trial Report will be prepared once the final database lock for this extension trial has been performed.

7.2.2 Primary endpoint analyses

Refer to Section 7.2.6 for the description of safety analyses including that for the primary endpoint. The primary endpoint will be summarized based on Treated Set for Maintenance Treatment (TS-MT).

7.2.3 Secondary endpoint analyses

Secondary endpoint will be assessed descriptively. Further details will be provided in the TSAP.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. 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 study medication, will be assigned to the on-treatment period for evaluation.

All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

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. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity, and causal relationship of all treatment emergent 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. Exposure adjusted incidence rate of all treatment emergent adverse events will also be presented.

The exposure adjusted incidence rate (per 100 subject years) of a selected treatment emergent adverse event is defined as the number of subjects experiencing the adverse event per treatment group during time at risk divided by the total time of subjects at risk in that treatment group to contribute the event to the analysis multiplied by 100 (per 100 subject year), where:

Time at risk [subject years] = (date of onset of TEAE – study drug start date + 1) / 365.25

If, for a subject, the selected treatment emergent adverse event didn’t occur then the time at risk will be censored at min (date of death, last contact date per EoS page, drug stop date +

112 days). For each selected treatment emergent AE, the exposure adjusted incidence rate will be calculated as:

Incidence rate [1/100 Subject years (pt-yrs)] = 100 * number of subjects with TEAE / Total TEAE-specific time at risk [subject years].

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Immunogenicity data will be analysed descriptively.

[redacted]

7.2.7 Interim Analyses

In order to ensure the patient's safety during the trial, an external DMC, independent of the trial and project teams, will be set-up to review all available safety data as well as selected efficacy data at regular intervals following first-patient-in. A DMC SAP will be produced which describes the analyses required for assessment by the DMC. Further details will be provided in a DMC charter.

As the primary aim of this study is to collect long-term safety and efficacy data on the use of Spesolimab (BI 655130) in this population, multiple interim analyses may be done over the 5-year conduct phase of this trial to support, for example, regulatory interactions, CTA and MAA/BLA submissions, but also to provide important safety and efficacy information to the sponsor to guide further development of the compound, and to the investigators via IB updates and publications.
Since patients will be enrolled into this study over a time period of several years and in line with the exploratory nature and open label design of the study, such analyses will be performed on demand and are not feasible to be pre-defined.

A CTR describing all data collected within this trial will be produced once the last patient in the trial has completed the final follow-up visit.

7.3 HANDLING OF MISSING DATA

Every effort will be made to collect complete data at all visits. However, missing data will still occur and approaches to handle this are proposed below.

For the safety data, including the primary endpoint, no missing data imputations are planned.

For other efficacy endpoints, rules for handling of missing data will be specified in the TSAP if necessary.

7.4 RANDOMISATION

Given the single arm nature of this trial, no randomization will be performed.

7.5 DETERMINATION OF SAMPLE SIZE

Given the descriptive nature of this trial, no sample size calculation has been performed. The sample size of this open label extension trial is determined based on the sample size of the preceding trials.

Approximately 500 patients who meet the entry criteria are expected for inclusion into this trial, rolling over from the preceding trials of Spesolimab (BI 655130).

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the 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. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

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 trial patients against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective 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 trial, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.”

The investigator or delegate must give a full explanation to trial 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 trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.
Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.
A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

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

Before providing any copy of patient´s source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social

security number) have properly been removed or redacted from any copy of the patients' source documents.

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

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

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

8.3.2 Direct access to source data and documents

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

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.
Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:
Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first patient in the whole trial signs informed consent.
The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.
Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

A project-independent, fully-external data-monitoring committee (DMC), will be established to assess the progress of the clinical trial, including an unblinded safety and efficacy assessment at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop either a single Spesolimab (BI 655130) dose or the trial due to safety or ethical concerns. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.
DMC recommendations as well as the final BI decision will be reported to the appropriate Regulatory Authorities (Ras)/Health Authorities (Has), IRBs/Ecs, and to investigators as requested by local law. The tasks and responsibilities of the DMC are specified in a charter.

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, responsible for coordinating all required activities, in order to

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

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

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.
A central laboratory service, a central images service, and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P19-01888 Bachelez H, Choon SE, Marrakchi S, Burden AD, Tsai TF, Morita A, et.al. Inhibition of the Interleukin-36 Pathway for the Treatment of Generalized Pustular Psoriasis. N Engl J Med. 2019. 380(10).

R08-5197 Lange P, Nyboe J, Appleyard M, Jensen G, Schnohr P. Relationship of the type of tobacco and inhalation pattern to pulmonary and total mortality. Eur Respir J. 1992. 5: 1111-1117.

R11-4890 Sampson HA, et.al. Second symposium on the definition and management of anaphylaxis: summary report - second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. 2nd Symp of the National Institute of Allergy and Infectious Disease (NIAID)/Food Allergy and Anaphylaxis (FAA) Network on the Definition and Management of Anaphylaxis, Jul 2005. J Allergy Clin Immunol. 2006. 117(2): 391-397.

R13-3515 Woodworth T, Furst DE, Alten R, Bingham C, Yocum D, Sloan V, et.al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol. 2007. 34(6): 1401-1414.

R15-1421 Onoufriadis A, Simpson MA, Pink AE, Meglio P di, Smith CH, Pullabhatla V, et.al. Mutations in IL36RN/IL1F5 Are Associated with the Severe Episodic Inflammatory Skin Disease Known as Generalized Pustular Psoriasis. Am J Hum Genet. 2011. 89(3): 432-437.

R16-0928 Setta-Kaffetzi N, Simpson MA, Navarini AA, Patel VM, Lu HC, Allen MH, et.al. AP1S3 Mutations Are Associated with Pustular Psoriasis and Impaired Toll-like Receptor 3 Trafficking. American Journal of Human Genetics. 2014. 94: 790-797.

R16-0950 Setta-Kaffetzi N, et.al. Rare pathogenic variants in IL36RN underlie a spectrum of psoriasis-associated pustular phenotypes. J Invest Dermatol. 2013. 133: 1366-1369.

R16-3543 Bissonnette R, Suarez-Farinas M, Li X, Bonifacio KM, Brodmerkel C, Fuentes-Duculan J, et.al. Based on Molecular Profiling of Gene Expression, Palmoplantar Pustulosis and Palmoplantar Pustular Psoriasis Are Highly Related Diseases that Appear to Be Distinct from Psoriasis Vulgaris. Plos One. 2016. 11(5): e0155215.

R16-3544 Moessner R, et al. Palmoplantar Pustular Psoriasis Is Associated with Missense Variants in CARD14, but Not with Loss-of-Function Mutations in IL36RN in European Patients. Journal of Investigative Dermatology. 2015. 135: 2538-2541.

R16-3546 Hashigucci K, et.al. Polymorphism in the tumor necrosis factor B gene is associated with Palmoplantar pustulosis. Tissue Antigens. 1999. 54: 288-290.

R16-3553 Wang TS, Chiu HY, Hong JB, Chan CC, Lin SJ, Tsai TF. Correlation of IL36RN mutation with different clinical features of pustular psoriasis in Chinese patients. Arch Dermatol Res. 2016. 308: 55-63.

R16-3560 Kingo K, Moessner R, Koks S, Raetsep R, Krueger U, Vasar E, et.al. Association analysis of IL19, IL20 and IL24 genes in palmoplantar pustulosis. British Journal of Dermatology. 2007. 156: 646-652.

R16-3561 Tauber M, Bal E, Pei XY, Madrange M, Khelil A, Sahel H, et al. IL36RN mutations affect protein expression and function: a basis for genotype-phenotype correlation in pustular diseases. J Invest Dermatol. 2016.

R16-5334 Bhushan M, Burden AD, McElhone K, James R, Vanhoutte FP, Griffiths CEM. Oral liarozole in the treatment of palmoplantar pustular psoriasis: a randomized, double-blind, placebo-controlled study. British Journal of Dermatology. 2001. 145: 546-553.

R17-2617 Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et.al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis. 2015. 74: 2107-2116.

R17-3632 Mahil SK, Catapano M, Meglio P Di, Dand N, Ahlfors H, Carr IM, et.al. An analysis of IL-36 signature genes and individuals with IL1RL2 knockout mutations validates IL-36 as a psoriasis therapeutic target. Sci Transl Med. 2017. 9: eaan2514.

[redacted]

[redacted]

R96-2382 The EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy. 1990. 16: 199-208.

[redacted]

R20-2256 National Psoriasis Foundation (NPF) COVID-19 Task Force. Updated: COVID-19 recommendations. Website.www.psoriasis.org/advance/coronavirus (access date: 15 July 2020); National Psoriasis Foundation (NPF); 2020.

R20-2257 National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: severe asthma (NICE guideline, published: 3 April 2020). Website.www.nice.org.uk/guidance/ng166 (access date: 15 July 2020) ; National Institute for Health and Care Excellence (NICE); 2020.

R20-2258 American Academy of Allergy Asthma & Immunology (AAAA). An update on COVID-19 for the practicing allergist/immunologist (July 9, 2020). Website.education.a aaai.org/resources-for-a-i-clinicians/Update-for-AI_COVID-19 (access date: 15 July 2020); American Academy of Allergy Asthma & Immunology (AAAA); 2020.

9.2 UNPUBLISHED REFERENCES

c03320877 Investigator's Brochure Spesolimab (BI 655130). Current Version.

10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Palmoplantar Pustulosis Area and Severity Index (PPP ASI)

Score	0	1	2	3	4	5	6
Erythema (E)	None	Slight	Moderate	Severe	Very severe		
Pustules (P) (total)	None	Slight	Moderate	Severe	Very severe		
Desquamation (D) (scaling)	None	Slight	Moderate	Severe	Very severe		
Area affected (%)*	0	<10	10<30	30<50	50<70	70<90	90 - 100

* where area assessed is glabrous skin on the palms/ soles

PPP ASI = [(E+P+D) Area x 0.2 (right palm)] + [(E+P+D) Area x 0.2 (left palm)] + [(E+P+D) Area x 0.3 (right sole)] + [(E+P+D) Area x 0.3 (left sole)]

10.1.2 Palmoplantar Pustulosis Physician Global Assessment (PPP PGA)

Components	
Erythema*	0=Clear; 1=Almost Clear; 2=Mild, 3=Moderate, 4=Severe
Pustules	0=Clear; 1=Almost Clear; 2=Mild, 3=Moderate, 4=Severe
Scaling/Crusting	0=Clear; 1=Almost Clear; 2=Mild, 3=Moderate, 4=Severe

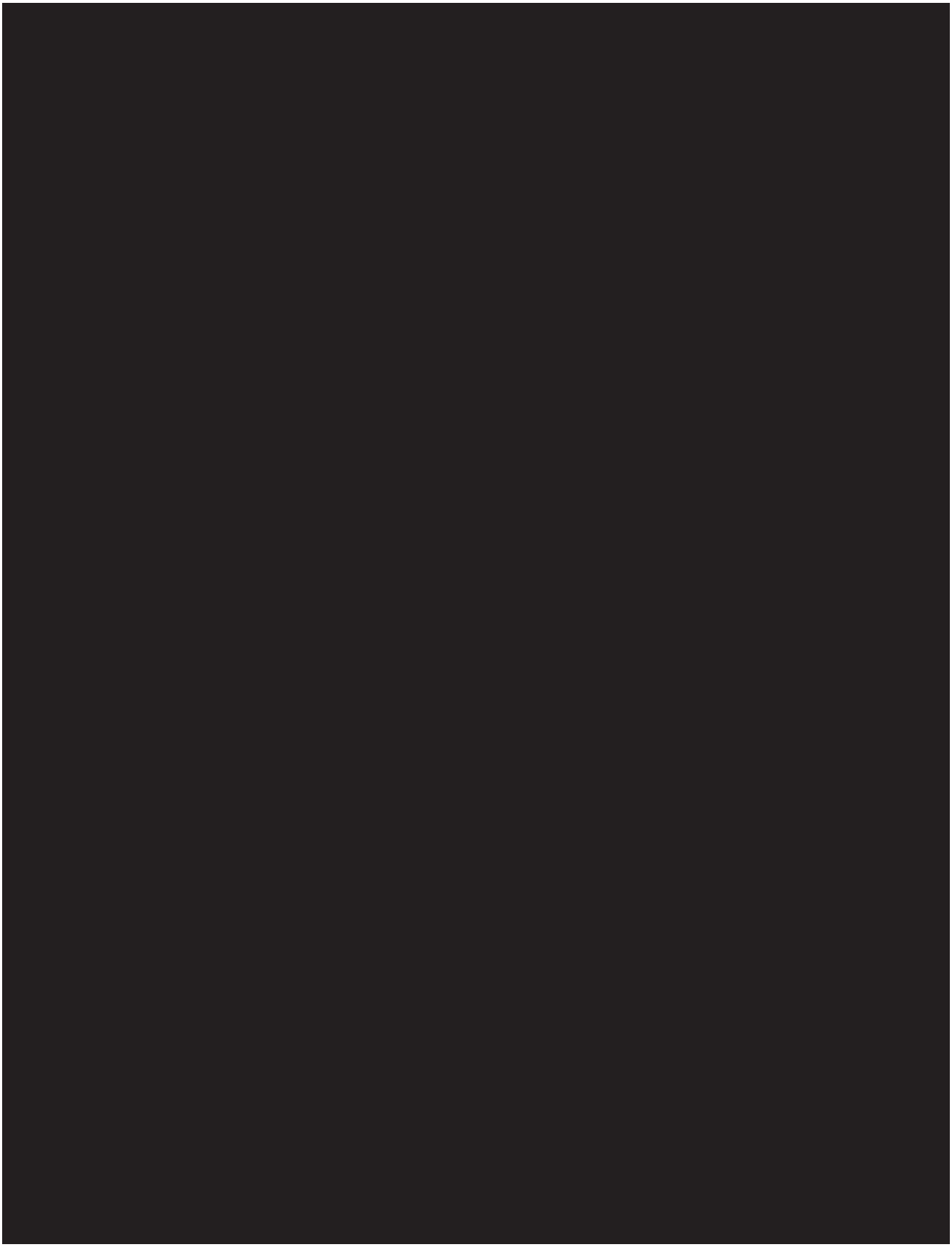
*Do not score eroded area, physiological erythema, frictional hyperkeratosis and calluses

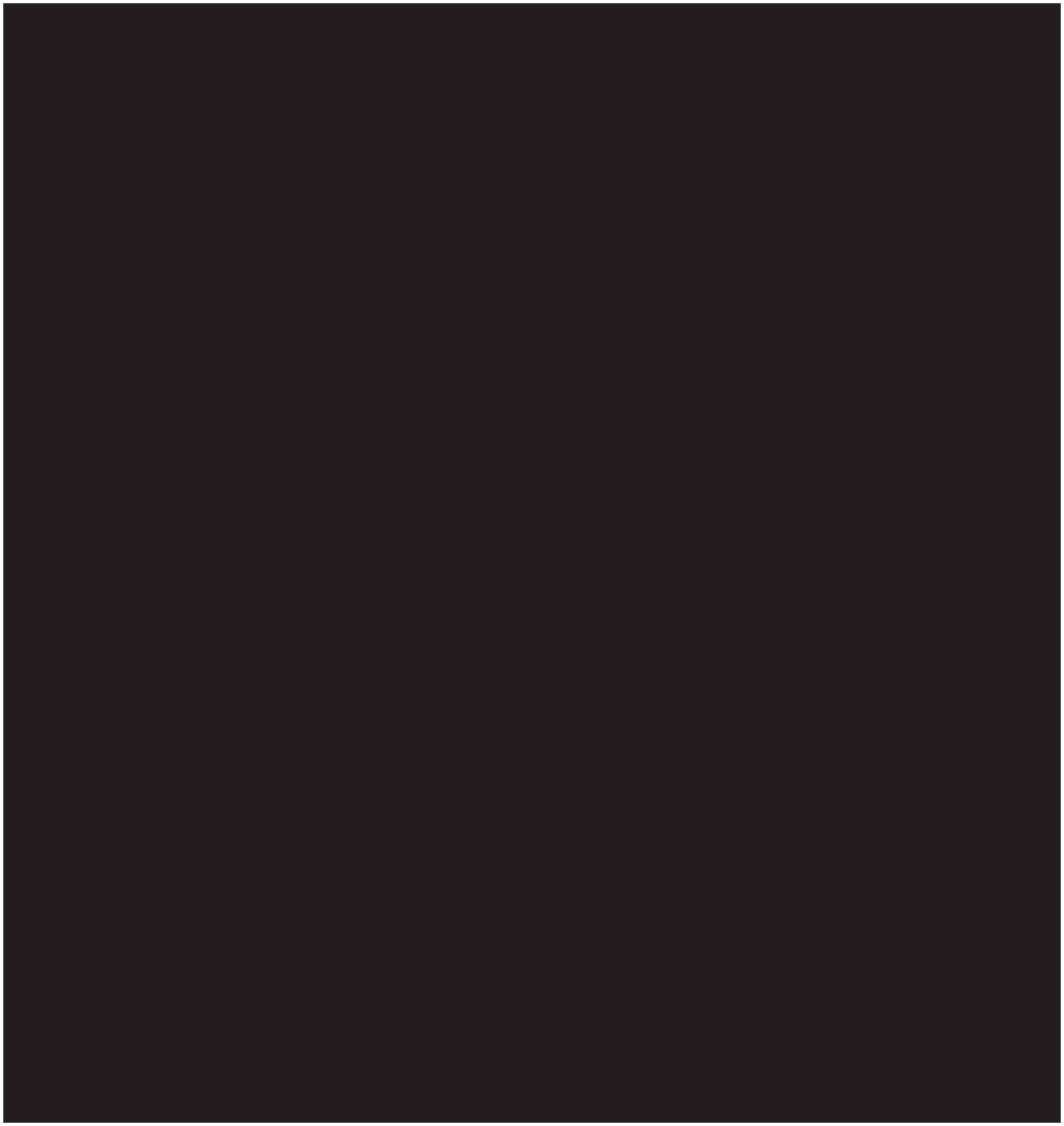
Each of the components (erythema, pustules, scaling/crusting) should be scored and recorded.

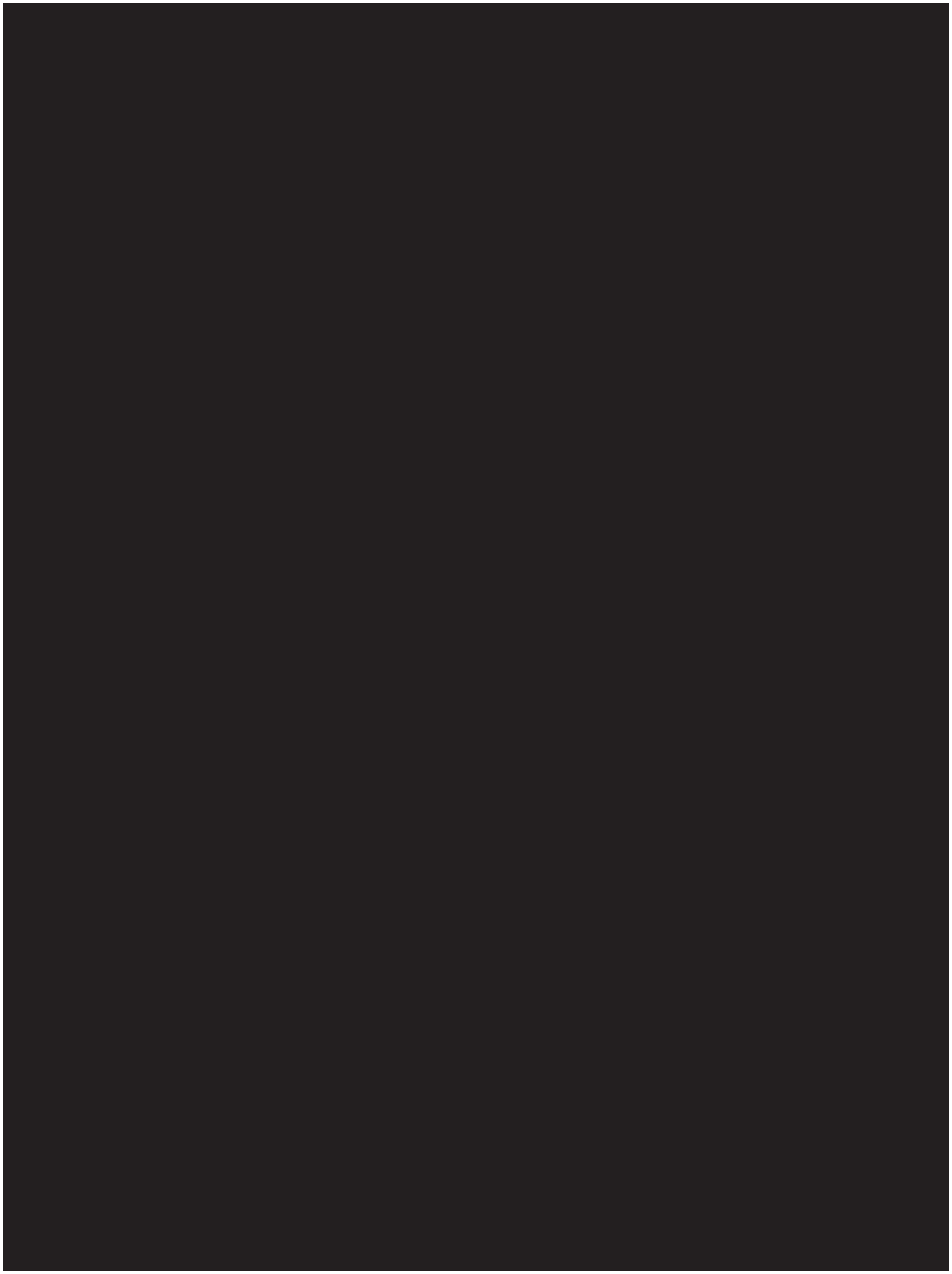
The PPP PGA total score is derived as the mean of all individual components.

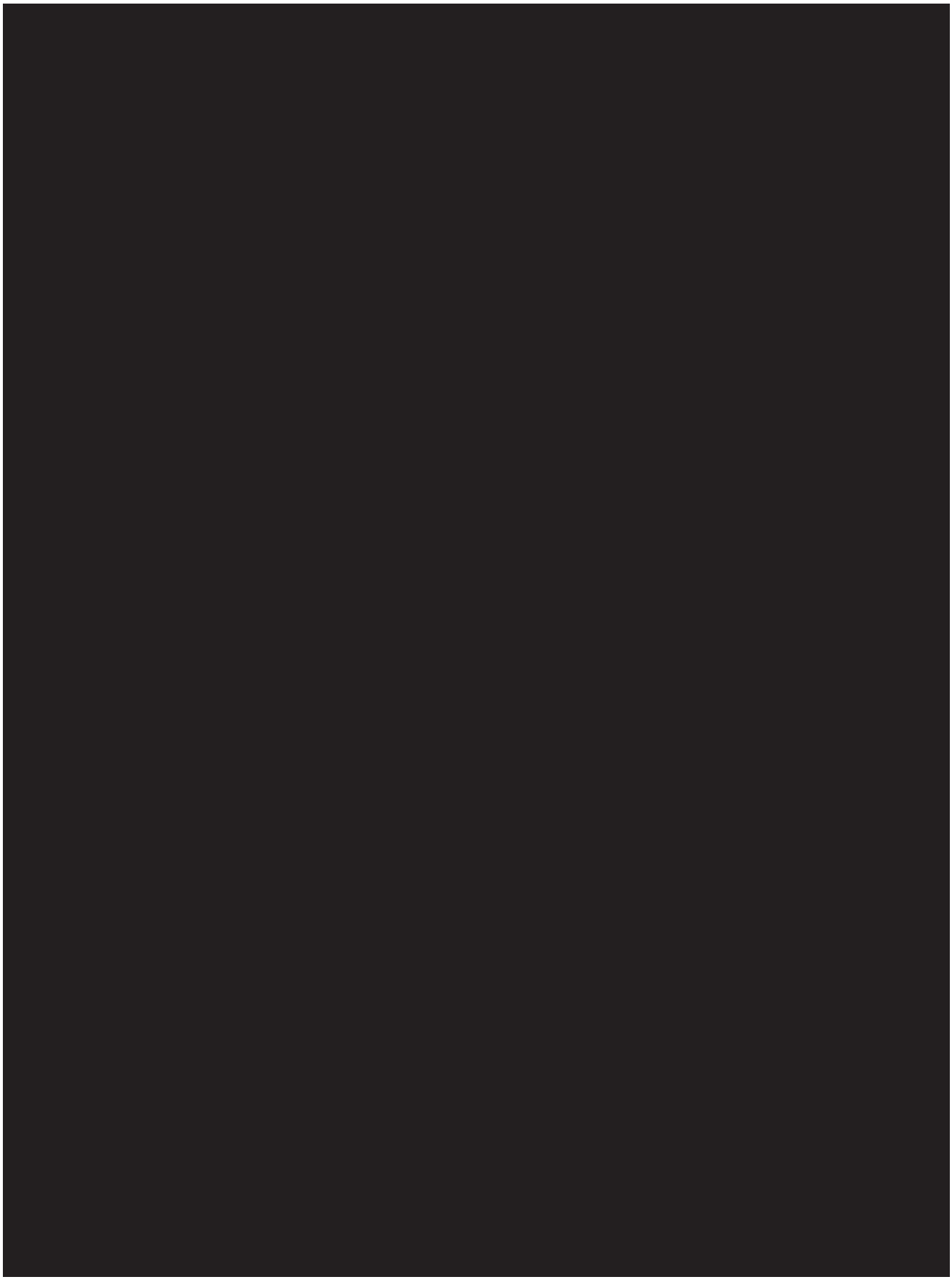
PPP PGA Total Score:

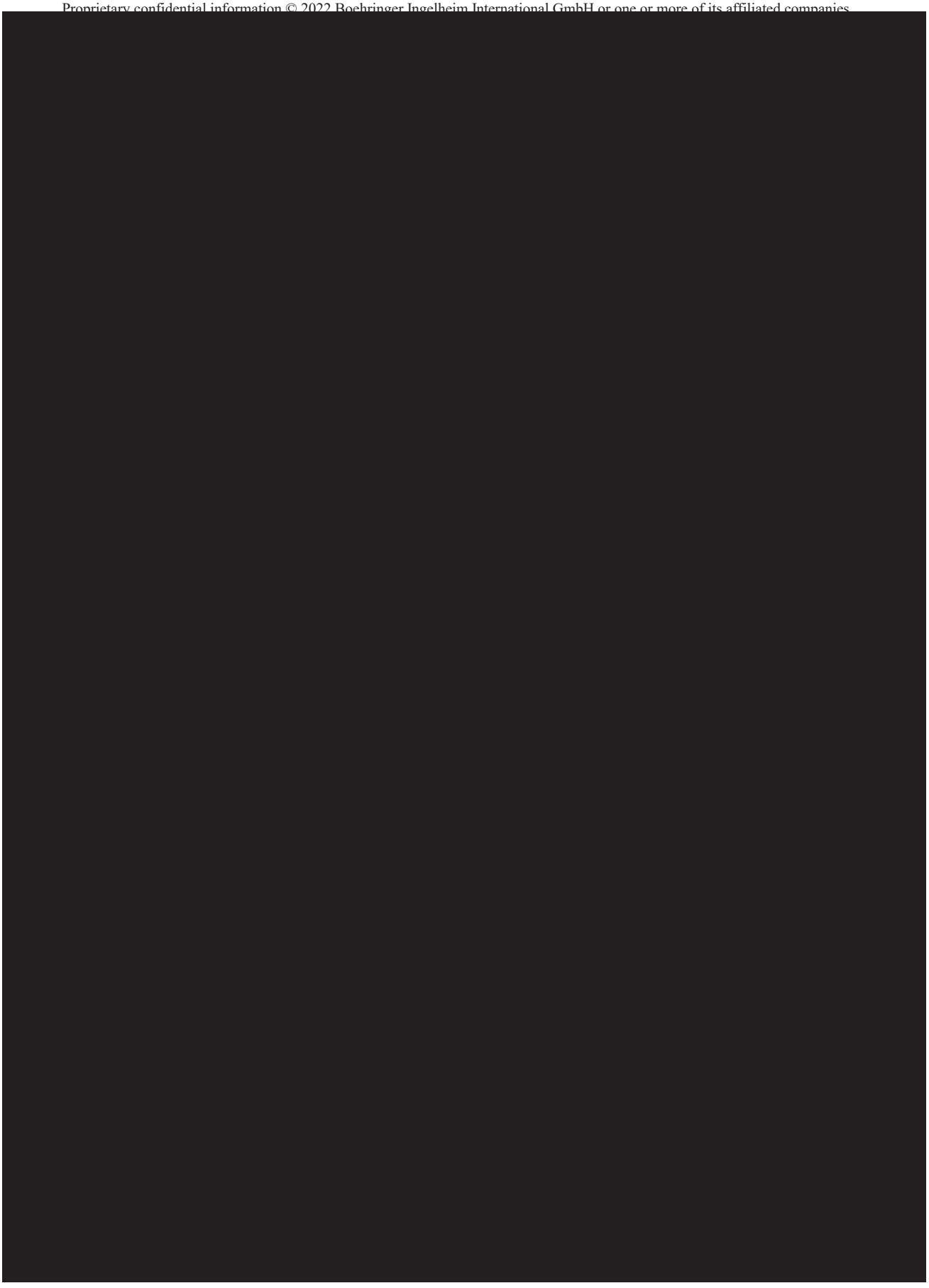
0 = If mean=0 for all three components
1 = If 0 < mean <1.5
2 = If (1.5 <= mean <2.5)
3 = If 2.5 <= mean <3.5
4 = If mean >=3.5

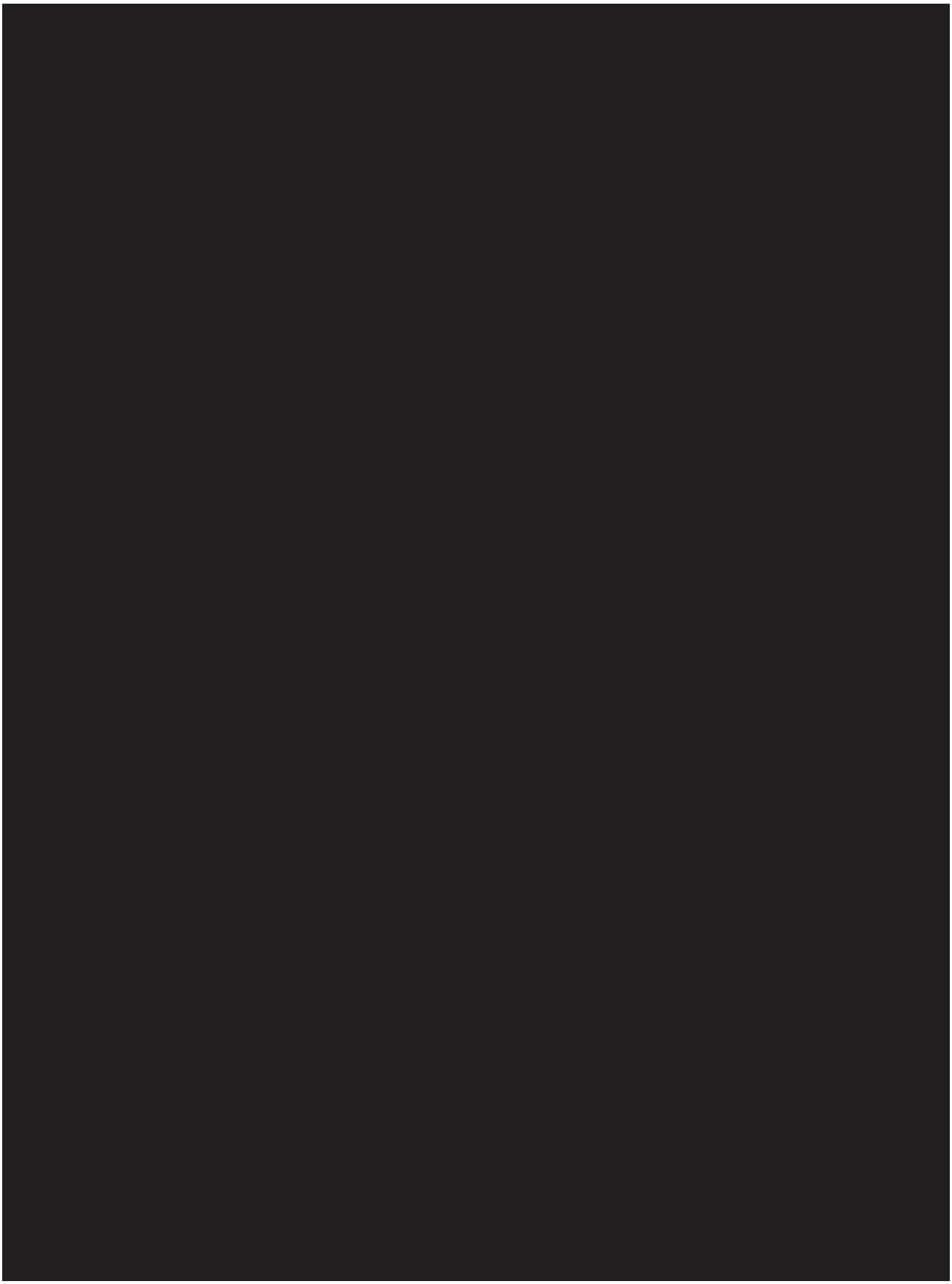


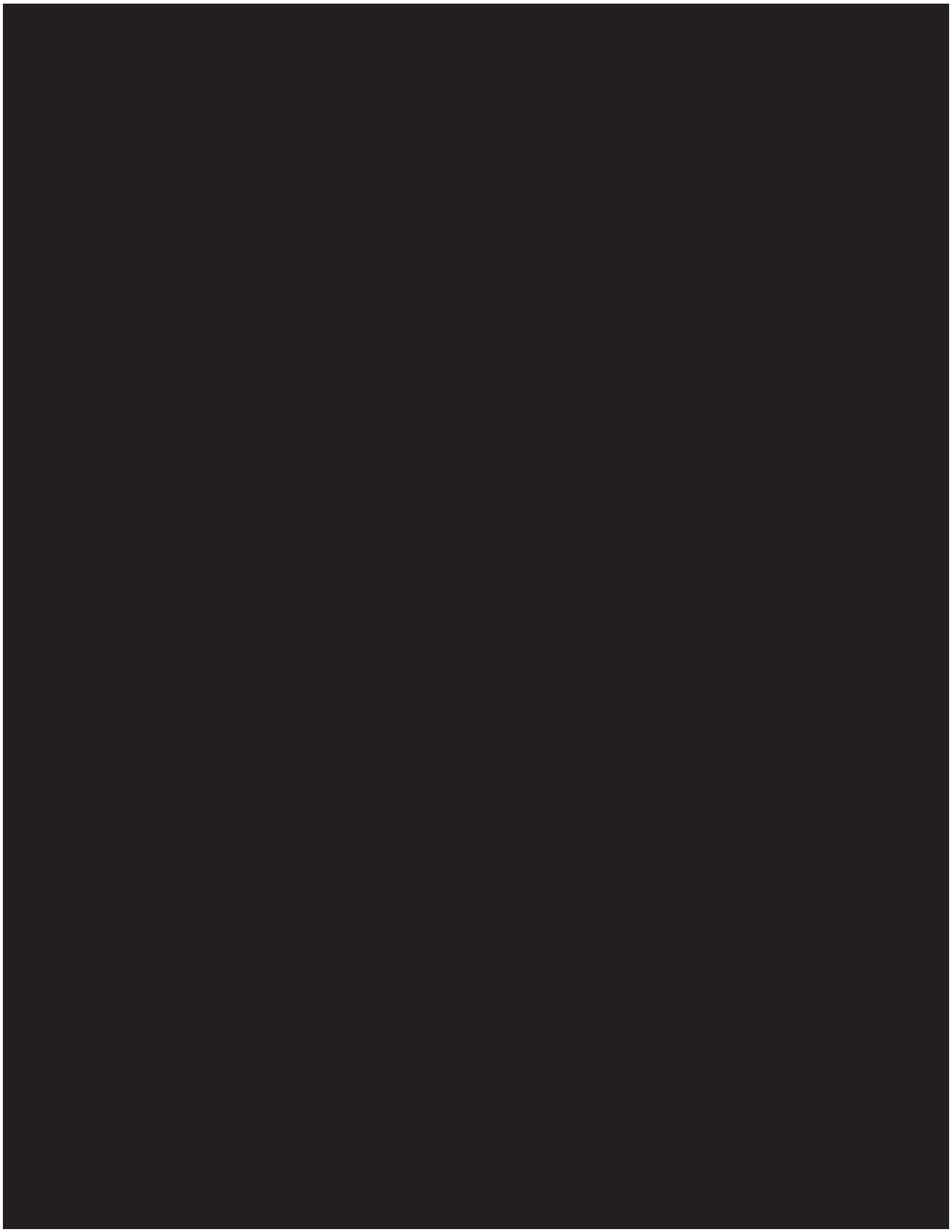


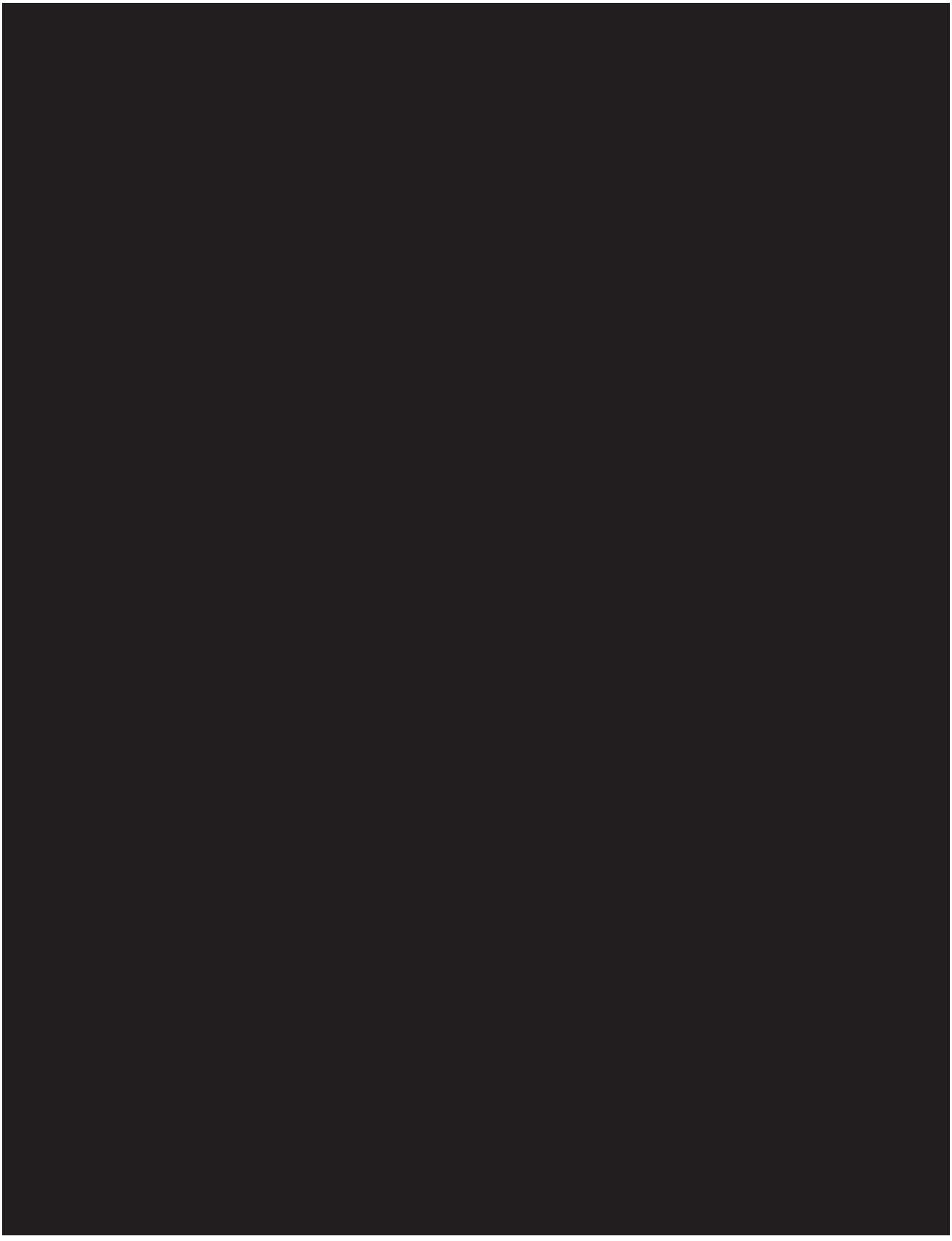












10.2 DIAGNOSIS OF ANAPHYLAXIS

Clinical Criteria for diagnosing anaphylaxis [R11-4890]

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 (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (eg, 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 (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (eg, 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.

10.3 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA ([redacted]

Please see ISF for the complete table and [R13-3515]

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
	Asymptomatic, or transient Short duration (< 1 week) No change in life style No medication or OTC	Symptomatic Duration (1–2 weeks) Alter lifestyle occasionally Meds relieve. (may be prescription), Study drug continued	Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized<24h Temporary study drug discontinuation, or/and dose reduced	At risk of death Substantial disability, especially if permanent. Multiple meds Hospitalised >24h Study drug discontinued

10.4 SMOKING HISTORY BASED ON CALCULATION OF PACK YEARS

Calculation of pack years based on number of cigarettes:

$$\text{Pack years} = \frac{\text{Number of cigarettes/day} \times \text{years of smoking}}{20}$$

The following equivalents for the tobacco content should be used for smokers other than cigarettes smokers (R08-5197):
One plain or filter cigarette = 1 gram of tobacco
One cigar = 5 grams of tobacco
One cheroot or cigarillo = 3 grams of tobacco
One gram of pipe tobacco = 1 gram of tobacco
Calculation of pack years based on tobacco contents:

$$\text{Pack years} = \frac{\text{Number of grams/day} \times \text{years of smoking}}{20}$$

10.5 TRIAL BIOMARKER PLAN

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		17 Aug 2020
EudraCT number **EU number**		2020-000189-41
BI Trial number		1368-0024
BI Investigational Medicinal Product(s)		Spesolimab, BI 655130
Title of protocol		An open-label, single arm, long term trial of Spesolimab treatment in patients with Palmoplantar Pustulosis (PPP) who have completed previous BI Spesolimab trials
Global Amendment due to urgent safety reasons		
Global Amendment		**X**
Section to be changed		1.4.2 Risks
Description of change		Added Benefit/Risk Assessment in the context of COVID-19 pandemic
Rationale for change		Benefit/Risk information for investigators regarding patients on Spesolimab needed
Section to be changed		1.3.3 Exclusion Criteria
Description of change		Time frame for exclusion criterion #7 was adapted: changed from “history of malignancy at screening to “history of malignancy within 5 years prior to screening in parent trial”.
Rationale for change		Alignment between parent trial 1368-0016 and roll over trial to avoid losing patients from parent trial with an older history of malignancy
Section to be changed		4.2.1 Restrictions on previous and concomitant medications
Description of change		- Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen/paracetamol:

		changed from “not allowed/restricted use” to “allowed but recommended to be maintained at stable dose and ot to change medication” - Phototherapy: changed from “not allowed” to “allowed if palms and soles are exempted”
Rationale for change		Alignment between parent trial 1368-0016 and roll over trial to avoid losing patients from parent trial due to different medication restrictions.
Section to be changed		5.1.8 Target Plaque Severity Score
Description of change		Clarification added that the same target region from parent trial needs to be assessed.
Rationale for change		Target region was not correctly described.

11.2 GLOBAL AMENDMENT 2

Date of amendment		22 Oct 2021
EudraCT number **EU number**		2020-000189-41
BI Trial number		1368-0024
BI Investigational Medicinal Product(s)		Spesolimab, BI 655130
Title of protocol		An open-label, single arm, long term trial of Spesolimab treatment in patients with Palmoplantar Pustulosis (PPP) who have completed previous BI Spesolimab trials
Global Amendment due to urgent safety reasons		
Global Amendment		**X**
Section to be changed		Flow Chart incl. foot note 6 and Section 5.2.1 Physical examination
Description of change		Flow Chart: the word “weight” was removed; Foot note 6 to Flow Chart: “incl. weight” was added to “complete physical examination”; Section 5.2.1: separate sentence on weight measurement was removed. “incl. weight” added to complete physical examination”, “without weight”

		added to targeted physical examination.
Rationale for change		Clarification for the time point of the weight measurement was needed => weight measurement only at the time points of COMPLETE physical examination.
Section to be changed		Flow Chart
Description of change		End of Study (EoS): visit window was changed from ±7 days to +7 days.
Rationale for change		To cover the whole REP of 16 weeks only the +7 days visit window is acceptable.
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		Exclusion criterion nr 14: in addition to the conventional units the SI units were newly added.
Rationale for change		Depending on the country sites are used to work with different lab units (conventional vs SI unit). To avoid converting of the values by the sites, both units are now present.
Section to be changed		4.2.1 Restrictions on previous and concomitant medications
Description of change		The following text in brackets was deleted: All concomitant or rescue therapies will be recorded ~~(including time of intake and dose on study days)~~ on the appropriate pages of the CRF.
Rationale for change		Time of intake and dose on study days is not recorded in the CRF.
Section to be changed		5.2.2 Vital signs
Description of change		The word “approx.” was added to the time point when post-dose vitals signs should be taken.
Rationale for change		Alignment of wording between the following sections: footnote nr 7 of Flow Chart, section 5.2.2 “Vital signs” and section 6.2.2. “Treatment period”
Section to be changed		5.2.3 Safety laboratory parameters incl. table
Description of change		The words in bold were added: All analyses (except for the urine **pregnancy** dipstick tests **which are done locally at the investigational site**) will be performed by a central laboratory, the respective reference ranges will be provided in the ISF. Table 5.2.3.1: Urine Pregnancy test[1] (only for female patients of childbearing potential). At the drug administration visits, the test will be performed **and checked at the investigational site** prior to the administration of study drug. Urinanalysis: Dipstick (qualitative), **test and analysis done by central lab…**
Rationale for change		Clarification that urine dipstick tests for pregnancy

		are done at the investigational site but dipstick tests for urinalysis (urine macro panel) are done at central lab.
Section to be changed		Table 5.2.3: 1 Safety laboratory tests
Description of change		Urinalysis: Urine RBC/Erythrocytes and Urine/WBC Leucocytes has been removed from urine dipstick test and were replaced by "Blood";
Rationale for change		Correction was needed because the dipstick urinalysis analyses "blood" only; in case urinalysis is positive, microscopic analysis is performed for Urine Sediment Erythrocytes and Urine Sediment Leucocytes;
Section to be changed		5.2.6.2.1 AE Collection
Description of change		Text was corrected to reflect that after the 1st IMP administration in the extension trial, no further AE updates should be done in the parent trial.
Rationale for change		Time of 1st IMP administration in the extension trial has been defined as EoS for the parent trial. After EoS no further updates are to be made for the parent trial.
Section to be changed		6.2.1 Screening period (Medical History)
Description of change		Following information was added: "If a new condition developped but recovered during the parent trial this can be recorded in the extension trial if considered relevant information by the investigator."
Rationale for change		Clarification was needed for conditions that are not considered "ongoing" from the parent trial (baseline condition) but were not yet medical history when the parent trial started as they developed during the parent trial, e.g. recovered AE during parent trial which does not qualify as baseline condition (because no longer ongoing after IC signature for OLE) but is still considered relevant information by the investigator can be added as medical history.
Section to be changed		6.2.2 Treatment Period
Description of change		Added: Any observed local tolerability reaction, e.g. "swelling", "induration", "heat", "redness", "pain", and other findings should be reported as an adverse event.
Rationale for change		Clarification that the type of the observed local tolerability reaction should be specified and reported as an Adverse Event

11.3 GLOBAL AMENDMENT 3

Date of amendment		23 Jun 2022
EudraCT number **EU number**		2020-000189-41
BI Trial number		1368-0024
BI Investigational Medicinal Product(s)		Spesolimab, BI 655130
Title of protocol		An open-label, single arm, long term trial of Spesolimab treatment in patients with Palmoplantar Pustulosis (PPP) who have completed previous BI Spesolimab trials
Global Amendment due to urgent safety reasons		
Global Amendment		**X**
Section to be changed		Table 1.4.2: 1 Risks
Description of change		The risk "Peripheral Neuropathy" was added to the table including a summary of data and mitigation strategy.
Rationale for change		Added to inform about the newly added potential risk "peripheral neuropathy" deriving from the three cases reported as Guillain-Barré syndrome by the investigator in Spesolimab trials (details in the CTP). The cases were considered as peripheral neuropathy by the external neurologist expert panel's assessment.
Section to be changed		1.4.2 Risks
Description of change		Differentiation between suspected or diagnosed, non-severe/non-serious and severe/serious COVID-19 infection added.
Rationale for change		Clarification was needed because paragraph contained unclear instructions.
Section to be changed		3.3.3 Exclusion criteria
Description of change		The following Exclusion criterion was added: "Presence of acute demyelinating neuropathy."
Rationale for change		Added as mitigation strategy to account for the three cases reported as Guillain-Barré syndrome by the investigator in Spesolimab trials. The cases were considered as peripheral neuropathy by the external neurologist expert panel's assessment (details in the CTP). This way the selection of patients with acute demyelinating neuropathy would be avoided.

Section to be changed		3.3.4.2 Implications due to loss of treatment response
Description of change		"Patients who need to take rescue medication need to be discontinued from the trial. Rescue therapy is defined as the use of topical corticosteroids or other topical treatment applied on the palms and/or soles, systemic immunomodulating treatments or biologics and therapy such as tonsillectomy, for the treatment of worsening of PPP. For the complete list and all details of restricted medication see Section 4.2.1 and Table 4.2.1: 1." **was changed to** "Patients who need to take rescue medication must be discontinued from the trial. Rescue therapy is defined as the use of topical corticosteroids or other topical treatment, systemic immunomodulating treatments or biologics and therapy such as tonsillectomy, for the treatment of worsening of PPP. For the complete list and all details of restricted medication see Section 4.2.1 and Table 4.2.1: 1."
Rationale for change		Clarification was needed that patients must be discontinued in case of rescue medication and the definition of rescue medication was updated to cover also cases where a PPP worsening extends beyond palms/soles.
Section to be changed		3.3.4.2 Implications due to loss of treatment response
Description of change		"A patient who meets the trial treatment discontinuation criteria may be discontinued from the trial treatment and administered standard of care therapy as judged by the investigator. " **was changed to** "A patient who meets the trial treatment discontinuation criteria at 2 consecutive visits must be discontinued from the trial treatment and administered standard of care therapy."
Rationale for change		Update was needed to ensure that patients who have no longer a benefit from the IMP discontinue the trial and receive treatment acc. to local standard of care.
Section to be changed		3.3.4.3 Implications of specific adverse events
Description of change		Following information was added: "Peripheral Neuropathy If peripheral neuropathy is suspected, treatment with spesolimab should be temporarily

		discontinued until a full neurological investigation has been conducted. After completion of the neurological investigation, treatment can be restarted based on medical judgement of the investigator."
Rationale for change		Added as mitigation strategy to account for the three cases reported as Guillain-Barré syndrome in Spesolimab trials. The cases were considered as peripheral neuropathy by the external neurologist expert panel's assessment (details in the CTP).
Section to be changed		4.2.1 Restrictions on previous and concomitant medications and table 4.2.1: 1
Description of change		1) Other systemic immunomodulating treatment is not allowed for the treatment of PPP but no longer prohibited for other conditions. 2) Topical treatment for PPP is now prohibited on all areas affected by PPP, even if extended beyond palms/soles; 3) Topical corticosteroids for other conditions than PPP are now prohibited on all regions affected by PPP, not only on palms/soles; 4) Topical treatments (other than topical corticosteroids) for other conditions than PPP are now allowed if they do not affect the PPP assessment. 5) Footnote to table 4.2.1: 1 adapted and the word "should" was replaced by the word "must".
Rationale for change		1) To get in alignment with the parent trial where the same approach was followed. 2) To cover also cases where the topical treatment for PPP extends beyond palms/soles– this change is connected with the change of "3.3.4.2 Implications due to loss of treatment response"; 3) To cover also cases where topical corticosteroids are applied to other regions where PPP might extend to. 4) To prohibit topical treatments (other than topical corticosteroids) only to regions that may affect the PPP assessment. 5) To clarify that patients must be discontinued if prohibited medication is taken and to clarify that in case of discontinuation "EoT"- and "EoS"-visit needs to be done.
Section to be changed		5.2.6.1.4 Adverse events of special interest
Description of change		Added Peripheral Neuropathy as an Adverse events

		of special interest.
Rationale for change		To update reporting requirements to ensure all cases of suspected peripheral neuropathy including the non-serious ones are analyzed quickly.
Section to be changed		[redacted]
Description of change		[redacted]
Rationale for change		Clarification was needed.

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	24 Jun 2022 09:19 CEST
Approval-Biostatistics		24 Jun 2022 11:30 CEST
Approval-Clinical Program [redacted]		26 Jun 2022 01:53 CEST
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