Clinical Trial Protocol

	Document Number:	**c15875404-04**
EudraCT No.: **EU Trial No:**	2017-004231-37	
BI Trial No.:	1368-0013	
BI Investigational Product(s):	Spesolimab (BI 655130)	
Title:	Effisayil™ 1: Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity	
Lay Title:	A study to test BI 655130 in patients with a flare-up of a skin disease called Generalized Pustular Psoriasis	
Clinical Phase:	II	
Clinical Trial Leader:	[redacted] Phone: [redacted]	
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]	
Status:	Final Protocol (Revised Protocol (based on Global Amendment 2)	
Version and Date:	**Version: 3.0**	**Date: 26 Jun 2020**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	N/A
Active ingredient name:	Spesolimab (BI 655130)
Protocol date	27 June 2018
Revision date	26 Jun 2020
Trial number	1368-0013
Title of trial:	Effisayil™ 1: Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity
Coordinating Investigator:	[redacted] Phone: [redacted]; FAX: [redacted]
Trial site(s):	Multi-center trial conducted in 11 to 20 countries.
Clinical phase:	II
Objective(s):	To evaluate efficacy, tolerability and safety of BI 655130 compared to placebo in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity.
Methodology:	Multi-center, placebo-controlled, randomized, double blind
Number of patients entered:	51 patients
Number of patients on each treatment:	34 patients on BI 655130 and 17 patients on placebo
Diagnosis:	Patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity.
Main in- and exclusion criteria	Main inclusion criteria: Patients will be **enrolled (screened)** into the trial, if they meet the following criteria: • 1a) Patients with GPPGA of 0 or 1 and a known and documented history of GPP per European Rare And Severe Psoriasis Expert Network (ERASPEN) criteria regardless of IL36RN mutation status,

	with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN). **OR** • 1b) Patients with an acute flare of moderate to severe intensity meeting the (ERASPEN) criteria of GPP with a known and documented history of GPP (per ERASPEN criteria) regardless of IL36RN mutation status, with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN). **OR** • 1c) Patients with first episode of an acute GPP flare of moderate to severe intensity with evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN). For these patients the diagnosis will be confirmed retrospectively by a central external expert/committee. • Patients may or may not be receiving background treatment with retinoids and/or methotrexate and/or cyclosporine. Patients must discontinue retinoids/methotrexate/cyclosporine prior to receiving the first dose of BI 655130/ placebo. • Male or female patients, aged 18 to 75 years at screening. • Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP and local legislation prior to start of any screening procedures. • 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. 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.\ Main Exclusion Criteria: • Patients with SAPHO (Synovitis–acne–pustulosis–hyperostosis–osteitis) syndrome. • Patients with primary erythrodermic psoriasis vulgaris. • Patients with primary plaque psoriasis vulgaris without presence of pustules or with pustules that are restricted to psoriatic plaques.

	• Drug-triggered Acute Generalized Exanthematous Pustulosis (AGEP). • Immediate life-threatening flare of GPP or requiring intensive care treatment, according to the investigator's judgement. Life-threatening complications mainly include, but are not limited to, cardiovascular/cytokine driven shock, pulmonary distress syndrome, or renal failure. • Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin. • Patients with dose escalation of their maintenance therapy with cyclosporine and/or methotrexate and/or retinoids within the 2 weeks prior to receiving the first dose of BI 655130/ placebo. • The initiation of systemic agents such as cyclosporine and/or retinoids and/or methotrexate 2 weeks prior to receiving the first dose of BI 655130/ placebo. **Treatment (Visit 2) will be initiated immediately in patients:** • Who meet the inclusion criteria above • Who are presenting with an acute GPP flare of moderate to severe intensity, defined by emergence of: a) Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of at least 3 (moderate), and b) presence of fresh pustules (new appearance or worsening of pustules), and c) GPPGA pustulation sub score of at least 2 (mild), and d) at least 5% of Body Surface Area (BSA) covered with erythema and the presence of pustules • And who do not meet any of the exclusion criteria above.
Test product(s):	BI 655130 solution for infusion 60 mg/ml
dose:	900 mg, single dose
mode of administration:	i.v.
Comparator products:	Placebo comparator
dose:	Not applicable
mode of administration:	i.v.
Duration of treatment:	Single dose
Endpoints	**Primary Endpoint:**

	The primary endpoint of the study is: • A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 indicating no visible pustules at Week 1. Key Secondary Endpoint: The Key secondary endpoint of the study is: • A GPPGA score of 0 or 1 at Week 1. **Secondary Endpoints:** Secondary Endpoints of the study at Week 4 which are included in the statistical testing strategy in a hierarchical manner subsequent to performance of the tests on the primary endpoint and key secondary endpoint are: • A Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) 75 at Week 4. • Change from baseline in Pain Visual Analog Scale (VAS) score at Week 4. • Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4. • Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score at Week 4. Secondary endpoints of the study which are not included in the statistical testing hierarchy are: • A GPPGA 0 or 1 at Week 4. • A GPPGA pustulation subscore of 0 indicating no visible pustules at Week 4. • A GPPASI 50 at Week 1. • A GPPASI 50 at Week 4. • The percent reduction in GPPASI from baseline at Week 1. • The percent reduction in GPPASI from baseline at Week 4.

	The following safety endpoint is also defined: • The occurrence of Treatment Emergent Adverse Events (TEAEs).
Safety criteria:	AEs and Serious Adverse Events (SAEs), AEs of Special Interest, intensity of AEs per the Rheumatology Common Toxicity Criteria (RCTC) version 2.0, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR], body temperature, body weight), physical examination, infusion site reactions, [redacted]
Statistical methods:	The trial is designed to demonstrate superiority of BI 655130 in the primary endpoint, achievement of pustule clearance at week 1, and the key secondary endpoint, GPPGA (0, 1) at Week 1, relative to placebo. The primary analysis, on each of the primary and key secondary endpoints, will use a Suissa-Shuster test (pooled method) to compare the proportion of patients who achieve a response on BI 655130 versus placebo at week 1. A further hypothesis on the secondary endpoints, GPPASI 75 at Week 4, Pain VAS score at Week 4, PSS score at Week 4 and FACIT Fatigue Score at Week 4, will be tested in a hierarchical manner if the test of the null hypotheses for both primary and key secondary endpoints has previously been rejected. All safety data in this study will be descriptively summarized.

FLOW CHART

Trial Period	**Screening**	**Treatment**	**Follow-up Period[3,21]**													
Visit	**V1[1]**	**V2[1]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10[3]**	**V11[3]**	**V12[3]**	**V13[3]**	**V14/ EoS[2, 3,24]**	**V15/ EoS[2,25]**	**V16/ EoS[2,26]**
Week*		**1**								**2**	**3**	**4**	**8**	**12**	**13-18**	**16-28**
Day	**-6 months to day -1**	**1****	**2**	**3**	**4[5]**	**5[5]**	**6[5]**	**7[5]**	**8**	**15**	**22**	**29**	**57**	**85**	**92-127**	**113-197**
Window										±3d	±3d	±3d	±7d	±7d	±7d	±7d
Informed consent	X[6]	X[6]														
Infection testing	X[7]														X[7]	
IL36RN mutation status[9]	X															
Demographics	X															
Medical history	X															
Smoking history	X															
Physical examination[4]	X[C]	X[C,T,8]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[C,T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]
Vital signs[10a,10b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Fever Assessment[11]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[12]	X[S]	X[U,(S),8]							X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]
12 lead-ECG[13]	X	X[8]							X	X	X	X	X	X	X	X
Safety laboratory tests[14]	X	X[14,8]	X	X	X	X	X	X	X[14]	X[14]	X[14]	X[14]	X[14]	X[14]	X	X
Review of in-/exclusion criteria	X	X														
[redacted]																
GPPGA		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
GPPASI		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

FLOW CHART (CONT'D.)

Trial Period	Screening	Treatment	Follow-up Period[3,21]													
Visit	**V1[1]**	**V2[1]**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10[3]**	**V11[3]**	**V12[3]**	**V13[3]**	**V14/ EOS[2, 3, 24]**	**V15/ EOS[2,25]**	**V16/ EoS[2,26]**
Week*		**1**								**2**	**3**	4	**8**	**12**	**13-18**	**16-28**
Day	**-6 months to day -1**	**1****	**2**	**3**	**4[5]**	**5[5]**	**6[5]**	**7[5]**	**8**	**15**	**22**	**29**	**57**	**85**	**92-127**	**113-197**
Window										±3d	±3d	±3d	±7d	±7d	±7d	±7d
PSS, [redacted][19]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
[redacted] Pain VAS, FACIT-fatigue[19]		X							X	X	X	X	X	X	X	X
[redacted]																
IRT call	X	X							X	X	X	X	X	X	X	X
Dispense/administration study drug[3,21]		X							X[22]							
Local tolerability[20] – post dose		X							X[22]							
[redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X[29]	X[29]	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion														X	X	X
Open Label Extension Trial														X[23]		

ADA, anti-drug antibody; C, complete physical examination; [redacted] d, Day; [redacted] ECG, Electrocardiogram; EoS, end of study; FACIT-fatigue, Functional Assessment of Chronic Illness Therapy - Fatigue; Fup, Follow-up; GPPASI, Generalized Pustular Psoriasis Area and Severity Index: GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; [redacted]; IHC, Immunohistocompatibility Complex; IRT, Interactive Response Technology; [redacted]; Nab, neutralizing Antibodies; PK, pharmacokinetic; PRO, Patient Reported Outcome; PSS, Psoriatic Symptom Scale; RNASeq, RNA Sequencing; S, serum; T, Targeted physical examination; U, urine; V, Visit; VAS, Visual Analog Scale; Wk, week.

***Week in the flow chart represents the end of each week (e.g. End of Wk1=D8, End of Wk2 =D15, End of Wk3 = D22, End of Wk4 =D29 etc.).**
****The day of first study drug administration = Day 1. All subsequent study Days are counted from this Day 1.**

[1]Visit 1 and Visit 2 can be on the same day if required (see also footnote 8). Initiation of randomized treatment at Visit 2 can only begin if the patient meets the criteria for Initiation of Treatment (see Section 3.3.4).
[2] Should a patient prematurely discontinue from the treatment, every effort should be made to keep the patient in the trial and complete all of the remaining study visits. If this is not possible, assessments at V9 (Wk1), V12 (Wk4), and EoS (V14 or V15 or V16 as applicable) should be completed or at a minimum an early EoS visit.
[3] If a patient qualifies for rescue treatment with open label BI 655130 at either a scheduled or unscheduled visit from after Day 8 and up to and including Week 12, all procedures/measurements listed for V9 (with the exception of skin biopsy, Whole Blood for RNA sequencing, Soluble Protein Biomarkers in Serum and Whole Blood for Flow Cytometry) are to be performed prior to dosing and an IRT call is to be placed prior to dosing.
[4] C = Complete Physical Examination; T = Targeted physical examination. Refer to Section 5.2.1 for additional details.

[5]Per physician's assessment, Days 4 through 7 are optional if the patient has achieved complete pustular clearance (GPPGA pustulation sub score = 0) at the prior visit.
[6]Informed consent will be signed at the screening visit (V1). For patients completing V1 and V2 > 6 weeks apart, it is recommended that the patient is asked to re-confirm (verbally) his/her consent to participate in the trial at Visit 2.
[7]Infection testing includes tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see Table 5.2.3: 1). EoS infection testing should only be done once at V14 or V15 or V16 as applicable.
[8]These procedures do not need to be repeated/performed when V1 and V2 are performed on the same day.
[9] IL36RN mutation status is to be obtained from the patient's historical data if available.
[10]Vital signs: a) On non-study–drug administration days, vital sign assessments are to be done prior to blood sampling; b) On study drug administration days, vital signs will be assessed at pre-dose, at approximately 5 minutes after the end of infusion, and 120 mins after the end of infusion.
[11] Fever assessments will be recorded on dosing days at three time points. If the patient will receive medication for fever treatment, the fever assessment will be performed prior to taking the anti-fever treatment. These fever assessments must be taken whether or not the patient has an elevated temperature and whether or not the patient takes anti-fever treatment. The fever assessments times are to be separated by intervals of 2 to 4 hours on dosing days. At all other visits (non-dosing days), fever will be assessed once a day and will be completed prior to receiving medication for fever treatment, if anti-fever treatment is given.
[12]Only applicable for women of childbearing potential. S – serum pregnancy test (performed at screening). U – urine pregnancy tests will be performed on-site and only at study drug administration visits. 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 pregnancy test, a serum pregnancy (S) test will be done.
[13]ECG measurements should always precede blood sampling and drug administration (including visits for rescue treatment).
[14] Safety laboratory tests include clinical chemistry, haematology, coagulation, and urinalysis, and will be performed centrally. Local Labs are to be used for dosing decisions prior to i.v. administration. Please refer to Section 5.2.3 for further details.

[redacted]

[19]These measurements are to be completed by the patient on his/her own, without any help from or interpretation by other people. If the patient is too sick to complete the questionnaires him/herself but is able to reply verbally, a member of the study team should read the instructions, questions, and response options aloud to the patient and collect the patient's verbal response in as neutral and unbiased a manner as possible. If this is not possible either, the questionnaires are not to be completed. The order of completion for PROs is recommended to be as follows: PSS; [redacted] pain VAS; FACIT-Fatigue; [redacted]
[20]Local tolerability will be assessed during the study drug administration and for approximately 2 hours after the study drug administration.
[21] After Wk1/D8 and through the follow-up period, should a patient who previously achieved a clinical response (GPPGA 0 or 1) to initial treatment (either BI655130 or placebo or escape medication) experience a recurrence of a GPP flare (see Table 3.1:1), treatment with a single i.v. dose of 900 mg BI 655130 is to be administered. After D8, only one rescue dose with BI 655130 is permitted if a patient experiences a recurrence of a GPP flare. Subsequent flares are to be treated with escape treatment (SoC) per physician's discretion.
[22] Only applicable to patients who meet the qualification for treatment with Open Label (OL) single i.v. dose of 900 mg BI 655130 at Wk1/D8 (see Table 3.1:1)
[23]Patients who achieved a clinical improvement to study treatment (not including escape treatment) and show no flare symptoms of moderate/severe intensity at V14 or V15 will be offered to enter into an open label extension (OLE) trial (1368-0025), if they have completed this study (EoS/V14 or V15) and meet the inclusion criteria for the OLE trial.
[24]Patients who receive rescue treatment with OL BI 655130 between Wk7-Wk12 will not have V14. See also footnote 25.
[25]Only for patients who receive rescue treatment with OL BI 655130 between Wk7 – Wk12. V15 is to be conducted 6 weeks (+/-7days) after rescue treatment with OL BI655130 and includes a response evaluation. If at V15, the patient qualifies to enter OLE trial, then V15 will be considered as EoS. If not, then the patient will have an additional 10 weeks follow-up and have an EoS at V16.

[26]Only for patients who do not qualify to enter into the OLE trial. V16 is to be conducted 16 weeks (+/-7days) after the last dose of trial medication (excluding the Escape treatment).

[redacted]

If the date of EOS visit for this trial is not the same as the date of first dose of trial medication on the OLE trial (1368-0025), the investigator must continue to capture the AEs in this trial until the patient receives 1st dose in the OLE trial. Please refer to section 5.2.6.2 for further details.

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ABBREVIATIONS

[redacted]

AE	Adverse event
AESI	Adverse events of special interest
AD	Atopic Dermatitis
ALT/GPT	Alanine transaminase
AP	Alkaline phosphatase
AST/GOT	Aspartate transaminase
BI	Boehringer Ingelheim
BP	Blood pressure
BSA	Body Surface Area
CML	Local Clinical Monitor
CRA	Clinical Research Associate
(e)CRF	(electronic) Case report form

[redacted]

CRP	C-reactive protein
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supply Unit
DILI	Drug induced liver injury

[redacted]

DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EOS	End of Study
ERASPEN	European Rare And Severe Psoriasis Expert Network
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy - Fatigue
FIH	First-in-Human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GGT	Gamma-glutamyl transferase
GPP	Generalized Pustular Psoriasis
GPPASI	Generalized Pustular Psoriasis Area and Severity Index
GPPGA	Generalized Pustular Psoriasis Physician Global Assessment
HV	Healthy Volunteers
IB	Investigator's brochure
IEC	Independent Ethics Committee
IL	Interleukin
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator site file
i.v.	Intravenous

JDA	Japanese Dermatological Association
mAb	Monoclonal antibody
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MIP	Macrophage Inflammatory Protein
Nab	Neutralizing Antibody
OL	Open label
OLE	Open label extension
[redacted]	
PSS	Psoriasis Symptom Scale
[redacted]	
PoC	Proof of Concept
PPS	Per-Protocol set
PRO(s)	Patient Reports Outcome(s)
REP	Residual effect period
RS	Randomized set
SAE	Serious adverse event
s.c.	Subcutaneous
SD	Single dose
SOC	System Organ Class
SoC	Standard of Care
SOP	Standard Operating Procedure
SRD	Single-rising dose
SS	Safety set
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TCM	Trial Clinical Monitor
TEAE	Treatment-emergent adverse event
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAS	Visual Analog Scale
WOCBP	Woman Of Childbearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Clinical Presentation of Generalized Pustular Psoriasis (GPP):

GPP is a severe skin disease characterized by the repeated occurrence of acute flares caused by systemic inflammation affecting the skin and internal organs (R15-1421, R16-0933). The classic presentation of acute GPP was first described as a recurrent pustular form of psoriasis by von Zumbusch in 1909 (R16-0932). While GPP and plaque psoriasis can occur at the same time in an individual patient (R17-3403), GPP is distinct from plaque psoriasis in clinical presentation, pathophysiology, histopathology, response to therapies, epidemiology and genetics.

The clinical presentation of GPP is quite different from psoriasis vulgaris (PV) in its' episodic nature, often with normal appearing skin between very acute and severe disease flares. GPP is clinically characterized by the preponderance of pustules as the primary lesion on an erythematous base rather than red plaques covered with silvery scales representing the primary lesion of typical plaque psoriasis. In addition, the histopathological hallmarks of GPP are distinct spongiform pustules of Kogoj located in the subcorneal portion of the epidermis. GPP may be associated with systemic symptoms (fever, increased CRP and neutrophilia) and severe extra-cutaneous organ manifestations (liver, kidney failure, CV shock). While patients with GPP may have pre-existing or co-existing PV, it is possible to clinically distinguish patients with primary plaque disease (PV) who have a secondary pustular component from patients who have *primary* pustular disease (GPP) with a concomitant plaque component, based on the sequence of manifestations (primary lesion pustule rather than plaque) and the localization of a GPP pustule on an erythematous base rather than a PsO plaque.

As descriptions for GPP are discordant among standard dermatology textbooks (R17-3403), the European Rare And Severe Psoriasis Expert Network (ERASPEN) has defined consensus criteria that include as key diagnosis criteria for acute GPP the presence of primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques), with or without systemic inflammation, with or without plaque-type psoriasis, either relapsing (>1 episode) or persistent (>3 months).

Chronic GPP describes the state in between disease flares that may be characterized by the complete absence of symptoms or the persistence of residual skin symptoms such as erythema and scaling and minor pustulation.

Treatment options

Current treatment options for controlling acute flare of GPP and maintenance of response are limited and do not provide sustained efficacy (R16-0933). No treatments are currently approved for GPP in the US or centrally approved for GPP in the EU, though retinoids, oral steroids, cyclosporine or methotrexate are being recommended (R17-3600). Although these treatments are described to be effective in 70 – 84% of patients (R17-3600) these data observations are based on a retrospective cohort study from Japan without clearly defined

endpoints (R17-3626). Furthermore, these treatments cannot be used long-term due to side effects and contraindications (retinoids: teratogenicity, hair loss; cyclosporine: excessive hair growth, renal toxicity; MTX: liver toxicity).

Secukinumab (Cosentyx®), infliximab (Remicade®), ixekizumab (Taltz®), brodalumab (Lumicef®), adalimumab (Humira®), guselkumab (Tremfya®) and Risankizumab are only registered in Japan for the treatment of GPP and plaque psoriasis. For secukinumab, authorization was granted on the basis of long-term treatment data (52 weeks) derived from a single open label clinical trial conducted in 12 patients with chronic GPP and an endpoint at 16 weeks (R16-1462). Treatment trials supporting licensing in Japan have treated residual disease for an extended period of time, providing no evidence of how to appropriately treat acute GPP flares.

Biologics (mostly TNF inhibitors, occasionally IL-1 or IL-17 inhibitors) are increasingly used to treat more severe, extensive or treatment resistant patients with GPP, based on small published case series (R17-3603). However, these drugs are also associated with limitations in efficacy (incomplete and delayed responses are frequent) and safety as well as contraindications (infusion reactions, tuberculosis, cardiovascular disease).

Unmet Medical Need

Acute GPP flares of varying severity occur in most patients and may be idiopathic or triggered by external stimuli, such as infection, corticosteroid use or withdrawal, non adherence and dose reduction of current standard of care treatment, stress or pregnancy (R16-0933). Moderate or severe GPP flares cause significant morbidity and mortality (R16-0933) due to tender, painful skin lesions, extreme fatigue, high fever, peripheral blood neutrophilia and acute phase response and sepsis. The acute phase is associated with a mean duration of hospitalization of 10 days (range 3-44 days) (R16-0933). The observed mortality rate of 7% reported in a retrospective study (R16-0933) with 102 GPP cases seen in a tertiary hospital in Johor, Malaysia is likely an underestimate as not all GPP patients were included in the study. Mortality rates are also likely underestimated due to lack of identifying the cause of death as GPP and are largely driven by infectious complications and extra-cutaneous organ manifestations such as renal, hepatic, respiratory and cardiac failure (R16-0933). After responding to treatment or spontaneous flare cessation, it is estimated that up to 50% of patients may suffer from chronic GPP characterized by persistent erythema and scaling that may also include joint symptoms.
Moreover, in countries with lower incidence of GPP, the differential diagnosis can be delayed. This is partly due to the absence of a treatment protocol for GPP once it is diagnosed.

Based on the limitations described above, current therapeutic options are not suitable for life-long treatment and do not provide sustained responses in most patients. Therefore, there is a high need to develop (i) a highly effective treatment with rapid onset of action for patients presenting with an acute GPP flare; and (ii) to develop an effective treatment of chronic GPP, which reliably prevents the occurrence of flares and is safe and tolerable for lifelong treatment.

Role of IL-36R Signaling in GPP

The classic presentation of GPP flares as described by von Zumbusch is strongly correlated with polymorphisms in the IL36-R signaling pathway (R15-1421, R14-5158). Individuals with loss-of-function mutations of the IL36RN gene which encodes an endogenous IL36R antagonist (IL-36RN) have dramatically higher incidence of GPP, indicating that uncontrolled upregulation of IL36 signaling due to defective IL36RN antagonism leads to the inflammatory episodes observed in GPP. Genetic human studies have demonstrated the occurrence of GPP clusters in families with a loss of function mutation in IL36RN, which results in uncontrolled IL36R signaling (R14-5158). Mutations in other genes linked to the IL36 pathway such as CARD14 (R16-0929) also lead to GPP. A recently published gene expression study indicates sustained activation of IL-1 and IL-36 in GPP, inducing neutrophil chemokine expression, infiltration, and pustule formation, suggesting that the IL-1/ IL-36 inflammatory axis is a potent driver of disease pathology in GPP (R17-3602). Moreover, a recent meta-analysis investigated 233 published GPP cases. They found that 49 (21.0%) of 233 cases carried recessive IL36RN alleles. Those 49 recessive IL36RN alleles defined a GPP phenotype characterized by early onset and high risk of systemic inflammation (R16-0930).

IL36R is a cell surface receptor involved in inflammatory responses in skin and gut. It is a novel member of the IL1R family that forms a heterodimeric complex with the IL1R accessory protein. The heterodimeric IL36R system with stimulating (IL36α, IL36β, IL36γ) and inhibitory ligands (IL36Ra) shares a number of structural and functional similarities to other members of the IL1/IL1R family, such as IL1, IL18 and IL33 (R17-3602). All IL1 family members (IL1α, IL1β, IL18, IL36α, IL36β, IL36γ, and IL38) signal through a unique, cognate receptor protein which, upon ligand binding, recruits the common IL1RacP subunit and activates NFkB and MAP kinase pathways in receptor-positive cell types. In human skin tissues, IL36R is expressed in keratinocytes, dermal fibroblasts and infiltrating myeloid cells. IL36R activation in skin tissue drives the production of inflammatory mediators (e.g. CCL20, MIP-1β, TNF-α, IL12, IL17, IL23, TGF-β) and modulates the expression of tissue remodeling genes (e.g. MMPs, TGF-β). Therefore, the link between GPP and mutations in the IL36RN is somewhat analogous to the well-established neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis caused by absence of interleukin-1–receptor antagonist. In this case, absence of the receptor antagonist allows unopposed action of interleukin-1, resulting in life-threatening systemic inflammation with skin and bone involvement (R17-3602). These clinical features responded to empirical treatment with the recombinant interleukin-1–receptor antagonist anakinra (P09-07583).

1.2 DRUG PROFILE

1.2.1 Mode of action

BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signaling. Binding of 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 diseases including generalized pustular psoriasis (GPP), palmoplantar pustulosis (PPP), Atopic Dermatitis (AD) and inflammatory bowel disease (IBD).

1.2.2 Nonclinical pharmacology

Preclinical Studies
BI 655130 binds to human IL36R with a binding avidity of less than 1 pM. BI 655130 inhibits IL36 ligand-stimulated NF-κB activation in HT29 and transformed epithelial cells and in primary human dermal fibroblasts or intestinal myofibroblasts with IC90 values in a consistent range of 0.7 to 3.7 nM. BI 655130 also inhibits IL8 release in primary human intestinal myofibroblasts and IFNγ secretion in human PBMC stimulated with IL36α, IL36β, or IL36γ combined with IL12. Mutations of two key residues (L234 and L235) to alanine were made to BI 655130 to abrogate FcR binding activity and function. Direct assessment of the impact of the mutations in the IgG1 FcR binding sites on both antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) effector functions revealed that the mutations abrogate both ADCC and CDC effector functions and indicate that BI 655130 will be a non-depleting therapy in vivo.

Toxicology studies
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 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 (hematology, 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, 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 BI 655130 dosing in humans.

1.2.3 Clinical experience

In the First-in-Human (FIH) study, BI 655130 or placebo (PBO) was administered to 78 healthy volunteers with 58 subjects assigned to single ascending i.v. doses from 0.001 mg/kg to 10 mg/kg body weight and 20 subjects assigned to placebo. Safety and tolerability of all tested i.v. doses was good. There were no SAEs. AEs categorized as related to treatment were observed in 3/20 (15.0%) subjects in the placebo group and in 8/58 (13.8%) subjects treated with BI 655130. The most frequent treatment-emergent AEs were nasopharyngitis (BI

655130: 20.7%; PBO: 15.0%), headache (BI 655130: 8.6%; PBO: 15.0%), influenza like illness (BI 655130: 6.9%; PBO: 10.0%), and diarrhea (BI 655130: 3.4%; PBO: 10.0%). There were two AEs of moderate intensity (injection site haematoma, headache), all remaining AEs were of mild intensity. There were no serious AEs, no AEs that led to discontinuation of trial drug, no protocol-specified AEs of special interest and no other significant AEs according to ICH E3.

No relevant changes were observed in safety laboratory tests, vital signs, and electrocardiograms (ECGs). Importantly, there were no relevant differences in frequencies of subjects with treatment emergent AEs between the treatment groups, and no dose-dependency was observed.

PK analysis showed that exposure (AUC0-tz and Cmax) to BI 655130 increased with increasing dose in an approximately dose-proportional manner from 0.3 to 10 mg/kg. The effective half-life of BI 655130 is approximately 4 weeks in the linear dose range. Overall, PK data so far suggests target-mediated drug disposition (TMDD) kinetics for BI 655130. Anti-drug antibodies (ADA) were detected in 9 subjects (8 subjects on BI 655130 and 1 subject on placebo), 3 of those had preexisting levels. Pharmacodynamic effects in this FIH Single Rising Dose trial were assessed by indirect target engagement (ITE) of IL36R by BI 655130 using an ex-vivo whole blood stimulation assay (c09985235-01). The analyses indicate for doses of 3 mg/kg and above, the percent inhibition of macrophage inflammatory protein (MIP)-1β was at least 94% as compared to baseline during the entire time course up to 1680 hrs (10 weeks).

In a multiple rising dose trial, 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 weekly for 4 weeks (i.e. 4 administrations) or a single dose of 20mg/kg (8 subjects each, 3:1 on active or PBO). Overall, multiple i.v. doses of 3 mg/kg, 6 mg/kg, and 10 mg/kg, as well as single and multiple doses of 20 mg/kg BI 655130 were found to be safe and well tolerated by the healthy male subjects in this trial. The incidence and intensity of drug related AEs appeared to be higher in the 20 mg/kg multiple dose BI 655130 treatment group than in the other treatment groups, mainly driven by headache. No dose-dependent AEs or other clinically relevant changes in safety laboratory tests, vital signs, or ECG were observed. For further details refer to the current Investigator`s Brochure (IB; c03320877).

The open-label, single group phase I study trial (1368.11) was conducted to investigate the safety, tolerability, pharmacokinetics, pharmacogenomics, and efficacy of a single intravenous dose of BI 655130 (10 mg/kg) in 7 patients with acute flare of generalized pustular psoriasis. The proof-of-concept (PoC) for IL36R inhibition in GPP was achieved in these patients who showed rapid clinical responses to single administrations of BI 655130. Five of these 7 patients became clear or almost clear of GPP 1 week after the infusion, and all of them reached this status 4 weeks after treatment. Within 48 hours of treatment, pustules were completely cleared in 3 patients; pustules were cleared by Week 1 in 5 patients, and by Week 2 in 6 patients. The early response in the skin was also accompanied by an early response in systemic components (C-Reactive Protein [CRP] approaching normalization within 4 weeks). A major improvement in GPPASI was observed in all patients very early with a mean (SD) percent change from baseline of 73.2% (16.2) at Week 2; by

Week 4, this was further reduced to 82.0%, and was maintained to Week 20 (83.6%). Additional improvements (mean [SD]) from baseline to Week 2 were observed in FACIT-F, 12.3 (10.1); Pain-VAS, –45.9 (32.3); and PSS, –5.14 (3.18), all of which were also sustained through Week 4. For further details and most recent results refer to the current IB (c03320877) and published article in the New England Journal of Medicine (P19-01888).

A placebo controlled Phase II study (1368-0015) has also been conducted in 59 patients with palmoplantar pustulosis (PPP), 38 of whom received infusions of BI 655130 at doses up to 900 mg every 4 weeks (0, 4, 8 and 12 weeks) and were followed-up through week 32. Two Serious AEs (SAEs) were reported (one patient each in the 300 mg BI 655130 and placebo arm). While the majority of AEs were mild or moderate and expected for the population, a severe AE was reported in 2 patients for each of the three study arms (300 mg BI 655130, 900 mg BI 655130 and placebo). Four AEs (10.5%) in patients treated with BI 655130 and three AEs (14.3%) in patients treated with placebo led to discontinuation of trial medication. Three patients in the 900 mg BI 655130 arm and two in the placebo arm experienced a significant AE. No AEs of special interest (AESI) were reported. No clinically relevant abnormalities with respect to safety laboratory and vital signs were observed.

While the proportion of patients who achieved ppPASI50 at Week 16 in the total population was similar in all treatment groups (6 of 19 in 900 mg BI 655130 arm, 6 of 19 in 300 mg BI 655130 arm, and 5 of 21 in placebo arm) the baseline disease severity within the trial population was lower than expected, with half of the patients having a baseline ppPASI total score ≤ 16.70. In patients with baseline disease scores > 16.7, post-hoc subgroup analyses indicated efficacy for both doses of BI 655130 relative to placebo. The mean percent reduction from baseline in ppPASI total score was 40%, 24% and 8%, at week 16 for BI 655130 900 mg, BI 655130 300 mg, and placebo respectively in this subgroup. The mean percent reduction from baseline in pustular severity was 57%, 30% and 5% for the 900 mg BI 655130, 300 mg BI 655130 and placebo groups respectively at week 16 of this subgroup, indicating a dramatic reduction in pustule severity with evidence of a dose response relationship.

Summary
BI 655130 is an anti-IL36R antibody with a high clinical activity to block IL36R signaling as demonstrated in patients with Generalized Pustular Psoriasis, a severe inflammatory skin disease driven by uncontrolled IL36 activity. BI 655130 has been tested in healthy volunteers who received multiple doses every week for 4 weeks. These weekly doses of 20 mg/kg i.v. were all found to be safe in the subjects treated. In addition, IL36R inhibition shows a favorable nonclinical safety profile. BI 655130 has also been tested in acute flare of GPP patients. In these patients, BI 655130 was well tolerated, with no serious adverse events or other clinically notable safety concerns. In a larger trial investigating patients with PPP no safety signals have been identified for BI 655130. While the primary endpoint was not successful, efficacy was demonstrated in a post-hoc analysis for both doses of BI 655130 tested in patients with a baseline disease score > 16.7 based on the ppPASI.

For further details and most recent results refer to the current IB (c03320877).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Current treatment options for controlling acute flare of GPP, complete resolution of symptoms and prevention of reoccurrence of flares are limited and do not provide sustained efficacy (R16-0933). No treatments are currently approved for GPP in the US or centrally approved for GPP in the EU, though a combination of retinoids, cyclosporine or methotrexate has been recommended as primary options for controlling worsening of chronic GPP (R17-3600). The use of these for acute flare of GPP is based on anecdotal retrospective case reports, making this trial prospectively testing a treatment that has shown efficacy for acute flare more important to conduct. In addition, long-term use of these treatments is limited due to side effects and contraindications (retinoids: teratogenicity, hair loss; cyclosporine: excessive hair growth, renal toxicity; MTX: liver toxicity). Side effects, such as hair loss, excessive hair growth and teratogenicity particularly limit the use of these treatments in women. Biologics (mostly TNF inhibitors, occasionally IL-1 or IL-17 inhibitors) are increasingly used to treat more severe, extensive or treatment resistant patients with GPP, based on small published case series (R17-3603, R16-2960). However, these drugs are also associated with limitations in efficacy (incomplete and delayed responses are frequent) and safety (risk of infections and infusion reactions).

Based on the limitations described above, current therapeutic options are not suitable for life-long treatment and do not provide sustained responses in most patients. Therefore, to address the high unmet needs in GPP there is a critical need to develop (i) a highly effective treatment with rapid onset of action for patients presenting with an acute GPP flare; and (ii) to develop an effective treatment that also reliably reduces the occurrence of flares and leads to complete resolution of manifestations such as widespread erythema and scaling, and is safe and tolerable for lifelong treatment. In addition, a search of the current literature did not yield any published studies focusing on moderate to severe GPP flares. Thus, our PoC approach (1368.11) and subsequent development plan (1368-0013) further address the need for GPP treatment options.

The strong genetic link between the IL36 signaling pathway and GPP and experimental data identifying IL-36 as the dominant cytokine driving GPP (R17-3602) suggest that inhibition of IL36R signaling with the humanized anti-IL36R antibody BI 655130 might be beneficial in treatment of GPP - similar to the strong responses seen in IL1R antagonist deficient patients with sterile multifocal osteomyelitis after treatment with Anakinra. In addition, a recent characterization of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defenses (R17-3632).

Based on this rationale, an open-label, single arm study trial (1368.11) has been conducted to investigate proof-of-concept of a single dose of BI 655130 in patients with GPP. In total, seven patients have been treated with a single IV administration of 10mg/kg of BI 655130.

As described in Section 1.2.3, inhibiting IL36R activity results in a rapid and sustained improvement in GPP clinical skin and systemic symptoms. In study 1368.11, 7 patients were randomised into this open label, single dose, single arm trial of BI 655130. All patients received a single intravenous dose of 10mg/kg BI 655130. AEs reported within 20 weeks after administration of the trial medication were considered on-treatment.

In total, 7 out of 7 patients (100%) were reported with at least 1 AE while on treatment. In 4 patients (57.4%), AEs that were considered drug-related by the investigators were reported. None of the reported AEs was severe, serious, or led to discontinuation.

At the preferred term level, the most frequently reported treatment-emergent AE was arthralgia (3 out of 7 patients [42.9%]). Eosinophilia, chills, oedema peripheral, pyrexia, upper respiratory tract infection, and eczema were each reported in 2 patients (28.6%). In 1 patient, an infusion-related reaction was reported. The patient felt "heat" after the infusion of the trial medication during Visit 3. This event was not accompanied by other symptoms, in particular vital signs remained stable. This event was transient and did not require any treatment.

There were no clinically relevant safety laboratory or vital signs abnormalities on treatment with BI 655130.

Overall, BI 655130 was well tolerated in the patients who participated in trial 1368.11.

Based on these results, the objective of this subsequent GPP trial is to evaluate efficacy, safety, and tolerability of BI 655130 compared to placebo in patients with GPP presenting with an acute flare of moderate to severe intensity.

The results from this trial will support the first registration of BI 655130 in GPP patients.

In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking (please see Section 5.4.3). If the patient agrees, banked samples may be used for future biomarker research and drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), or to gain a mechanistic or genetic understanding of drug effects and thereby better match patients with therapies.

1.4 BENEFIT - RISK ASSESSMENT

Patients who experience moderate to severe flares of GPP have a need for treatment to rapidly reverse the progressively worsening signs and symptoms of their condition. The completed PoC trial 1368.11 demonstrates that BI 655130 treatment rapidly stops the flare and clears pustules, the primary lesions in GPP. As the first trial to investigate treatment of acute flares, in contrast to subacute residual/chronic GPP, the results support further development of treatment for this most dangerous aspect of GPP. The trial design calls for screening for confirmed diagnosis of flaring GPP followed by monitoring for up to 6 months for the next acute flare. The benefit of participation in this trial for qualifying patients is the opportunity to have their next GPP flare monitored prospectively and treated in a controlled setting with treatment targeted at the primary immune process driving the pathology of their disease. BI 655130 treatment has successfully treated GPP flare rapidly resolving symptoms with sustained effect for at least 20 weeks subsequent to a single dose of BI 655130. By

contrast current recommended treatment options are supported by anecdotal reports of GPP flare with improvement that can be expected to be lost without continued treatments.

Preclinical profiles of BI 655130 and clinical data from healthy volunteer trials suggest that BI 655130 is safe, tolerable and may address an unmet medical need in GPP patients. Data from the completed PoC trial 1368.11 demonstrate that 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 (c03320877).

No relevant animal species is available for toxicology testing of the highly human specific antibody BI 655130. However, preclinical toxicology studies with a mouse surrogate antibody have demonstrated the safety of IL-36R inhibition in mice (c03320877).

As of September 2018, BI 655130 has been given to 212 subjects in ongoing and clinically completed trials. BI 655130 was well tolerated. Most reported adverse events were of mild or moderate intensity, but there have also been a small number of patients experiencing severe or serious adverse events in clinical trials. It is unknown whether these adverse events were caused by BI 655130. Overall adverse events observed in subjects who received BI 655130 were comparable to adverse events observed in those who received placebo and no dose-limiting adverse effects were observed (for details refer to IB; (c03320877)).

As with any immune modulating agent, BI 655130 has the potential to impair immune function resulting in a risk of infection. A recent characterization of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signaling pathway inhibition does not compromise host defenses (R17-3632). The role of IL-36 in tumor immunity is not well established at this time, but an increased risk of cancer from an IL-36R antagonist, though considered small, cannot be excluded. These risks will be addressed by careful safety monitoring and risk mitigation measures, which will be implemented in this trial of a novel and 1st-in-class MoA: (a) exclusion of patients with history or increased risk of malignancies or infections; (b) close clinical monitoring for AEs, including use of Rheumatology Common Toxicity Criteria (RCTC) for severity grading, definition of emerging malignancies, sepsis and disseminated intravascular coagulation as always-serious adverse events, definition of opportunistic infections and infusion and anaphylactic reactions as adverse events of special interest (AESI); (c) selection of sites experienced in treatment of GPP patients; and (d) implementation of a fully independent data-monitoring committee (DMC).

Other risks related to trial-specific procedures include blood sampling, intravenous infusion of study medication, and tissue biopsy, which can cause local bruising, inflammation, nerve damage and pain. In addition, the management of any latent Tuberculosis, and any untoward risks of placebo administration will be carefully monitored and addressed as described in Section 4.2.

Reactions to i.v. administered biologic agents represent the manifestations of systemic hypersensitivity reactions and include anaphylaxis, pruritus, hypotension and respiratory distress. Systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. Specific safety measures will be taken during

the trial. During and following the i.v. infusion, the patients will be monitored for systemic hypersensitivity including (See Section 4.2.1.1 for further details) infusion reactions at the site according to Instructions for Preparation and Handling of BI 655130.

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 on unintentional exposure of an embryo or fetus to the investigational drug, WOCBP must agree to the requirements for the pregnancy testing and contraceptive methods described in the protocol.

Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´safety, see also Section 5.2.6.

Summary of benefit-risk assessment

The trial presents a benefit for the patient of monitoring until the next GPP flare as well as monitoring and careful management during and after the occurrence of that flare. Considering the medical need of the development of an effective and well tolerated drug for treating GPP flares, the benefit of this trial is considered to outweigh the potential risks for and justifies the administration of BI 655130 to patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity. Due to the lack of mechanism- or compound-related safety signals and the antagonistic mode of action of BI 655130 it is considered likely that GPP patients will not be exposed to undue risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The primary objective of this trial is to evaluate efficacy, safety, and tolerability of one single i.v. dose of BI 655130 compared to placebo in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity.

2.1.2 Primary endpoint

The primary endpoint of the study is:

- A GPPGA pustulation sub-score of 0 indicating no visible pustules at Week 1.

For the estimand concept on the above-defined primary binary endpoint definition(s), any use of escape medication (see Section 3.1) prior to Week 1 will be considered to represent a non-response at the Week 1 timepoint.

2.1.3 Key Secondary endpoint

The key secondary endpoint of the study is:

- A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 1.

For the estimand concept on the above-defined key secondary binary endpoint definition(s), any use of escape medication (see Section 3.1) prior to Week 1 will be considered to represent a non-response at the Week 1 timepoint.

2.1.4 Secondary endpoints

Secondary Endpoints at Week 4:

Secondary Endpoints of the study at Week 4 which are included in the statistical testing strategy in a hierarchical manner subsequent to performance of the tests on the primary endpoint and key secondary endpoint (see Section 7.2) are:

- A Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI) 75 at Week 4.
- Change from baseline in Pain Visual Analog Scale (VAS) score at Week 4.
- Change from baseline in Psoriasis Symptom Scale (PSS) score at Week 4.

- Change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue score at Week 4.

Other secondary endpoints of the study at Week 4 are:

- A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 4.
- A GPPGA pustulation sub-score of 0 indicating no visible pustules at Week 4.
- A GPPASI 50 at Week 4.
- The percent reduction in GPPASI from baseline at Week 4.

For the estimand concept on each of the above-defined binary secondary endpoint definition(s) at week 4, any use of escape medication prior to Week 4, or OL BI 655130 use at D8, or any rescue medication with BI 655130 prior to Week 4 will be considered to represent a non-response at the Week 4 timepoint. For continuous endpoints, refer to Section 7.3.3.

Secondary Endpoints at Week 1:

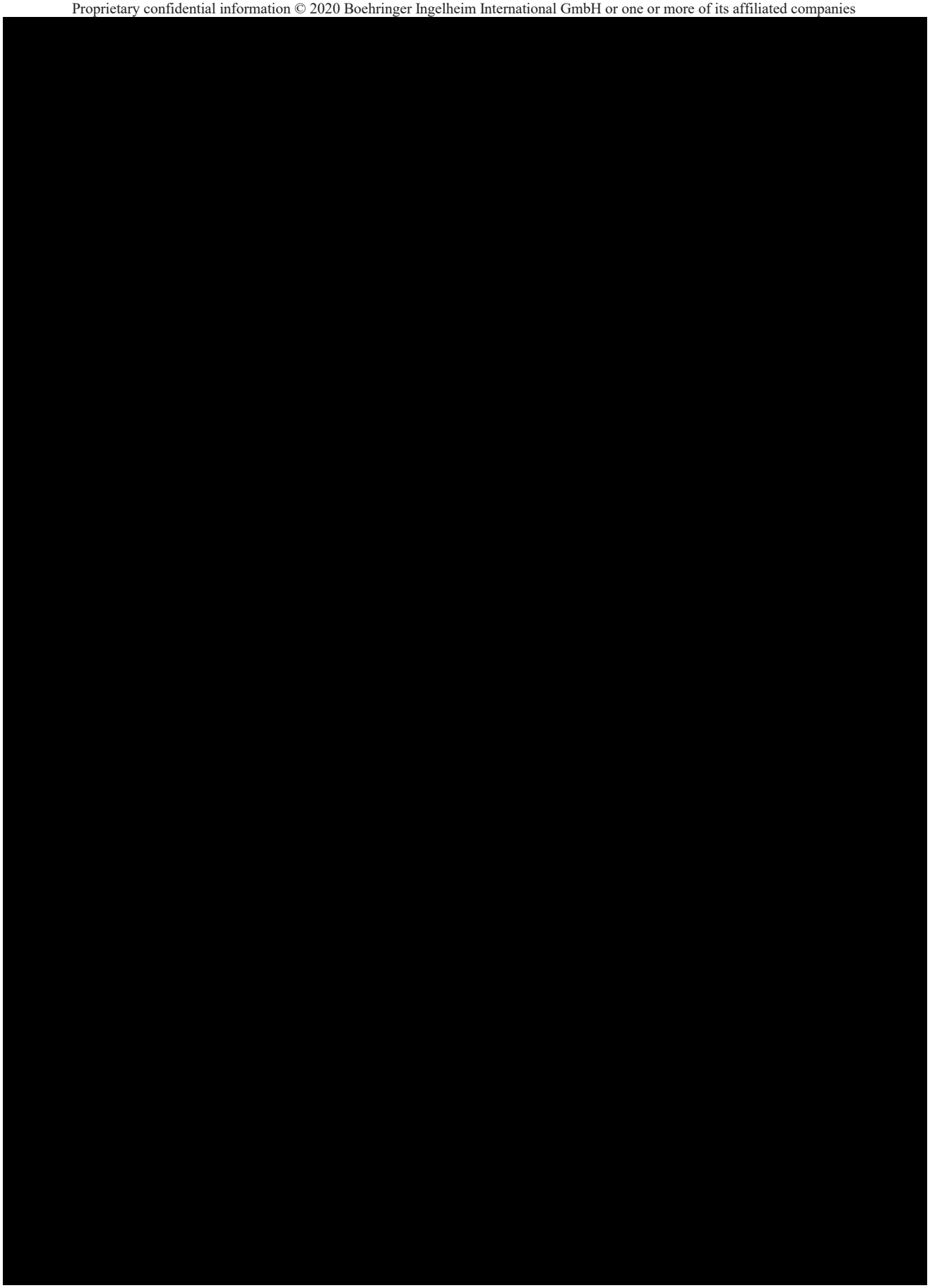
Additional secondary endpoints of the study at week 1, where (for binary endpoint(s) only), any use of escape medication prior to week 1 will be considered to represent a non-response at the Week 1 timepoint, are:

- A GPPASI 50 at Week 1.
- The percent reduction in GPPASI from baseline at Week 1.

Secondary Safety Endpoints:

The following safety endpoint is also defined:

- The occurrence of Treatment Emergent Adverse Events (TEAEs)



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multicenter, randomized, double-blind, placebo-controlled Phase II study with one dose of BI 655130/placebo in patients with GPP presenting with an acute flare of moderate to severe intensity. The primary objectives of this trial are to assess the efficacy, safety and tolerability of a single intravenous (i.v.) dose of BI 655130 in comparison to placebo in patients with generalized pustular psoriasis (GPP) presenting with an acute flare of moderate to severe intensity.

Approximately 11 to 20 countries will participate by using sites/centers experienced in the management of GPP.

Fifty-one patients with generalized pustular psoriasis (GPP) presenting with an acute flare of moderate to severe intensity are required to be randomized to receive BI 655130/ placebo (2:1) into this trial.
Patients are considered enrolled (screened) in the study once they have signed the informed consent.

Patients eligible to receive treatment after screening will be able to participate in this study and will be randomized at a ratio of 2:1(BI 655130/Placebo) to one of two treatment groups as shown in Figure 3.1: 1. All patients will receive the first dose of study medication (900 mg i.v. BI 655130 or Placebo) on Day 1 of Week 1 (Randomization). Based on the subsequent treatment response patients will then be followed for 12 to 28 weeks (see Flow Chart). Study Week in the flow chart represents the end of each week (e.g. End of Wk1=D8, End of Wk2 =D15, End of Wk3 = D22, End of Wk4 =D29 etc.).

During Week 1, D1, D2, D3 and D8 are mandatory visits, however, D4 – D7 are optional visits and need not be attended if a patient has already achieved complete pustular clearance (GPPGA pustulation sub score =0) at the previous visit.

At the discretion of the investigator, patients may be hospitalized prior to, during or following first study drug administration. Thereafter, the decision to discharge a patient from the hospital will also be at the discretion of the investigator, based on the evolution of the GPP flare and the patient's health status.

If the severity and progression of the disease worsens within the first week (Wk1/D2-D7) (see Table 3.1:1 for definition of disease worsening), the investigator can treat the patient with a Standard of Care (SoC) treatment of his/her choice (escape medication). If the disease condition is stable, it is recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing an escape medication (SoC) since there will be an option to administer OL BI 655130 instead at this time. If escape medication is administered within the first week, the patient will not be eligible to receive treatment with OL single i.v. dose of 900 mg of BI 655130 on D8. For escape medication use during the trial after Week 1, please refer to Table 3.1:1.

At the Week 1/Day8 visit, the primary endpoint and key secondary endpoint will be assessed. Patients who did not receive escape treatment and who have a GPPGA ≥ 2 at Wk1 and a GPPGA pustulation subscore of ≥2 will be eligible to receive treatment with a single open label i.v. dose of BI 655130 900 mg. All randomized patients will continue through the subsequent visits until the End of Study (EoS) as outlined in the Flow Chart. If patients receiving escape medication during Wk1 (D2-D7) are not willing to attend all subsequent visits then assessments at V9 (Wk1), V12 (Wk4) and EoS (V14 or V15 or V16 as applicable) should be encouraged or at the very minimum an early EoS visit.

After Wk1/D8 and through the follow-up period, if a patient who previously achieved a clinical response (GPPGA 0 or 1), either with BI 655130 at D1 or placebo at D1 or escape medication or OL BI 655130 at D8, experiences a recurrence of a GPP flare (see Table 3.1: 1 for definition), a rescue treatment with a single i.v. dose of 900 mg BI 655130 is to be administered. This could occur at a scheduled or unscheduled visit anytime between after D8 and Week 12. After D8, only one rescue dose with BI 655130 is permitted if a patient experiences a recurrence of a GPP flare. Subsequent flares are to be treated with escape treatment (SoC) per physician's discretion.

Patients who achieved a clinical improvement to BI 655130 and who show no flare symptoms of moderate/severe intensity at V14 or V15 visit will be offered to enter into an open label extension (OLE) trial (1368-0025), if they have completed this study (EoS/V14 or V15 visit, see below) and meet the eligibility criteria for the OLE trial.

For patients who qualify to enter OLE, prior to entering into the OLE trial:

- Patients who do not require rescue treatment with OL BI 655130 are to be followed until Week 12 (V14/EoS).
- Patients who receive rescue treatment with OL BI 655130 between Wk2-Wk6 are to be followed until Week 12 (V14/EoS).
- Patients who receive rescue treatment with OL BI 655130 between Wk 7-Wk12 are to be followed for additional 6 weeks from administration of rescue treatment up to Wk 13 –Wk18 (V15/EoS).

Patients who do not qualify to enter into the open label extension (OLE) trial (1368-0025), will be followed for 16 weeks (EoS/V16/Wk16-Wk28) after the last dose of trial medication, which is the latest timepoint of trial medication given during the study (i.e. the latest of V2, V9 if OL BI 655130 is given, rescue with OL BI 655130 if given).

Individual patient participation is concluded when the patient has completed the last planned visit. The "last-patient-last-visit-primary-endpoint" is the last scheduled primary endpoint visit (Week 1/D8) completed by the last patient. The end of the trial is defined as "last patient out", i.e. last scheduled visit (EoS) completed by last patient.

Table 3.1: 1 Study definitions

Criteria for Randomization/Initiation of Treatment	Randomized Treatment at Visit 2 will be initiated immediately in patients: • Who meet all of the inclusion/exclusion criteria at screening **And** • With GPP presenting with an acute flare of moderate to severe intensity, defined by the emergence of: a) a GPPGA score of at least 3 (moderate), and b) presence of fresh pustules (new appearance or worsening of pustules), **and** c) GPPGA pustulation sub score of at least 2 (mild), **and** d) at least 5% of Body Surface Area (BSA) covered with erythema and the presence of pustules
Qualification for treatment with Open Label (OL) single i.v. dose of 900 mg BI 655130 **at Wk1/D8**	Patients with a GPPGA ≥2 at Wk1 **and** pustular component of GPPGA ≥2 at Wk1 after receiving the first dose.
Recurrence of GPP Flare: Criteria to receive rescue treatment with Open Label (OL) single i.v. dose of 900 mg BI 655130 **after Wk1/D8**	After Wk1/D8 and through week 12, if there is ≥ 2 point increase in the GPPGA score and the pustular component of GPPGA ≥ 2 after achieving a clinical response (GPPGA 0 or 1) to initial treatment (either with BI 655130 at D1 or placebo at D1 or escape medication or OL BI 655130 at D8). **Note**: Only one rescue dose with BI 655130 is permitted if a patient experiences a recurrence of a GPP flare. Subsequent flares are to be treated with Standard of Care (SoC) per physician's discretion.
Disease Worsening of GPP: Scenarios when Escape treatment in case of Disease Worsening may be given:	Disease worsening is defined as worsening of clinical status or GPP skin and/or systemic symptoms as defined by the investigator. Escape treatment is the Standard of Care (physician's choice) in the investigator's opinion to treat the disease worsening of GPP. **Note**: The SoC options are multiple dose extended duration treatments. • Wk1/D2-D7: If the severity and progression of the disease worsens within the first week and requires

Table 3.1: 1 Study Definitions (cont'd.)

	immediate treatment, then the investigator can treat the patient with the escape medication of his/her choice. However, if the disease condition is stable, it is recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing an escape medication since there will be an option to administer OL BI 655130 instead at this time.
	
	• After D8:
	  • Patients who do not achieve a clinical response (GPPGA 0 or 1) but have disease worsening subsequent to D8 can receive an escape treatment chosen by the investigator.
	  • Patients who have achieved a clinical response and later have disease worsening that is not severe enough to meet the criteria for recurrence for GPP flare can receive the escape medication. However, it is recommended to wait until the patient meets the criteria for recurrence of GPP flare since there will be an option to administer rescue medication with OL BI 655130 instead at this time.
	  Note: Only one rescue dose with BI 655130 is permitted if a patient experiences a recurrence of a GPP flare. Subsequent flares are to be treated with Standard of Care (SoC) per physician's discretion.

BSA, Body Surface Area; D, day; ERASPEN, European Rare And Severe Psoriasis Expert Network; GPP, Generalized Pustular Psoriasis; GPPGA, Generalized Pustular Psoriasis Physician Global Assessment; OL, open label; Pts, patients; Wk, week.

The study design is illustrated in Figure 3.1: 1.

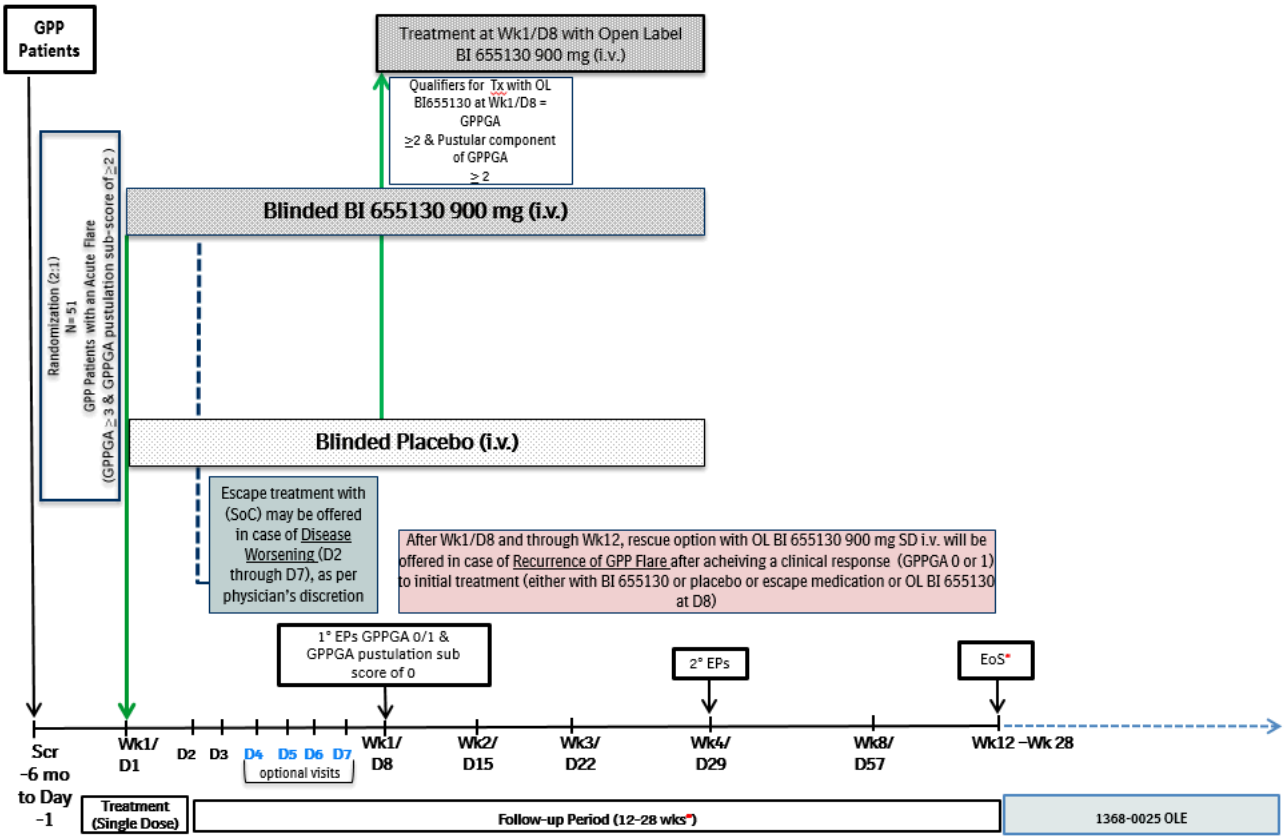


Figure 3.1: 1 Study design

Refer to Table 3.1:1 for Key study definitions and Rescue criteria.

*Patients who do not require rescue treatment with OL BI 655130 are to be followed until Wk 12 (V14/EoS) prior to entering into OLE (1368-0025) trial.

*Patients who receive rescue treatment with OL BI 655130 between Wk2-Wk6 are to be followed until Wk 12 (V14/EoS) prior to entering into the OLE trial. If at V14, they qualify to enter OLE trial, then V14 will be considered as EoS for these patients. If not, then the patients will have an additional 10 weeks follow-up and have an EoS at V16 (Wk16-28).

*Patients who receive rescue treatment with OL BI 655130 between Wk7 – Wk12 are to be followed for additional 6 weeks and have a response evaluation at V15 (Wk13-18). These patients will not have V14 visit. If at V15, they qualify to enter OLE trial, then V15 will be considered as EoS for these patients. If not, then the patients will have an additional 10 weeks follow-up and have an EoS at V16 (Wk16-28).

*Patients who do not qualify to enter into the OLE trial are to be followed for 16 weeks (EoS/V16/Wk16-28) after the last dose of trial medication, which is the latest time point of trial medication given during the study (i.e. the latest of D1, D8 if OL BI655130 is given, rescue with OL BI 655130 if given).

D, day; EoS, End of Study; Eps; Endpoints; Fup, Follow-up; GPP, generalized pustular psoriasis; GPPGA, generalized pustular psoriasis physician global assessment; i.v., intravenous; R, randomization; Scr, screening; SD, single dose; Wk, week.

An overview of all relevant trial activities is provided in the Flow Chart. For visit schedules and details of trial procedures at selected visits, refer to Sections 6.1 and 6.2, respectively.

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

This phase II trial with BI 655130 and placebo is to be conducted in patients with GPP presenting with an acute flare of moderate to severe intensity.

Based on data from 1368.11 which demonstrated rapid treatment onset of effect and flare resolution, a parallel group, randomized, double-blind and placebo controlled trial was considered most appropriate to evaluate the efficacy and safety of BI 655130 in patients with GPP. Also based on 1368.11 trial, the best option that can be offered for failing placebo patients is BI 655130. In the 1368.13 trial, any patients regardless of originally randomized treatment group, who experiences disease worsening and/or has recurrence of flare during the trial duration, will be offered escape treatment (SoC – physician's choice) and/or rescue treatment with open label BI 655130. Refer to Section 3.1 for details regarding criteria for qualifying for escape treatment with SoC or rescue treatment with OL BI 655130.

No active control group is included in this trial as there is currently no drug approved for the induction treatment of acute flares of moderate to severe GPP. Secukinumab (Cosentyx®), infliximab (Remicade®), ixekizumab (Taltz®), brodalumab (Lumicef®), adalimumab (Humira®), guselkumab (Tremfya®) and Risankizumab are only registered in Japan for the treatment of GPP and plaque psoriasis. For secukinumab, authorization was granted on the basis of long-term treatment data (52 weeks) derived from a single open label clinical trial conducted in 12 patients with chronic GPP and an endpoint at 16 weeks (R16-1462). Moreover, due to the absence of approved drugs and a commonly accepted treatment algorithm, patients in this trial will have a very heterogenous pre-treatment history as different SoC are available in different countries, which prevents the selection of suitable active comparator which is relevant for all patients. Considering an add-on design in treatment-naïve patients or patients with a defined treatment history would make enrolment of this study non-feasible. In addition, given the lack of a known effect size for SoC treatments (e.g., biologics, retinoids, or cyclosporine), because these drugs have not been tested in clinical trials in acute GPP, the expected sample size would of necessity be much larger in an acute flare setting in order to account for potentially smaller treatment differences than might be observed in a comparable trial where placebo is used as the comparator. This approach is not feasible in a rare disease such as GPP where recruitment is much slower and driven by a population with very few patients.

Thus, study 1368-0013 will be a single-dose, placebo-controlled study of patients with acute GPP flares of moderate to severe intensity receiving 900 mg BI 655130 and then followed for an additional 12 weeks. Patients who satisfy the inclusion/exclusion criteria of subsequent open-label extension trial (1368-0025) will receive an option to continue receiving treatment for GPP with s.c. dosing. See Section 3.1 for additional details on the trial design.

Please also refer to Section 4.1.3 for further details.

3.3 SELECTION OF TRIAL POPULATION

Eleven to 20 countries have been invited to participate in order to minimize the risk of under recruiting and to meet the goal of 51 patients entered. Recruitment will be very challenging

due to the rareness of the disease and because GPP patients must have an acute flare of moderate to severe intensity in order to be randomized on the trial.

For this trial, it is planned to include patients with active disease regardless of the mutation status (the status will be investigated during the trial) for the following reason:

- Efficacy has been seen in GPP patients both with and without the IL36RN mutation (early response to flare treatment with BI 655130 in 1368.11).
- In addition to the described IL36RN mutation, other mutations in the same gene and other genes linked to the IL36 pathway have been described (please see Section 1.1 "Medical Background"). This points to a general role of the IL36 pathway as disease trigger/driver.
- Because rapid treatment of flares is critical, patients can be included without the need for screening for mutation status.

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

3.3.1 Main diagnosis for trial entry

This study will assess treatment of patients with GPP presenting with an acute flare of moderate to severe intensity.

At screening, the diagnosis of GPP is based on the consensus diagnostic criteria defined by the ERASPEN (R18-1705).

These diagnosis criteria include:

Primary, sterile, macroscopically visible pustules on non-acral skin (excluding cases where pustulation is restricted to psoriatic plaques)
- With or without systemic inflammation
- With or without plaque-type psoriasis
- Either relapsing (>1 episode) or persistent (>3 months)

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

3.3.2 Inclusion criteria

Patients will be **enrolled (screened)** into the trial, if they meet the following criteria. Please refer to Section 3.3.4 for criteria for initiation of randomized treatment:

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

OR

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

OR

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

2. Patients may or may not be receiving background treatment with retinoids and/or methotrexate and/or cyclosporine. Patients must discontinue retinoids/methotrexate/cyclosporine prior to receiving the first dose of BI 655130 or placebo.
3. Male or female patients, aged 18 to 75 years at screening.
4. Signed and dated written informed consent prior to admission to the study in accordance with ICH-GCP and local legislation prior to start of any screening procedures.
5. Women of childbearing potential must be ready and able to use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in Section 4.2.2.3 as well as in the patient information. Note: A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is not a method of permanent sterilization. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

3.3.3 Exclusion criteria

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

1. Patients with SAPHO (Synovitis–acne–pustulosis–hyperostosis–osteitis) syndrome.
2. Patients with primary erythrodermic psoriasis vulgaris.
3. Patients with primary plaque psoriasis vulgaris without presence of pustules or with pustules that are restricted to psoriatic plaques.
4. Drug-triggered Acute Generalized Exanthematous Pustulosis (AGEP).
5. Immediate life-threatening flare of GPP or requiring intensive care treatment, according to the investigator's judgement. Life-threatening complications mainly include, but are not limited to, cardiovascular/cytokine driven shock, pulmonary distress syndrome, or renal failure.
6. Severe, progressive, or uncontrolled hepatic disease, defined as >3-fold Upper Limit of Normal (ULN) elevation in AST or ALT or alkaline phosphatase, or >2-fold ULN elevation in total bilirubin.

7. Treatment with:
    a. Any restricted medication as specified in Table 4.2.2.1: 1, or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator.
    b. any prior exposure to BI 655130 or another IL36R inhibitor
8. Patients with dose escalation of their maintenance therapy with cyclosporine and/or methotrexate and/or retinoids within the 2 weeks prior to receiving the first dose of BI 655130/ placebo.
9. The initiation of systemic agents such as cyclosporine and/or retinoids and/or methotrexate 2 weeks prior to receiving the first dose of BI 655130/ placebo.
10. Patients with congestive heart disease, as assessed by the investigator.
11. Active systemic infections (Fungal and bacterial disease) during the last 2 weeks prior to receiving first drug administration, as assessed by the investigator.
12. Increased risk of infectious complications (e.g. recent pyogenic infection, any congenital or acquired immunodeficiency (e.g. HIV), past organ or stem cell transplantation), as assessed by the investigator.
13. Relevant chronic or acute infections including HIV or viral hepatitis. For patients screened while having a flare (inclusion criteria 1b or 1c), if Visit 1 HIV or viral hepatitis results are not available in time for randomization, these patients may receive randomized treatment as long as the investigator has ruled out active disease based on available documented history (i.e. negative HIV and viral hepatitis test results) within 3 months prior to Visit 2. A patient can be re-screened if the patient was treated and is cured from acute infection.
14. Active or Latent TB:

    QuantiFERON® (or if applicable, T-Spot®) TB test will be performed at screening. If the result is positive, the patient may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. Active TB patients must be excluded. If presence of latent tuberculosis is established, then treatment should have been initiated and maintained according to local country guidelines. For patients screened while having a flare (inclusion criteria 1b or 1c), if the TB test results are not available in time for randomization, these patients may receive randomized treatment (provided they meet all other inclusion/exclusion criteria) as long as the investigator has ruled out active disease based on available documented history (i.e. negative for active TB) within 3 months prior to Visit 2.
15. History of allergy/hypersensitivity to a systemically administered trial medication agent or its excipients.
16. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
17. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s).

18. Women who are pregnant, nursing, or who plan to become pregnant while in the trial. Women who stop nursing before the study drug administration do not need to be excluded from participating; they should refrain from breastfeeding up to 16 weeks after the study drug administration (see Section 4.2.2).
19. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to receiving first dose of study drug or planned during the study, e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator.
20. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or any condition) other than GPP, surgical procedure, psychiatric or social problems, medical examination finding (including vital signs and electrocardiogram (ECG)), or laboratory value at the screening outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol, comply with all study visits/procedures or to complete the trial, compromise the safety of the patient or compromise the quality of the data.

3.3.4 Initiation of randomized treatment

Treatment (Visit 2) will be initiated immediately in patients:

- Who meet the inclusion criteria (Section 3.3.2).

- Who are presenting with an acute GPP flare with moderate to severe intensity, defined by emergence of:

    a) GPPGA score of at least 3 (moderate), and
    b) presence of fresh pustules (new appearance or worsening of pustules), and
    c) GPPGA pustulation sub score of at least 2 (mild), and
    d) at least 5% of Body Surface Area (BSA) covered with erythema and the presence of pustules

- And who do not meet any of the exclusion criteria (Section 3.3.3).

3.3.5 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole with different implications, please see Sections 3.3.5.1 and 3.3.5.2 below.

Every effort should be made to keep the treated patients in the trial, if possible; on treatment or at least to collect important trial data. Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, as well as the explanation of the consequences of withdrawal.

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and Case Report Form.

3.3.5.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- If a hepatic injury alert (as defined in Section 5.2.6.1) is detected without identification of an alternative cause in the work-up according to the "DILI checklist", the patient should not receive subsequent doses of OL BI 655130.
- For individual stopping rules related to specific adverse events, please see Section 4.2.1.1 Emergency procedures.

Patients who terminate study drug early should be encouraged to follow all study procedures per the Flow Chart and Sections 4.2.1 and 6.2.3.

For all patients the reason for withdrawal from trial treatment (e.g. adverse events) must be recorded in the Case Report Form (CRF). These data will be included in the trial database and reported.

3.3.5.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for trial participation at any time without the need to justify the decision. Once a patient is withdrawn from the trial, no further information may be collected for the purpose of the trial. Furthermore, it may also mean that further patient follow-up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see Section 3.3.5.1 above.

3.3.5.3 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 for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial

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 BI 655130 molecule is an anti-human IL-36 receptor monoclonal antibody heterodimer with a molecular weight of approximately 146 kDa.

BI 655130 solution for infusion (i.v. administration) is formulated at 60 mg/mL presented in a 10 mL vial with a nominal fill volume of 7.5 mL (450 mg).

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Study compound

Substance:	Spesolimab (BI 655130)
Pharmaceutical formulation:	Solution for infusion
Source:	BI Pharma GmbH & Co. KG, Biberach, Germany
Unit strength:	BI 655130 450 mg/vial (60 mg/mL), 7.5 mL fill volume
Posology:	900 mg single i.v. dose at Day 1
Route of administration:	i.v. infusion
Duration of use:	Single dose

At the time of use, the i.v. solution for dosing will be prepared as detailed in the instructions provided in the ISF.

Table 4.1.1: 2 Placebo comparator

Substance:	Placebo to BI 655130
Pharmaceutical formulation:	Solution for infusion
Source:	BI Pharma GmbH & Co. KG, Biberach, Germany
Unit strength:	Placebo to BI 655130 450 mg/vial (60 mg/mL), 7.5 mL fill volume
Posology:	0 mg on Day 1
Route of administration:	i.v. infusion
Duration of use:	Single Dose

4.1.2 Selection of doses in the trial

A fixed rather than weight-based dose regimen of single dose of 900 mg has been selected for the following reasons:

- Early trials of therapeutic monoclonal antibodies often investigate body-weight–based regimens to reduce the inter-subject variability in drug exposure. However, there is generally only a modest contribution of body weight to the overall pharmacokinetic (PK) and pharmacodynamic (PD) variability of monoclonal antibodies. Furthermore, monoclonal antibodies are highly target specific and offer a relatively large therapeutic window compared to new chemical entities. Therefore, most monoclonal antibodies are approved at fixed doses in antibody/target excess in order to cover target turnover and maximize efficacy (R10-6267, R13-4749, R13-4753, R13-4750, R13-4754).

- A dose of 10 mg/kg BI 655130 as a single i.v. infusion was chosen for the first trial in GPP (Proof of concept trial 1368.11) on the basis of the SRD trial 1368.1 that tested doses up to 10 mg/kg, which were all found to be safe and tolerable in the patient populations studied. The dose of 10mg/kg was chosen for Study 1368.11 as it was considered to provide greater assurance of achieving appropriate exposure levels in the skin and efficacy in GPP patients. In Study 1368.11, no severe or serious adverse events were reported, this confirms that in the GPP patients enrolled (n=7), the selected dose of 10mg/kg is safe and tolerable.

Thus, based on these data from 1368.11, it was considered reasonable to continue with the dose of 10 mg/kg and to maintain the PK exposures observed in the trial 1368.11. A fixed dose of 900 mg as a single IV infusion is recommended for flare treatment in the proposed trial (1368-0013) based on the evaluation of the PK data in GPP patients suggest that BI 655130 exposure in patients was lower when compared to PK in Healthy Volunteers (HVs) and based on flexibility to recruit subjects with a body weight greater than 70 kg.

Tests in healthy volunteers with doses up to 20 mg/kg (every week for 4 weeks in trial 1368.2) indicated that BI 655130 was found to be safe (see Section 1.2.3 and IB for further details (c03320877)). Thus, the selected fixed dose (900 mg i.v.) is within safety limits for patients with a lower weight.

The intended dose for treatment of a moderate to severe flare which can be life-threatening is the maximum practical dose to deliver at one time. Experience with biologics has consistently led to concern about under-dosing leading to inadequate response. In this trial those who have inadequate response at 1 week are allowed to receive a dose of BI 655130. Thus, there will be a test of a second dose at an appropriate interval to evaluate under-dosing as the explanation for treatment failure. Given (i) the rarity of the disease and in particular due to the rareness of flaring events precluding typical dose finding strategies, (ii) the serious and potentially life threatening nature of moderate/severe GPP and (iii) the favorable efficacy, safety and tolerability profile of BI 655130, exploration of lower doses in GPP patients presenting with a flare (trial 1368-0013) is considered to be not feasible or worthwhile.

4.1.3 Method of assigning patients to treatment groups

An Interactive Response Technology (IRT) will be used to screen eligible patients, perform drug assignment, manage initial/re-supply ordering of drug supplies and handle emergency un-blinding. 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.

During Visit 2 and after the patient's eligibility has been confirmed, the treatment will be assigned via IRT. Patients will be randomized to receive BI 655130 900 mg or placebo in a ratio of 2:1. The assignment will occur in a blinded fashion via IRT. The site is also required to register Visit 9 (Wk1/D8) in IRT. On registering the visit, IRT system will determine if a drug assignment (Treatment with open label BI 655130) is required. At the subsequent visits where study medication (Rescue with open label BI 655130) is to be administered (if applicable. i.e. in the event of recurrence of flare. Refer to Table 3.1:1), the site is required to complete the rescue medication module in the IRT.

At randomization as well as subsequent medication administration visits (if applicable), IRT will assign medication numbers. Site personnel will enter the medication numbers in the eCRF.

4.1.4 Drug assignment and administration of doses for each patient

The treatment to be evaluated is outlined in Table 4.1.4: 1 below. It will be assigned to each patient after the completion of the randomization visit (Visit 2), verification of all inclusion and exclusion criteria and verification of criteria for initiation of treatment (see Section 3.3.4).

Upon randomization, patients will receive the BI 655130 or placebo on Day 1. For further details concerning timing see the study Flow Chart. The start and end times of the infusion will be recorded. Detailed instructions for the preparation of the infusion solution, the volume to be administered, and the infusion rate are provided in the ISF.

In all patients, the infusion solution is intended to be intravenously administered over a period of 90 minutes. In case of safety concerns, e.g. due to systemic hypersensitivity including (See Section 4.2.1.1 for further details) infusion reactions, it is at the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited to slowing down the infusion rate, stopping the infusion, and provided no further safety concern exists, restarting at a slower rate. Regardless, the total duration of infusion should not exceed 180 minutes (3hours). Further based on his/her medical judgment the investigator will provide medications as needed.

The administration of the trial medication will be done under the supervision of the investigating physician or a designee. The so-called four-eye principle (two-person rule) is recommended for administration of trial medication and – if applicable – its preparation, if correct dosage cannot be ensured otherwise.

Table 4.1.4: 1 Treatments used in this trial.

Initial Treatment (Blinded)	**Wk1/Day 1**
900 mg SD i.v. BI 655130	2 x BI 655130 450 mg/vial (60 mg/mL)
0 mg SD i.v. Placebo to BI 655130	2 x Placebo to BI 655130 450 mg/vial (60 mg/mL)
Treatment with BI 655130 (Open Label)	**Wk1/Day8**
900 mg SD i.v. BI 655130	2 x BI 655130 450 mg/vial (60 mg/mL)
Rescue Treatment with BI 655130 (Open Label)	**After Wk1/Day 8 through Wk12**
900 mg SD i.v. BI 655130	2 x BI 655130 450 mg/vial (60 mg/mL)

SD, single dose; i.v., intravenous; Wk, week.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients and investigators involved in the trial conduct will always remain blinded with regard to the randomized treatment assignments until after database lock for the final trial analysis.

If the trial team agrees to perform the primary analysis and the final analysis separately (see Section 7.3), then a database lock for the primary analysis will be done and treatment will be unblinded to trial and project team members.

If the trial team agrees to perform the primary analysis and final analysis as one single analysis (at the time of trial completion), then patients, investigators, and sponsor personnel involved in the trial conduct will be unblinded to the randomized treatment assignments after the database lock has been performed.

The randomization codes will be provided to bio analytics prior to last patient out to allow for the exclusion from the analyses of PK samples taken from placebo patients. Bio analytics will not disclose the randomization code or the results of individual measurements until the trial has been officially unblinded to the sponsor. Sample drug levels and demographic data together with treatment assignments and dosing information may be made available to named individuals from bio analytics department for the purpose of PK dataset generation and analysis in accordance with sponsor's standard procedures.

A fully external DMC will perform an unblinded safety and efficacy assessment at specified intervals in order to ensure that patients are protected from potential harm, please refer to Section 8.7 for further details.

Section 4.1.5.2 provides the rules surrounding breaking of the randomization code.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator / pharmacist / investigational drug storage manager via IRT (for Japan: only to the investigator). It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure the safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

In case the automated unblinding option via the IRT system is malfunctioning, the IRT service provider can be contacted (24 hours a day coverage) and the treatment allocation can be obtained. IRT support has direct access to the database and the treatment information can be manually obtained in case the automated process is not working properly. Details about this process will be included in the ISF.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomization code for individual patients during trial conduct. The access to the code will only be given to authorized Pharmacovigilance representatives and not be shared further.

Treatment unblinding will be performed prior to each DMC meeting as a prerequisite for generation of the applicable DMC summaries required, as well as subsequent to the primary analysis database lock (if applicable), and the final trial database lock at which time the final trial analyses will be performed. Treatment unblind for the study will be officially released once database lock for the final trial analysis has been performed.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). The investigational product consists of a

carton holding a single vial of the trial medication. Each carton will have a unique medication number. 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.

Trial medication must be securely stored, e.g. in a locked refrigerator or at a pharmacy. If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately. Refer to the ISF for additional information.

The trial medication must be administered in the manner specified in the CTP and instructions for IMP preparation handling and administration of BI 655130 or Placebo.

4.1.8 Drug accountability

The investigator and/or pharmacist and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the Institutional Review Board (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 (if applicable)
- 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.

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

The investigator and/or pharmacist and/or investigational drug storage manager 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 alternative disposal of unused products.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation (see Section 3.3), are permissible. All concomitant medications should be carefully evaluated by the investigator and the Local Clinical Monitor (CML) should be contacted when there are questions regarding concomitant medications.

During the trial, if the severity and progression of the disease worsens, the investigator can treat the patient with Standard of Care (escape treatment) of his/her choice. Please refer to Table 3.1:1 for the details on the use of escape treatment during the trial. All efforts should be made to inform the patient of the importance of coming to the protocol specified visits (See Flow Chart) up to the EoS visit. Patients refusing to return to the study site (during the follow-up period) should at least provide safety information by phone at the respective visits.

Overall, the choice of the escape treatment i.e Standard of Care (SoC) treatment will be left at the discretion of the investigator. The sponsor will not provide/supply SoC treatment (s) to the sites.

4.2.1.1 Emergency procedures

Systemic hypersensitivity including Infusion reactions and anaphylactic reaction

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

- Immediately interrupt the infusion
- Treat with systemic anti-histamines, i.v. steroids, and in case of a severe allergic reaction (erg, anaphylactic reaction) epinephrine

Also draw a plasma sample for IgE and ADA/Nab as detailed in the Lab Manual (Central Laboratory). Consider also the evaluation of histamine, serum tryptase, and complement components.

In case of systemic hypersensitivity including infusion reactions, based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate systemic hypersensitivity including infusion reactions (according to RCTC grading (R13-3515) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of BI 655130 in the ISF. Regardless, the total duration of infusion should not exceed 180 minutes (3hours).

In case of anaphylactic reactions based on published criteria (Appendix 10.1.6; (R11-4890) that are suspected to be caused by the trial medication, the investigator should discontinue treatment with BI 655130.

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.

In case of potential systemic allergic reaction, blood samples for determination of serum tryptase will be collected 0.5 h, 2 h, 6 h, 24 h after onset of the event.

Severe infections (according to RCTC grading the ISF), serious infections, opportunistic or mycobacterium tuberculosis infections

Treatment of the infection should be initiated promptly according to local standard of care. No further trial medication should be administered until the active infection has resolved. Treatment with BI 655130 may be restarted when the patient has recovered according to investigator's assessment.

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

Malignancies

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

4.2.1.2 Additional treatments

No additional treatment is planned.

However, in case of AEs in need of treatment, the investigator can authorize symptomatic therapy. In those cases, patients will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.
All concomitant and/or rescue therapies will be recorded on the appropriate pages of the electronic CRF (eCRF).

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medications (or classes of medications) listed in Table 4.2.2.1: 1 must not have been taken before inclusion for the time periods as specified, and are not permitted throughout the study participation except in the following circumstances.

These drugs are permitted only when used as escape treatment in the event of disease worsening and/or recurrence of GPP flare. Escape treatment with any of the drugs listed in the table will exclude the patient from qualification to receive a treatment dose with open label BI 655130 at D8. However after D8, these patients will qualify to receive treatment with open label BI 655130 if they experience a recurrence of GPP flare (see Table 3.1:1 for definition of recurrence of GPP flare).

Table 4.2.2.1: 1 Restricted medications

Medication or class of medications	**Restriction duration (through EoS Visit[1])**
secukinumab (Cosentyx®), Risankizumab	2 months prior to Visit 2
tildrakizumab	2 months prior to Visit 2
rituximab, ustekinumab (Stelara®)	2 months prior to Visit 2
natalizumab, alemtuzumab, guselkumab, ixekizumab, adalimumab (Humira®), investigational products for psoriasis (non biologics)	2 months prior to Visit 2
brodalumab, efalizumab, visilizumab, briakinumab. infliximab (Remicade®)	2 months prior to Visit 2
IL36R inhibitors	not allowed before or during trial participation
etanercept (Enbrel®) live virus vaccinations	6 weeks prior to Visit 2
any investigational device or product (excludes psoriasis products) other systemic immunomodulating treatments (e.g. corticosteroids[2], cyclophosphamide), tofacitinib (Xeljanz®), apremilast (Otezla®) other systemic psoriasis treatments (e.g. fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g., PUVA). GMA (Granulocytes and monocytes adsorptive apheresis)	30 days prior to Visit 2

See Next Page (cont'd.)

Table 4.2.2.1: 1 Restricted medications (cont'd.)

Medication or class of medications	**Restriction duration (through EoS Visit[1])**
phototherapy (e.g., UVA, UVB) topical treatment for psoriasis or any other skin condition (e.g. topical corticosteroids, topical vitamin D analogues, tar, anthralin, topical retinoids	No treatment initiation of topical treatment 1 week prior to Visit 2, and use of these medications is not allowed Post Visit 2.
Anakinra	7 days prior to Visit 2
methotrexate, cyclosporine, retinoids	No treatment initiation 2 weeks prior to Visit 2 No dose escalation within 2 weeks prior to Visit 2 Must be discontinued prior to receiving the first dose of BI 655130/placebo and not allowed Post Visit 2

[1] In case of worsening of the flare (disease worsening), please refer to Section 4.2.1 for the details on the use of escape treatment.

[2] No restriction on inhaled corticosteroids to treat asthma or corticosteroid drops administered in the eye or ear.

4.2.2.2 Restrictions on diet and life style

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

4.2.2.3 Restrictions regarding women of childbearing potential

Women of child bearing potential (for the definition of WOCBP, please refer to Section 3.3.2) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly during the trial, and for a period of at least 16 weeks after the last study drug administration.

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

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

As monoclonal antibodies can be secreted in milk, women should refrain from breastfeeding once they receive the study drug and up to 16 weeks after, i.e. until BI 655130 is eliminated. They can start nursing again after this period.

4.3 TREATMENT COMPLIANCE

Administration of the trial medication will be done in the study center under the supervision of the investigator or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

The primary endpoint, the key secondary endpoint and the secondary endpoints, [redacted] are specified in Sections 2.1.2, 2.1.3, and 2.2.2, respectively.

Skin condition will be assessed by using the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA), the Generalized Pustular Psoriasis Area and Severity Index (GPPASI), and the Psoriatic Symptom Scale (PSS), Patients' questionnaires [redacted] Functional Assessment of Chronic Illness Therapy - Fatigue scale (FACIT-Fatigue), Pain VAS, [redacted] will be used as well.

[redacted]

Additional details for these assessments are provided below. Methodological details for the evaluation of the scores/index are described in the ISF.

Generalized Pustular Psoriasis Physician Global Assessment (GPPGA)

GPPGA relies on clinical assessment of the GPP patient's skin presentation. It is a modified PGA, a physician's assessment of psoriatic lesions, which has been adapted to the evaluation of GPP patients (R15-5200). The investigator (or qualified site personnel) scores the erythema, pustules, and scaling of all GPP lesions from 0 to 4. Each component is graded separately, the average is calculated, and the final GPPGA is determined from this composite score. A lower score indicates a lesser severity, with 0 being clear and 1 being almost clear.

GPPGA is provided in Appendix 10.1.1; this score will be measured at the timepoint noted in the study Flow Chart.

Generalized Pustular Psoriasis Area and Severity Index (GPPASI)

The GPPASI is an adaptation for GPP patients of the PASI, an established measure of severity and area of psoriatic lesions in patients with psoriasis (R96-3541). Similar adaptions have been used for PPP (R16-3360). In the GPPASI, the induration component has been substituted with the pustules component. It is a tool that provides a numeric scoring for a patient's overall GPP disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected by erythema, pustules and scaling and the severity of erythema, pustules, and scaling (desquamation) over 4 body regions.

GPPASI is provided in Appendix 10.1.2; this score will be measured at the timepoint noted in the study Flow Chart.

FACIT-Fatigue scale

The FACIT-Fatigue is a 13-item questionnaire (R10-6433, R07-4311, R16-0029) that assesses self-reported fatigue and its impact upon daily activities and function. Answers are based on a 5-point Likert scale. Responses of "not at all," "a little," "somewhat", "quite a bit," and "very much" are available for each question, and correspond to scores of 0, 1, 2, 3, and 4, respectively (total score range: 0-52). A minimal clinically important difference (MCID) of 3-4 points in change score has been reported (R16-0029). The recall period for items is 7 days.

The FACIT fatigue scale (Version 4) is provided in Appendix 10.1.4; this score will be measured at the timepoint noted in the study Flow Chart.

PSS

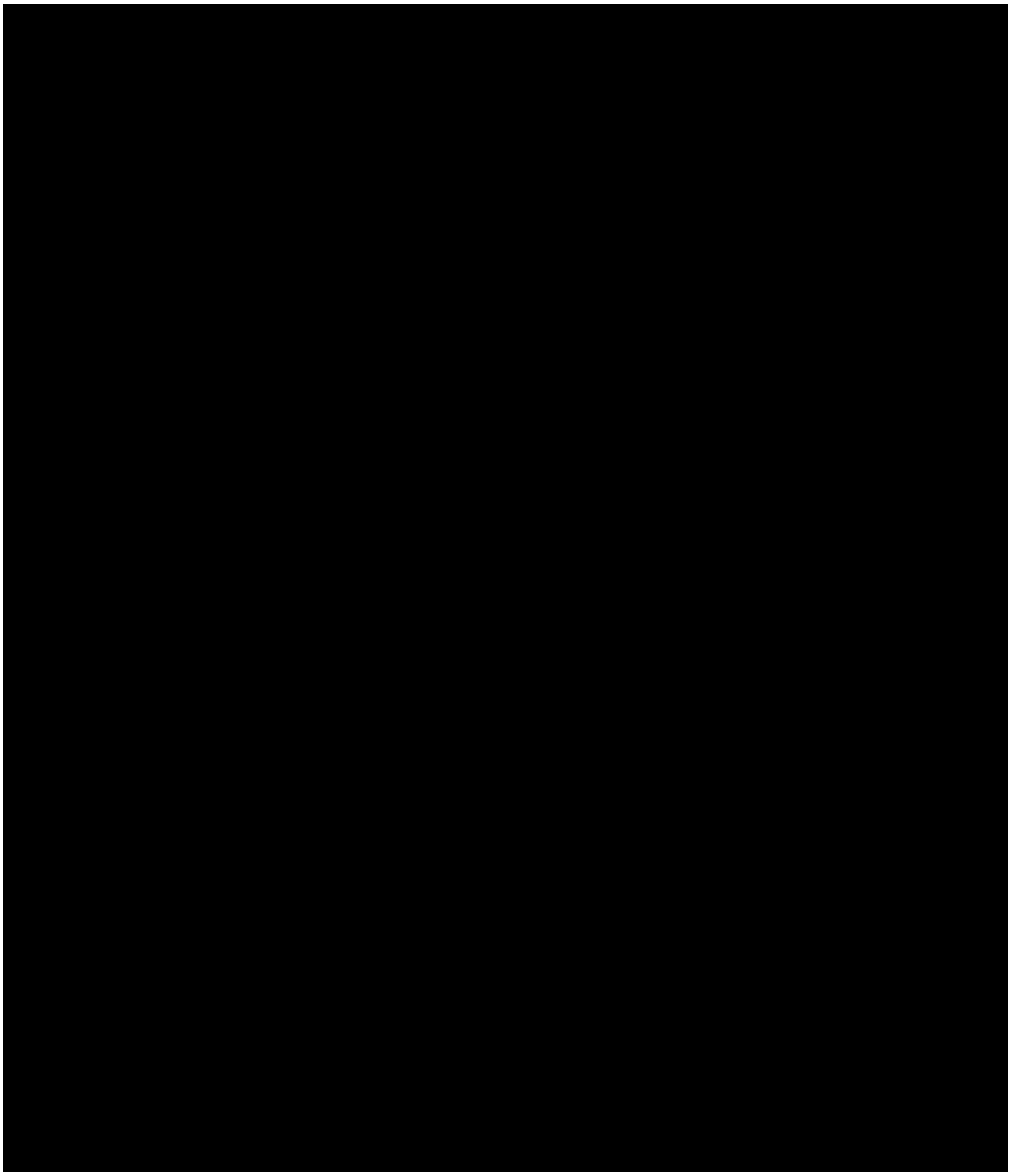
The PSS is a 4-item patient-reported outcome (PRO) instrument that was developed to assess the severity of psoriasis symptoms in patients with moderate to severe psoriasis (R18-1990). The symptoms included are: pain, redness, itching, and burning. Current symptom severity is assessed using a 5-point scale ranging from 0 (none) to 4 (very severe). The symptom scores are added to an unweighted total score (range: 0 to 16).

The PSS instrument is provided in Appendix 10.1.5.

Pain VAS

The pain VAS is a unidimensional measure of pain intensity (R18-1989). It is a continuous scale comprised of a horizontal or vertical line, usually 10 centimeters (100 mm) in length, anchored by word descriptors at each end ("no pain", "very severe pain"). The pain VAS is self-completed by the respondent. The respondent is asked to place a vertical (|) mark on the horizontal line to indicate the severity of the pain. Using a ruler, the score is determined by measuring the distance (mm) on the 10-cm line between the "no pain" anchor and the patient's mark, providing a range of scores from 0–100. A higher score indicates greater pain intensity.

Pain VAS will be measured at the timepoint noted in the study Flow Chart. The Pain VAS instrument is provided in Appendix 10.1.9.



5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events (including drug-related AEs)
- Adverse events of special interest (AESI)

- Serious adverse events
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to ISF for details)
- Safety laboratory tests
- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-lead Elecrocardiogram (ECG)
- Infusion site reactions
- Immunogenicity (ADA)

5.2.1 Physical examination

Complete and targeted physical examinations will be performed at visits as described in the Flow Chart. Height and weight of the patient will be recorded at the Screening Visit.

Complete physical examination will include vital sign assessment and general appearance as well as evaluation of all organ systems. Targeted physical examination will include vital sign assessment and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

Clinically relevant abnormal findings will be reported as baseline conditions or AEs.

5.2.2 Vital signs

Vital signs evaluations will be performed at visits as shown in the Flow Chart. This includes measuring temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least 5 minutes. All recordings should be made using the same type of blood pressure recording instrument on the same arm if possible. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements.

At visits with i.v. administration, vital signs will be assessed pre-dose, at approximately 5 minutes after the end of infusion and 120 minutes after the end of infusion. On non-study–drug administration days, vital sign assessments are to be done prior to blood sampling.

In addition to the temperature being measured along with the vital signs at time points shown in the Flow Chart, additional fever assessments will be recorded on dosing days at three time points. If the patient will receive medication for fever treatment, the fever assessment will be performed prior to taking the anti-fever treatment. These fever assessments must be taken whether or not the patient has an elevated temperature and whether or not the patient takes anti-fever treatment. The fever assessments times are to be separated by intervals of 2 to 4 hours on dosing days. At all other visits (non-dosing days), fever will be assessed once a day and will be completed prior to receiving medication for fever treatment, if anti-fever treatment is given.

During i.v. drug administration, patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the study drug administration.

Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further infusions might be considered and will be agreed on between investigator and BI clinical monitor.

5.2.3 Safety laboratory parameters

For the assessment of laboratory parameters, blood and urine samples will be collected by the trial site at the time points indicated in the Flow Chart.

The parameters that will be determined are listed in Table 5.2.3: 1. The laboratory tests will be performed at a central laboratory.

However, local labs are to be used for dosing decisions at visits involving i.v. administration of BI 655130 or placebo. The labs listed in Table 5.2.3: 2 are to be collected and assessed by the investigator prior to study drug infusion to allow for immediate subject management; however, split or concurrent samples must be drawn and sent to the central laboratory for analysis.

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the ISF and eDC system). The amount of blood taken from the patient concerned will be increased due to this additional sampling.

Clinically relevant abnormal findings (e.g. anemia, hypoproteinemia, hypoalbuminemia, hypocalcemia etc.) will be reported as baseline conditions or AEs. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit laboratory kit and should be repeated until normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria (R13-3515).

Instructions regarding sample collection, sample handling/processing and sample shipping are included in the laboratory manual in ISF.

Table 5.2.3:1 Safety Laboratory Tests (Central Lab Assessment)

Category	Test name
Haematology	Haematocrit Haemoglobin Red blood cell count (RBC) White blood cell count (WBC) Platelet count
Automatic WBC differential (relative and absolute)	Neutrophils, eosinophils, basophils, monocytes, lymphocytes
Manual differential WBC (if automatic differential WBC is abnormal)	Neutrophils (stabs), eosinophils, basophils, monocytes, lymphocytes
Coagulation	Activated partial thromboplastin time (aPTT) Prothrombin time (Quick's test and International Normalized Ratio [INR]) Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT) Alanine transaminase (ALT/GPT) Alkaline phosphatase (AP) Gamma-glutamyl transferase (GGT) Creatine kinase (CK) CK-MB, only if CK is elevated Lactate dehydrogenase (LDH) Serum tryptase Amylase[1] Lipase[1]
Substrates	C-Reactive Protein (CRP) Serum albumin Creatinine Total bilirubin Direct bilirubin Total protein Total cholesterol Triglycerides Plasma glucose BUN (blood urea nitrogen) Uric acid eGFR (estimated by CKD-EPI formula) (only at screening) Bilirubin Indirect (if total is elevated) Troponin (Reflex, in case of elevated CK) LDL-Cholesterol HDL-Cholesterol
Electrolytes	Sodium Potassium Chloride Calcium
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH

Table 5.2.3:1 Safety laboratory tests (Central Lab Assessment; cont'd.)

Category	Test name
Infection testing[2]	Hepatitis B Surface Antigen (qualitative) Hepatitis B core Antibody HBV-DNA (quantitative) at baseline and EoS Visit[3] QuantiFERON® (or if applicable, T-Spot®)TB[4,5] Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative)
Urine-Sediment (only if urine analysis abnormal)	microscopic examination
Specific gamma-globulin quantification IgE	IgE[6]
Urine Pregnancy test[7]. At the drug administration visits, the test will be performed prior to the administration of study drug	Human Chorionic Gonadotropin in urine
Serum Pregnancy test[7] (only for female patients of childbearing potential)	Human Serum Chorionic Gonadotropin

[1]To be done at screening.

[2]Only at Visit 1(refer to exclusion criteria Section 3.3.3 for details regarding infection testing) and EoS (V14 or V15 or V16 as applicable).

[3]An HBV-DNA test should be conducted if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative. A positive HBV-DNA test at screening will exclude the patient. These evaluations should be conducted at screening and EoS (V14 or V15 or V16 as applicable).

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

<For Japan> T-Spot® TB test may be performed at local labs instead of QuantiFERON®TB test.

[5]In subjects with a negative QuantiFERON® (or if applicable, T-Spot®) TB test, the test should be repeated at EoS (V14 or V15 or V16 as applicable). <For Japan> T-Spot® TB test may be performed at local labs instead of QuantiFERON®TB test.

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

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

Table 5.2.3: 2 Laboratory tests to be assessed prior to i.v. administration at V2, V9 or for any rescue treatment (Local Labs)

Category	**Test name**
Haematology	Haematocrit, Haemoglobin, Red blood cell count (RBC), White blood cell count (WBC), Platelet count
Coagulation	Activated partial thromboplastin time (aPTT),Prothrombin time (Quick's test and INR),Fibrinogen
Enzymes	Aspartate transaminase (AST/GOT), Alanine transaminase (ALT/GPT), Alkaline phosphatase (AP)
Substrates	C-Reactive Protein (CRP) , Serum albumin, Creatinine, Total bilirubin Direct bilirubin, eGFR (preferably estimated by CKD-EPI formula)
Electrolytes	Sodium, Potassium
Urine Pregnancy test [1]. Test will be performed 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

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

5.2.4 Electrocardiogram

ECG measurements will always precede blood sampling to avoid impact of sampling on the ECG results. The 12-lead ECGs will be recorded and reviewed prior to dosing as scheduled in the Flow Chart. The investigator or a designee will evaluate whether the ECG is normal or abnormal and whether it is clinically relevant, if abnormal. ECGs may be repeated for quality reasons and the repeated recording used for analysis. No central laboratory will be used for ECG recording.

Additional ECGs may be recorded for safety reasons. The electronic version, if applicable, or dated and signed printouts of the ECG, will be regarded as source data and will be stored in the patient's medical file.

Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as adverse events and will be followed up and/or treated as medically appropriate.

5.2.5 Local tolerability

Local tolerability will be assessed by the investigator according to 'swelling', 'induration', 'heat', 'redness', pain', or, other findings' at the times indicated in the Flow Chart. Local tolerability will be assessed during the IMP administration and for approximately 2 hours after the study drug administration. Grade the intensity of the local tolerability according to RCTC grading (cf. ISF).

Other Safety Parameters:

In case of an infusion reaction, monitor the patient per standard of care, grade the intensity of the reaction according to RCTC grading (cf. ISF) and proceed as described in Section 4.2.1.1.

All cases of malignancies, sepsis or other serious infections and disseminated intravascular coagulation that are detected during the trial will be reported as SAEs. Please refer to the current list
of "Always Serious AEs" provided in eDC.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of Adverse Events

Adverse event

An adverse event (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 unfavorable 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.

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 hospitalization
- requires prolongation of existing hospitalization,
- 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 which, when based on appropriate medical judgement, may jeopardize 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 hospitalization 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.

AEs considered “Always Serious”

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between 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”.

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has developed a list of further AEs, which by their nature, can always be considered to be “serious” even though they may not have met the criteria of an SAE as defined above. The latest list of “Always Serious AEs” can be found in the eDC system.

These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)

The term 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 above.

The following are considered as AESIs:

Hepatic injury

Hepatic Injury, is defined by the following alterations of hepatic laboratory parameters:

- An elevation of AST and/or ALT and/or AP ≥3-fold ULN plus 2 times the baseline, combined with an elevation of total bilirubin ≥2-fold ULN plus 1.5 times the baseline, measured in the
  same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN

Any patients with these lab abnormalities need to be followed up according to the 'Drug-Induced Liver Injury (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 analyzed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Systemic hypersensitivity reactions including Infusion reactions and anaphylactic reaction

Any suspicion of severe systemic hypersensitivity including infusion reactions and any anaphylactic reaction should be defined and assessed using the criteria discussed in the statement paper from Sampson HA (Section 4.2.1.1 and Appendix 10.1.6; (R11-4890).

Severe infections (according to RCTC grading in the ISF)

Opportunistic and mycobacterium tuberculosis infections

These include pneumocystis jirovecii, BK virus disease including PVAN, CMV, 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).

Protocol-specified AESI can be classified as serious or non-serious but all AESI must be reported in an expedited manner similar to serious adverse events on a SAE form (i.e. non serious AESI must be reported on the SAE form and follow the same reporting timelines as for serious AEs).

Intensity of AEs

The intensity grading of AEs will be performed according to RCTC Version 2.0 developed by the Outcome Measures in Rheumatology (OMERACT) organization (R13-3515). Refer to the ISF for intensity/severity classification.

Intensity options are:

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

Causal relationship of AEs

Medical judgement should be used to determine the relationship, 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 diminished).

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

AE Collection

The Investigator shall maintain and keep detailed records of all AEs in their patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

For patients rolling over into open label extension trial (1368-0025):
- From signing the informed consent of the parent trial onwards until the first dose of trial medication in the extension trial:
  - all AEs (non-serious and serious) and all AESIs.

For patients not rolling over into subsequent OLE trial (1368-0025):
- From signing the informed consent onwards until the individual patient's end of trial:
  - all AEs (serious and non-serious) and all AESIs.

- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient for AEs but should only report related SAEs and 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, but not on the CRF.

The follow-up period describes the period of time from the last administration of trial medication until the end of trial examination (last per-protocol contact).

AE reporting to 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 via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details 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 fax 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.

Information required

For each AE, the investigator should provide the information requested on the appropriate eCRF pages and, if applicable, the BI SAE form. The investigator should determine the causal relationship to the trial medication.

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

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

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after a 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.

Pregnancy

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 pregnancy test, a serum pregnancy test will be done. Women who underwent tubal ligation are still considered of childbearing potential and pregnancy testing is necessary as well. The testing schedule is specified in the Flow Chart.

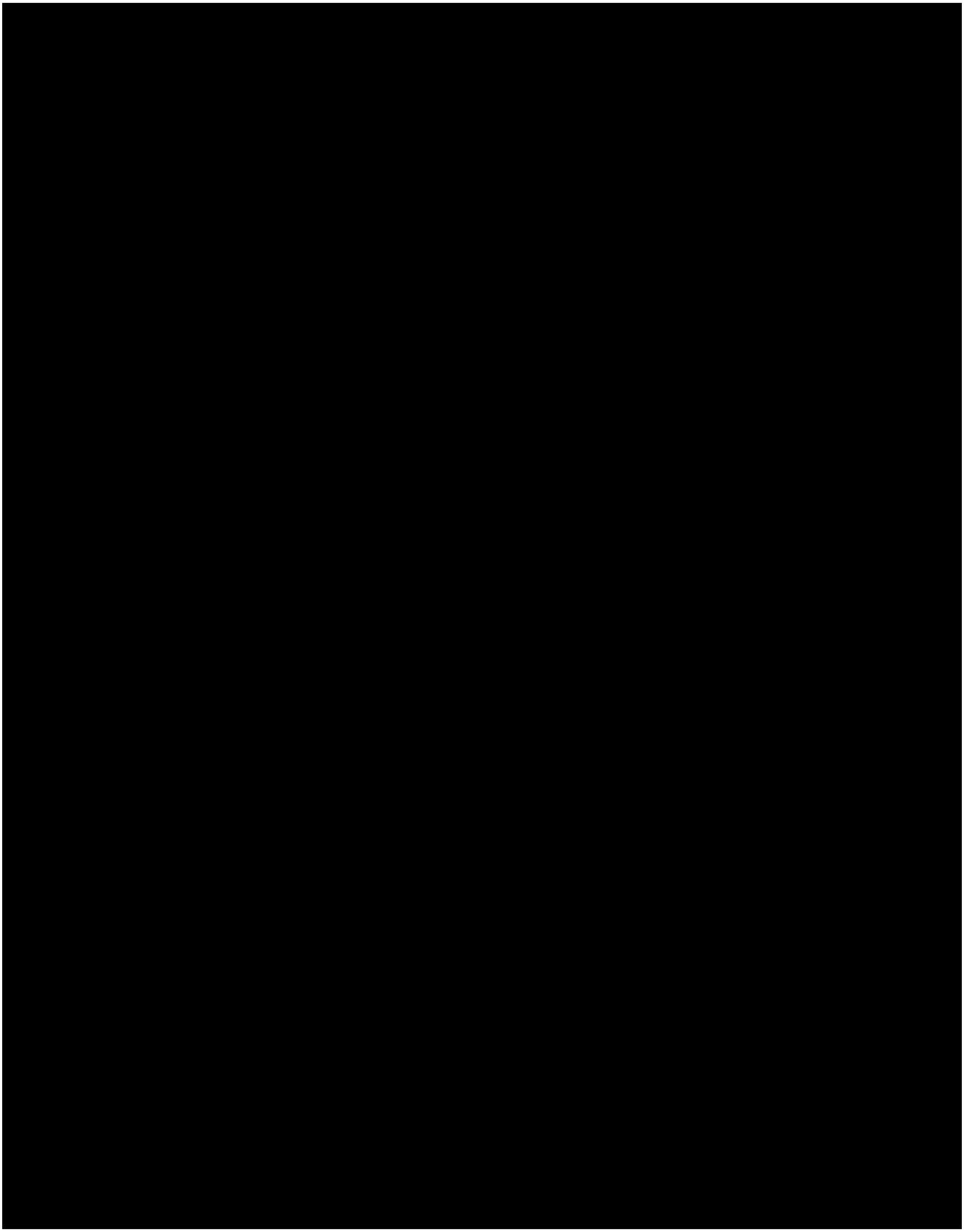
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must immediately (within 24 hours) report any drug exposure during pregnancy by means of Part A of the Pregnancy Monitoring Form to the sponsor's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

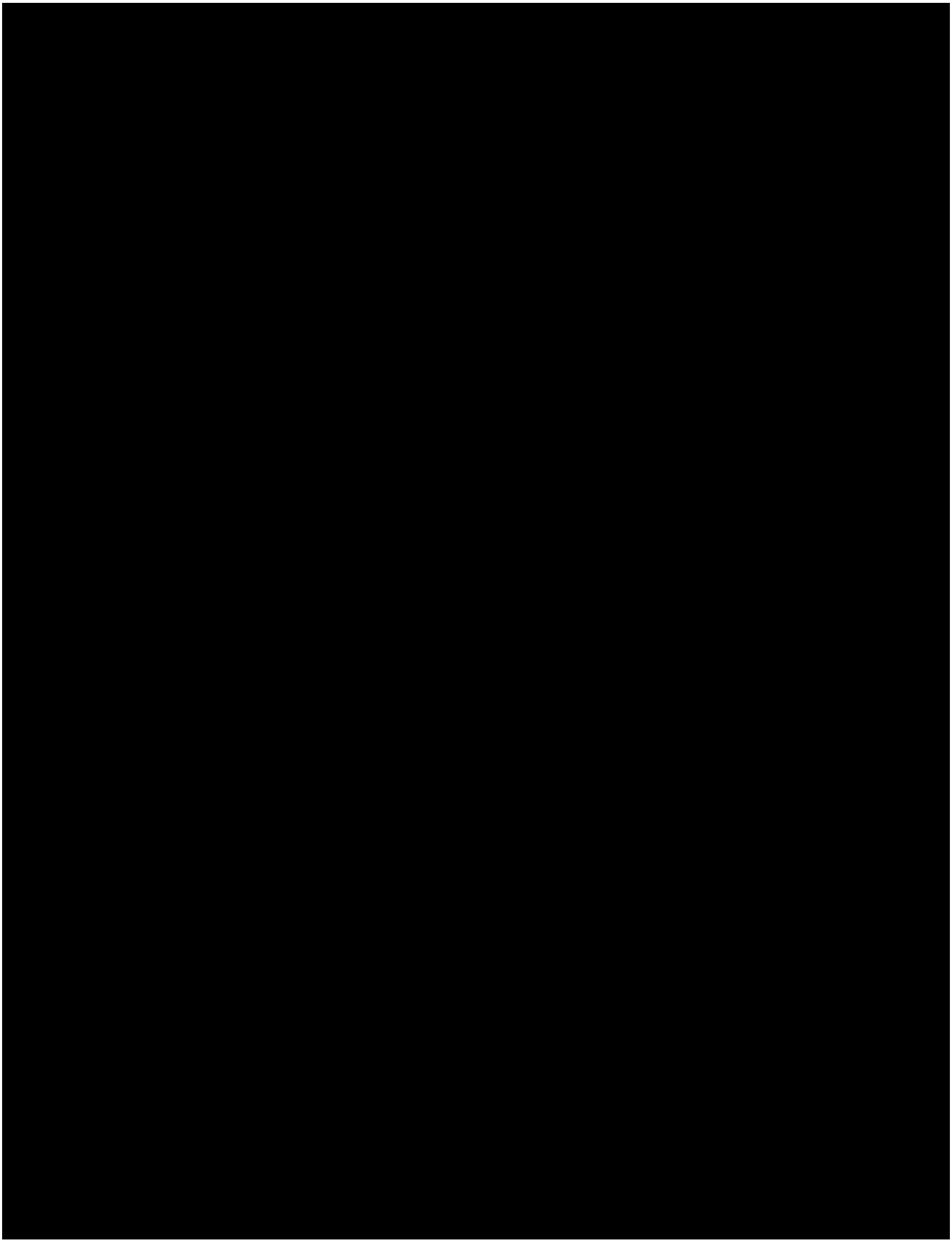
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

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.





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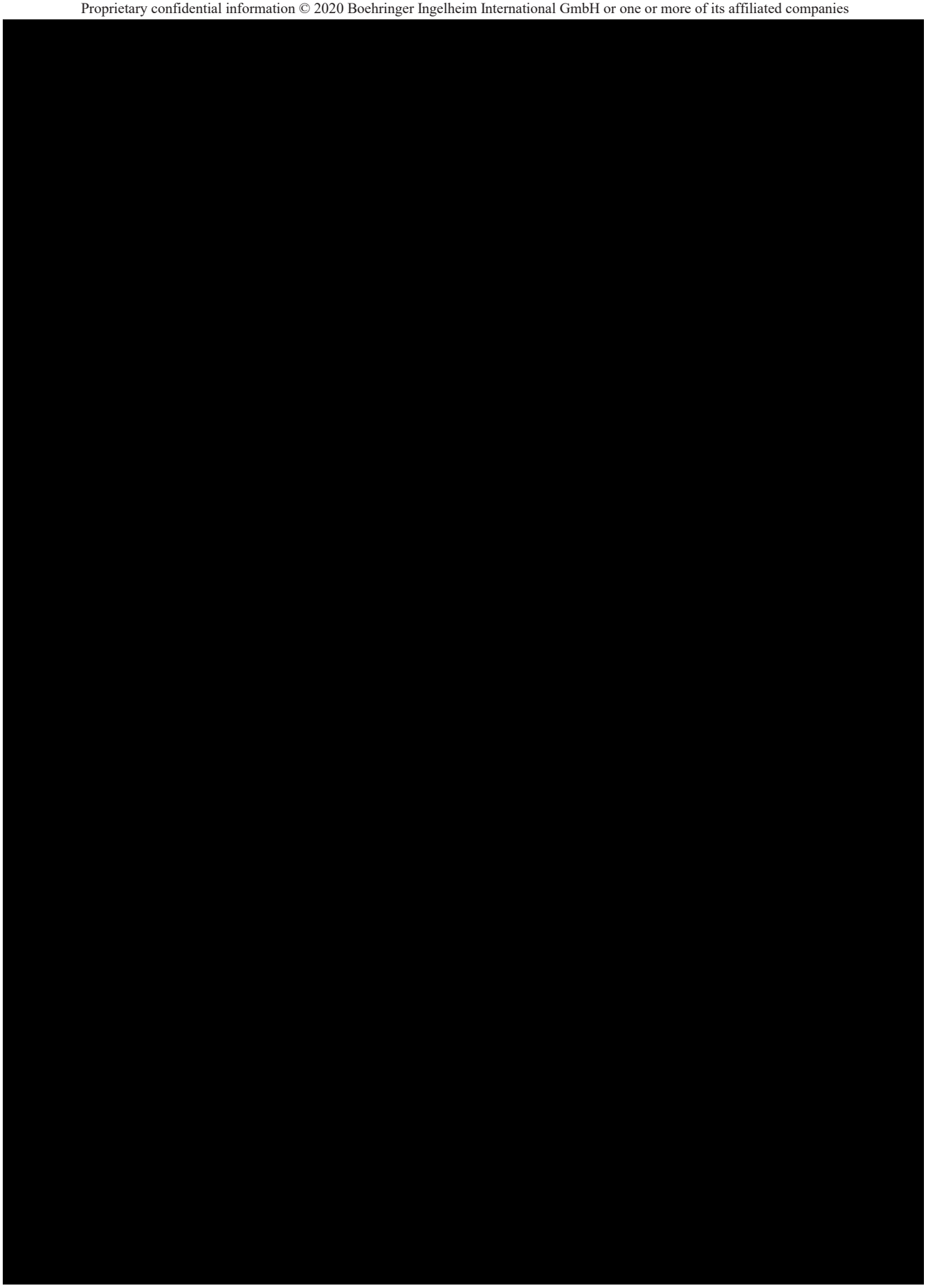

5.6 APPROPRIATENESS OF MEASUREMENTS

The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG variables that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an intravenously administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The biomarkers and pharmacogenomic parameters are outlined in Section 5.4 are of exploratory nature only.

Information about race should be obtained from all study participants as allowed by local regulations. This is because the prevalence and characteristics of psoriasis may differ between patients of different racial origin. It will thus be worthwhile to assess if patients of different race will respond differently to the study treatment.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule specified in the Flow Chart. Each visit date (with its window) is to be counted from Day 1 (V2).

All deviations from the planned visit schedule are to be documented. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of retesting of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

For detailed description of the trial procedures, please refer to the Flow Chart.

Details relating to study drug administration are provided in Section 4.1.4.

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 sections of this protocol. Refer to Section 5 for explanations of the specified assessments and procedural details.

Based on the investigator's clinical judgment, patients may be hospitalized prior to, during or following first study drug administration. If so, patients will perform the needed visits as inpatients. Subsequent visits will be conducted in accordance with the protocol and the investigator's judgment (For details, see Flow Chart and Section 3.1).

The patients' questionnaires (PSS, [redacted] pain VAS, FACIT-Fatigue, [redacted]) are to be completed by the patient on his/her own in a pre-specified order in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team, and, without any help from or interpretation by other people. If the patient is too sick to complete the questionnaires him/herself but is able to reply verbally, a member of the study team should read the instructions, questions, and response options aloud to the patient and collect the patient's verbal response in as neutral and unbiased a manner as possible. If this is not possible either, the questionnaires are not to be completed. The mode of administration should be documented in the electronic Case Report Form (eCRF).

At each applicable visit (see Flow Chart), the order of completion for PROs is recommended to be as follows:

- PSS
- [redacted]
- pain VAS

[redacted]

Separate from the PROs above, the evaluation of efficacy assessments (GPPGA, GPPASI, [redacted]) for a patient are to be conducted by the same physician throughout the study.

[redacted]

6.2.1 Screening period

Screening (Visit 1):

After patients have been informed about the trial, written informed consent in accordance with GCP and the local legislation must be obtained prior to performing any study related procedures.

Once consent is obtained, the patient is considered to have started the screening process, and is assigned a unique patient number by the IRT system. The patient is to be recorded on the enrolment log and be registered in the IRT system as a screened patient. 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 study until completion of all requirements is to be emphasized. No study procedures are to be done unless the patient has provided consent to take part in the study.

Demographics:

Informed consent date, gender, ethnicity and race (if allowed by local law) will be collected and reported in the eCRF.

Baseline Conditions:

Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the physical examination, ECG, safety labs, and any condition requiring therapy (excluding GPP) will be reported on the Baseline Condition eCRF page.

Infection screening:

Infection testing will include tuberculosis, hepatitis B, hepatitis C, and HIV assessments (see Table 5.2.3:1). Please also refer to applicable exclusion criteria in Section 3.3.3 for details regarding handling of infection test results for patients screened while having a flare (inclusion 1b and 1c).

Medical History:

Information on clinically significant previous and concomitant illnesses, other than GPP, or any clinically significant signs or symptoms that are present before informed consent, or pre-existing conditions identified through findings from assessments and examinations done during the screening visits will be recorded as medical and surgical history at screening. Regarding the GPP, a detailed history of the disease including evidence of systemic symptoms during a GPP flare in the past (i.e. fever, asthenia, myalgia, elevated C-reactive protein, leukocytosis with peripheral blood neutrophilia) and information of histopathological confirmation of diagnosis will be collected and reported in the eCRF. Also, previous and concomitant treatment for GPP will be recorded.

Mutation status:

Information on the presence or absence of IL36RN mutation (if available) will be collected in patient's historical data and reported in the eCRF.

Review of inclusion/exclusion criteria:

Selection criteria will be reviewed carefully.

IRT:

All patients who are screened must be registered with IRT.

Re-screening:

If a patient results in a screen failure (i.e. does not meet the eligibility criteria, or does not flare within the 6 month screening period) the patient must be registered as a screen failure in IRT system. However, re-screening of a previously screen failed patient will be permitted once. Upon re-screening, the patient will be assigned a new patient number. Details of IRT procedures can be found in the IRT manual located in the Investigator Site File (ISF).

For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to the Flow Chart.

6.2.2 Randomization Visit and Treatments

Patients will be randomized to receive a single dose of 900 mg BI 655130 or placebo (2:1) at Visit 2.

Please refer to Section 3.3.4 for details regarding criteria for initiation of treatment with BI 655130.

In cases where Visit 1 and Visit 2 are greater than 6 weeks apart, it is recommended that patient is asked to re-confirm (verbally) his/her consent to participate in the trial and this verbal re-consent must be documented. The first study drug administration is at Visit 2 Day 1).

For information pertaining to PK, ADA/Nab, and biomarkers, see Sections 5.3 and 5.4.

For information pertaining to laboratory tests, ECG, vital signs, local tolerability, and physical examination, see Sections 5.2.1 to 5.2.5.

Fasting is not required for blood sampling. Pharmacogenomic genotyping for targeted GPP-causing mutations (IL36RN, CARD14, AP1S3) are to be performed for all patients (see Section 7.3.7.2). DNA banking is optional and is only to be done for patients who have provided informed consent for this specific procedure.

Skin lesion photographs will be taken at all visits on site and are to be taken prior to any skin biopsies or study drug administration.

Skin biopsies (if applicable) and venipuncture (i.e. safety laboratories, PK, ADA/Nab, biomarkers) should be the last procedures done prior to study drug administration.

Study drug allocation via the IRT system and administration of study drug should be the last activity at Visit 2 with the exception of local tolerability and post dose vital signs assessments.

For women of child-bearing potential, pregnancy testing will be done as specified in the Flow Chart.

6.2.2.1 Clinical monitoring after study drug administration

During i.v. drug administration, vital signs will be assessed pre-dose, at approximately 5 minutes after the end of infusion, and 120 minutes after the end of infusion. Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after doses are administered. Hypersensitivity reactions should be treated according to medical standards.

6.2.2.2 Unscheduled visits

During the treatment period patients may be seen at an unscheduled visit if they experience worsening of the disease, recurrence of GPP flare, or have AEs that in the opinion of the investigator need intervention (e.g. escape or rescue treatment) or repeated laboratory testing.

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 that were missed at a previous visit. All unscheduled visits (including the reason for the visit) should be described and documented in the medical/source record, and in the eCRF.

6.2.3 Follow up period and trial completion

After receiving the single dose at Visit 2, patients will be followed for 12 -28 weeks depending on treatment response. Refer to Section 3.1 for details.

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

For the comprehensive list of the trial procedures required during the follow-up period, please refer to Flow Chart.

Trial Completion:

Trial completion is defined as a patient having reached the EoS visit within the specified window per protocol.

Treatment Completion:

Treatment completion is defined as a patient receiving the whole amount of prepared dose on D1.

Early Treatment Discontinuation:

In case the infusion of study drug is permanently discontinued before the whole amount of prepared solution has been administered to the patient, every effort should be made to keep the patient in the trial and complete all of the remaining study visits. If this is not possible, assessments of the primary and key secondary endpoints at V9 (Wk1), V12 (Wk4) and EoS Visit (V14 or V15 or V16 as applicable) should be completed or at a minimum an early EoS visit. Please refer to the Flow Chart.

Early Trial Discontinuation:

A patient not having reached the EoS visit within the specified window per protocol (e.g. due to withdrawal of consent, lost to follow-up, death etc.).

An open-label extension trial is planned, see Section 3.1 for details.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This trial is designed as a randomized, parallel-group, double-blind, and placebo-controlled trial with one active dose of BI 655130 in patients with GPP presenting with an acute flare of moderate to severe intensity.

The primary objective of this trial is to evaluate the efficacy, safety and tolerability of a single i.v. dose of BI 655130 in comparison to placebo at Day 1. The primary analysis, on each of the binary, primary endpoint, achievement of a GPPGA pustulation subscore of 0 at Week 1, and key secondary endpoint, achievement of a GPPGA of (0, 1) at Week 1, where any use of escape medication prior to observing the endpoint is considered to be a non-response, will compare the proportion of patients who achieve a response on BI 655130 to Placebo. Given the small sample size proposed to be used in this trial, an exact statistical test, the Suissa-Shuster Z-pooled test, will be used to perform the primary analysis. Confirmation of efficacy is then given if the proportion of patients achieving a response on the primary endpoint is statistically significantly higher for BI 655130 than for placebo. Formal statistical hypothesis testing will be performed at an overall 1-sided alpha level of 0.025.

Stratification of randomization will be performed in this trial for Japan versus non-Japan. This stratification is implemented for operational purposes only and is not intended to be used as an adjustment factor in the primary analyses of efficacy (see Section 7.6).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The null and alternative hypotheses are described below. Statistical testing will be performed based on one-sided hypotheses and p-values.

Test of the Primary Endpoint
The null hypothesis for the primary endpoint, the proportion of patients achieving a GPPGA pustulation subscore of 0, at Week 1 is

H_{01}: Effect of BI 655130 on the proportion of patients achieving a GPPGA pustulation subscore of 0 at Week 1 (where any prior use of escape medication will be considered to represent a non-response) ≤ Placebo;

versus the alternative hypothesis

H_{02}: Effect of BI 655130 on the proportion of patients achieving a GPPGA pustulation subscore of 0 at Week 1 (where any prior use of escape medication will be considered to represent a non-response) > Placebo.

Only if the null hypothesis, H_{01} of the primary endpoint is rejected, will the efficacy of BI 655130 in the treatment of acute GPP flares be confirmed.

Test of the Key Secondary Endpoint
Further hypothesis will be tested on the key secondary endpoint in a hierarchical manner if the null hypothesis of the primary endpoint H_{01} has been previously rejected.

The null hypothesis for the key secondary endpoint, the proportion of patients achieving a GPPGA score of (0, 1), at Week 1 is

H_{11}: Effect of BI 655130 on the proportion of patients achieving a GPPGA of 0 or 1 at Week 1 (where any prior use of escape medication will be considered to represent a non-response) ≤ Placebo;

versus the alternative hypothesis

H_{12}: Effect of BI 655130 on the proportion of patients achieving a GPPGA of 0 or 1 at Week 1 (where any prior use of escape medication will be considered to represent a non-response) > Placebo.

No adjustment of the 1-sided alpha-level of 0.025 is necessary.

Test of the Secondary Endpoints
Further hypotheses will be tested on the following secondary endpoints in a hierarchical manner if both null hypotheses of the primary endpoint and key secondary endpoint, H_{01} and H_{11}, have been previously rejected. Note that the study is not further powered for the performance of these additional statistical comparisons.

The null hypothesis for the secondary endpoint, the proportion of patients achieving a GPPASI 75 at Week 4 is

H_{21}: Effect of BI 655130 on the proportion of patients achieving a GPPASI 75 at Week 4 (where any prior use of escape medication/OL BI 655130 at D8/rescue medication with BI 655130 will be considered to represent a non-response) ≤ Placebo;

versus the alternative hypothesis

H_{22}: Effect of BI 655130 on the proportion of patients achieving a GPPASI 75 at Week 4 (where any prior use of escape medication/OL BI 655130 at D8/rescue medication with BI 655130 will be considered to represent a non-response) > Placebo.

If the null hypothesis on GPPASI 75 at Week 4 has been previously rejected, then a test on the null hypothesis for the secondary endpoint, the pain VAS at Week 4, will be performed next in the testing hierarchy. The null hypothesis is:

H_{31}: Change from baseline in pain VAS at Week 4 for BI 655130 ≥ Placebo (where negative change indicates an improvement from baseline);

versus the alternative hypothesis

H_{32}: Change from baseline in pain VAS at Week 4 for BI 655130< Placebo (where negative change indicates an improvement from baseline).

If the null hypothesis on the pain VAS at Week 4 has been previously rejected, then a test on the null hypothesis for the secondary endpoint, the total score of PSS at Week 4, will be performed next in the testing hierarchy. The null hypothesis is:

H_{41}: Change from baseline in total score of the PSS at Week 4 for BI 655130 ≥ Placebo (where negative change indicates an improvement from baseline);

versus the alternative hypothesis

H_{42}: Change from baseline in total score of the PSS at Week 4 for BI 655130< Placebo (where negative change indicates an improvement from baseline).

If the null hypothesis on the PSS at Week 4 has been previously rejected, then a test on the null hypothesis for the secondary endpoint, the total score on the FACIT-Fatigue at Week 4, will be performed next in the testing hierarchy. The null hypothesis is:

H_{51}: Change from baseline in the total score on FACIT-Fatigue at Week 4 for BI 655130 ≤ Placebo;

versus the alternative hypothesis

H_{52}: Change from baseline in the total score on FACIT-Fatigue at Week 4 for BI 655130 > Placebo.

Each of the above secondary endpoints will be tested in a hierarchical manner subsequent to rejection of the null hypothesis on the previous secondary endpoint hence no adjustment to the 1-sided alpha-level of 0.025 is necessary.

7.3 PLANNED ANALYSES

The primary analysis of this trial is planned to be performed once all randomized patients have completed the 12 week period or early discontinued from the trial; a database lock for the primary analysis will then be performed. Final analysis is planned to be performed at the end of the trial once all randomized patients have completed the trial (including any follow-up period) if applicable.

The primary analysis and final analysis may be performed as a single analysis (at the time of trial completion), if, prior to the time of the primary analysis, the trial team agrees that the expected time interval between the planned analyses is insufficient to justify the performance of separate analyses.

Details of treatment unblinding for the primary analysis and final analysis are described in Section 4.1.5.1. Details of the analysis to be performed will be described in the TSAP.

There will be 3 main patient populations in this trial for analyses: the randomized set (RS), the safety set (SS), and the per-protocol set (PPS).

Randomized Set
This patient set includes all randomized patients. Treatment assignment will be as randomized. This is the main analysis set for presentation of efficacy.

Safety Set
This patient set includes all patients who were randomized and received at least one dose of study drug. It will be the main analysis set for presentation of safety. Patients will be analyzed according to the actual treatment.

Per-Protocol Set
This patient set includes all patients in the RS who adhered to the CTP without any Important Protocol Violations (IPVs) potentially affecting the study outcome which lead to exclusion from the PPS. This set will be used for sensitivity analysis on the primary, key secondary, and secondary efficacy endpoints which are included in the testing hierarchy.

Important violations of the protocol will include violations of the key inclusion and exclusion criteria, incorrect medications taken, concomitant use of restricted medications, escape medication given without evidence for disease worsening, and any other violations of the protocol deemed important by the study team. All decisions concerning important protocol violations will be made prior to un-blinding of the database for the final trial analysis.

Further analysis sets, e.g. for the BM assessments, will be defined in the Trial Statistical Analysis Plan (TSAP).

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.

7.3.1 Primary endpoint analyses

The analysis for the primary endpoint includes the evaluation of patients achieving a GPPGA pustulation subscore of 0 at Week 1.

Any use of escape medication, e.g. use of restricted medication for disease worsening in Table 4.2.2.1: 1, prior to observing the primary endpoint is considered to reflect a failure to achieve the endpoint outcome, i.e. non-response (see primary endpoint definition in Section 2.1.2).

Due to the small sample size of the trial, an exact statistical test will be used to assess the statistical significance of the treatment effect versus Placebo. Since the traditional Fisher's exact test may be unnecessarily conservative, an alternative test, the Suissa-Shuster Z-pooled test, will be implemented in this trial. The Suissa-Shuster Z-pooled test always preserves the type I error level and is usually more powerful than the Fisher's exact test.

The primary endpoint will be tested, for the RS, using the Suissa-Shuster Z-pooled test at a 1-sided, alpha level of 0.025.

Secondary analysis of the primary endpoint will include:

- A sensitivity analysis utilizing the PPS;
- Analysis of an additional estimand whereby any use of escape medication prior to week 1 will be considered to represent a non-response. For patients who use other restricted medication but not for disease worsening prior to Week 1, data will be censored for further analysis following the use and imputed using the methods described in Section 7.5.
- Sensitivity analyses which utilize alternative methods for the handling of missing data as described in Section 7.5.
- A subgroup assessment according to the Japan vs. non-Japan strata will be assessed descriptively
- Sensitivity analyses to adjust for the covariates, IL36R mutation status (Yes vs. No) and baseline GPPGA total score (3 vs. 4) respectively using logistic regression.

Further analysis of the primary endpoint will include:

- Analysis of the time to first achievement of a response on the primary endpoint via Kaplan-Meier methods.

7.3.2 Key Secondary endpoint analyses

The analysis for the key secondary endpoint, for patients achieving a GPPGA score 0 or 1 at Week 1, will be performed in the same manner as described for the analyses of the primary endpoint.

Any use of escape medication, e.g. use of restricted medication for disease worsening in Table 4.2.2.1: 1, prior to observing the key secondary endpoint is considered to reflect a failure to achieve the endpoint outcome, i.e. non-response (see key secondary endpoint definition Section 2.1.3).

7.3.3 Secondary endpoint analyses

The treatment effect on the following secondary endpoints, 1) the proportion of patients achieving a GPPASI 75 at Week 4, 2) the change from baseline in pain VAS at week 4, 3) the change from baseline in total PSS score at week 4, and 4) the change from baseline in the total FACIT-Fatigue score at Week 4, will be tested in a hierarchical manner as a part of the pre-specified testing strategy, subsequent to the test of the primary endpoint and key secondary endpoint, which is defined in Section 7.2.

The analysis for the proportion of patients achieving a GPPASI 75 at Week 4 (where any use of escape medication/OL BI 655130 at D8/rescue treatment with BI 655130 prior to observing the endpoint(s) is considered to represent a failure to achieve the endpoint outcome, i.e. non-response) will be performed using the same approach as that defined for the primary endpoint analysis of the study based on the RS.

For the analysis of the continuous secondary endpoints which are included in the statistical testing strategy, the following estimand and testing approach will be implemented:

Any use of escape medication or OL BI 655130 at Day 8 or rescue medication with BI 655130 prior to an assessment timepoint will be considered as a non-response at this timepoint and assigned worst treatment outcomes in the analysis.

The effect of BI 655130 vs placebo will be evaluated by a Wilcoxon rank test using the randomized set. Any assessments after the use of escape medication or OL BI 655130 at D8 or rescue medication with BI 655130 will be assigned worst case ranks for the testing. Missing data will be further imputed and handled via assignment of ranks. All details regarding the ranking rules for test are defined in Table 7.5:1.

Sensitivity analysis for secondary endpoints will be described in TSAP.

Other secondary endpoints

For all patients who were treated with BI 655130 either through initial randomization, or through OL BI 655130 at D8, additional summaries of the following endpoints at Week 4 will be done where any use of escape medication prior to Week 4 is considered to represent a non-response:

- The proportion of patients with GPPGA 0 or 1 at Week 4,
- The proportion of patients with a GPPGA pustulation subscore of 0 indicating no visible pustules at Week 4

Other secondary endpoints will be presented in an exploratory manner using the methods described above. Frequencies and percentages will be presented for categorical endpoints; descriptive statistics will be used for continuous data. If applicable, 95% confidence intervals will also be displayed.

Analysis of treatment emergent AE will be described in Section 7.3.5.

[redacted]

7.3.5 Safety analyses

Adverse events will be coded using the current version of Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced.

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. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'; the residual effect period (REP) is defined as 16 weeks after the last dose of trial medication. Note that for patients who continue into the extension trial, TEAE up to the first dose in the extension trial will be available for display in the current study. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. For all subjects who received OL BI 655130 at D8 or rescue medication with BI 655130, safety assessments including adverse events, laboratories, vital signs etc. which occurred subsequent to such intake will be excluded from presentations according to the planned treatments; these data will, however, be included in summaries where all data after any use of BI 655130 are displayed.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class (SOC) and preferred term after coding according to the current version of the MedDRA.

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 years), 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 for patients who will not be rolled over to OLE study, the first dose of OLE study for patients who will be rolled over to OLE study, drug stop date + 112 days, date of Day 8 if OL BI 655130 is given, date of rescue medication if BI 655130 is given). 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 AE / Total AE-specific time at risk [subject years].

Laboratory data will be analyzed 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 highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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.

[redacted]

7.4 INTERIM ANALYSES

No interim analysis is planned in this trial.

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

7.5 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 primary and key secondary and secondary binary endpoints
With regards to the handling of missing data on the primary, key secondary and secondary binary efficacy endpoints, a Non Response Imputation will be applied as the primary imputation approach that is, imputing as a failure to achieve a response, however:

- If there are available data at the visits both before and after the visit with a missing outcome, then impute as a success only if both the preceding and the following

observations also represent a success and there is no use of escape medication, OL BI 655130 at D8 or rescue medication with BI 655130 within this imputation period;

- Otherwise, impute as a failure to achieve a response (i.e. no response imputation [NRI]).

NRI is a conservative imputation scheme because it assumes that withdrawal (or missing data due to any other reason) is related to treatment failure. Other imputation schemes will therefore be considered for the primary, key secondary and secondary binary efficacy analyses including:

- Best response imputation: impute all missing values based on the best response observed at visits prior to withdrawal/occurrence of missing data. If there is no non-missing data available, then the missing value will be imputed as a failure.

- If fewer than 3 patients have missing data on an endpoint at Week 1 then a list of all possible treatment differences will be generated whereby each of the potential responses (response, non-response) will be imputed for each patient in an exhaustive manner.

For secondary continuous endpoints

For secondary continuous endpoints at Week 4 which are included into the statistical testing strategy, the Wilcoxon rank test will be used.

In test, worst case ranks will be assigned to those with prior escape medication or OL BI 655130 at D8 or rescue medication with BI 655130 or death, and for patients with missing data at Week 4 for other reasons, LOCF method will be used for imputation.

The best possible baseline values are the lowest value 0 for Pain VAS and PSS and the highest value 52 for FACIT-Fatigue scale. The worst possible post-baseline values are the highest values 100 and 16 for Pain VAS and PSS and the lowest value 0 for FACIT-Fatigue scale. Therefore, the maximum value for the worst possible change from baseline (i.e., the worst possible post-baseline value - best possible baseline value) is 100 for Pain VAS, 16 for PSS and -52 for FACIT-Fatigue scale.

The ranking rules are outlined in Table 7.5:1.

Table 7.5: 1 Ranking rules for secondary continuous endpoint

	Category	**Ranking**	**Case description**	**Imputed change from baseline for further ranking score***
1	Missing data at week 4 but still alive and no use of either escape medication, OL BI 655130 at D8 or rescue medication with BI 655130 prior to Week 4.	Ranked by imputed value	Patient has available data at visit prior to Week 4	LOCF prior to Week 4
			Patient has no post-baseline value	102 for Pain VAS 18 for PSS and -54 for FACIT-Fatigue scale
2	Use of escape medication, OL BI 655130 at D8 or rescue medication with BI 655130 prior to Week 4 but still alive.	Ranked by OL BI 655130 at D8 or time to rescue medication or time to escape medication from randomization;	Patient has OL BI 655130 at D8 and has no escape medication or rescue medication prior to Week 4;	104 for Pain VAS 20 for PSS and -56 for FACIT-Fatigue scale

Table 7.5: 1 Ranking rules for secondary continuous endpoint (cont'd.)

	Category	**Ranking**	**Case description**	**Imputed change from baseline for further ranking score***
			Patient has rescue medication with BI 655130 x days from randomization and has no escape medication prior to Week 4;	106-x/1000 for Pain VAS 22-x/1000 for PSS and -58+x/1000 for FACIT-Fatigue scale
			Patient has escape medication y days after randomization and prior to Week 4;	108-y/1000 for Pain VAS 24-y/1000 for PSS and -60+y/1000 for FACIT-Fatigue scale
3	Patient died before the measurement at Week 4	Ranked by time to death from randomization	Patient died z days after randomization	110-z/1000 for Pain VAS 26-z/1000 for PSS and -62+z/1000 for FACIT-Fatigue scale

* Ranked values in this table are only for purpose of rank tests but not for any descriptive displays

[redacted] With respect to safety evaluations, it is not planned to impute missing values.

7.6 RANDOMISATION

BI will arrange for the randomization and the packaging and labeling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. Access to the codes will be controlled and documented.

Stratification for Japan versus non-Japan will be done in order to assure that sufficient patients per treatment group are recruited specifically to support individual country submission in Japan; these strata will be treated as operational strata and will not be included into the analyses of efficacy endpoints.

Within each stratum (Japan vs. non-Japan), patients will be randomized in a 2:1 ratio (BI 655130 vs. Placebo). The randomization will be done in blocks to achieve balanced allocation. The block size of the randomization will be documented in the CTR.

The process of randomization is done via an IRT. Practical aspects of the treatment allocation process are detailed in Section 4.1.3.

7.7 DETERMINATION OF SAMPLE SIZE

Based on an application of the defined testing strategy (see Section 7.2), a simulation based power calculation has been performed for sample size assessment on both the primary and key secondary endpoints. For this purpose, the correlation of the two endpoints is set to be 0.65 which is derived from efficacy data of POC study 1368.11.

The effect of BI 655130 on the proportion of patients achieving a GPPGA pustulation subscore of 0 at Week 1 and separately on the proportion of patients achieving a GPPGA score of (0, 1) at Week 1 will be compared relative to placebo respectively. It is expected that, after one week of treatment with BI 655130, at least 60% of patients will have complete GPPGA pustulation subscore of 0 and at least 60% of patients will have a GPPGA score of 0 or 1. In comparison, only 10% of patients on placebo are expected to have response to each of the primary endpoint and key secondary endpoint at Week 1.

The power estimates below for detecting the clinically relevant differences, for the primary endpoint, the proportion of patients with a GPPGA pustulation subscore of 0 at Week 1 and the key secondary endpoint, a GPPGA score of 0 or 1 at Week 1, were derived using R version 3.3.2, for a sample size of 51 patients (2:1 ratio), and a 1-sided type I error of 0.025. The results are as given in Table 7.7: 1.

Table 7.7: 1 Power to achieve statistical significance for the primary endpoint and key secondary endpoint on BI 655130 versus Placebo under various scenarios for N=51 (2:1)

Sample size: BI 655130 vs. placebo	**Primary endpoint/Key secondary endpoint: Proportion of patients achieving GPPGA pustulation subscore of 0 at Week 1 [BI 655130 vs. placebo]/ Proportion of patients achieving GPPGA of (0 or 1) at Week 1 [BI 655130 vs. placebo]**	**Power (%) to achieve primary endpoint**	**Power (%) to achieve both primary endpoint and key secondary endpoint**
34:17	0.5 vs 0.05/ 0.5 vs 0.05	95.7%	92.9%
34:17	0.55 vs 0.05/ 0.55 vs 0.05	98.1%	96.8%
34:17	0.6 vs 0.05/ 0.6 vs 0.05	99.4%	98.8%
34:17	0.65 vs 0.05/ 0.65 vs 0.05	99.9%	99.7%
34:17	0.5 vs 0.1/ 0.5 vs 0.1	85.3%	78.1%
34:17	0.55 vs 0.1/ 0.55 vs 0.1	92.0%	87.7%
34:17	0.6 vs 0.1/ 0.6 vs 0.1	96.3%	93.9%
34:17	0.65 vs 0.1/ 0.65 vs 0.1	98.5%	97.3%

Note: if the rates of response for both primary endpoint and key secondary endpoint were 0.55 on BI 655130 and 0.1 on placebo, separately, then the overall power to achieve both endpoints would be approx. 87.7%.

Therefore, with an expected response rate of 0.6 on BI 655130 and 0.1 on placebo for each of the primary endpoint and key secondary endpoint and a type I error of <0.025 (1-sided), for a total sample size of 51 patients, this trial will be able to detect an effect of BI 655130 relative to placebo, for both primary endpoint and key secondary endpoint simultaneously, with an overall power of 93.9%.

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 Tripartite 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.

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

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, and for Japan, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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 finalization of the Clinical Trial Report.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective 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 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 his/her 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 good documentation practices and be attributable, legible, contemporaneous, original and accurate. 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 three documented attempts to retrieve

previous medical records. If this fails, a verbal history from the patient, documented in their medical records, would be acceptable.

During the site visit the sponsor's Clinical Research Associate (CRA) or auditor must be granted access to the original patient file (please see Section 8.3.2). The investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number or applicable national identification number or information as per local laws) have properly been removed or redacted from any copy of the patients' source documents before sending them to the sponsor.

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 sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

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

The rights of the trial patient to privacy and protection of the data / patient notes obtained during the trial have to be ensured in accordance with local laws and regulations. Procedures for data handling and data protection need to be described in the patient information and informed consent form.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.

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

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 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

- Sample and data usage has to be in accordance with the separate biobanking informed consent
- 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, including 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
- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF

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 Out"). **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).

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

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of CMLs, CRAs, and participating trial sites.

The trial medication will be provided by the [redacted]

The trial will be conducted in each selected center under the supervision of the Principal Investigator. A Coordinating Investigator is responsible to coordinate investigators at different centers participating in this multicenter trial. Tasks and responsibilities are defined in a contract. Relevant documentation on the participating (principal) investigators and other important participants, including their curricula vitae, will be filed in the ISF.

A project-independent external Data Monitoring Committee (DMC) will be established to assess the safety and efficacy of BI 655130 in this clinical trial at specified intervals through the final timepoint (End of Study Visit). Measures will be put in place to ensure blinding of the sponsor and all other trial participants. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

A central laboratory service and vendors for photo documentation (skin lesions) and IRT (interactive response technology) will be used in this trial. Details will be provided in the applicable manuals available in the ISF.

On-site monitoring will be performed by BI or a contract research organization appointed by BI. Data management and statistical evaluation will be done by BI according to BI SOPs.

The organization of the trial in the participating countries will be performed by the respective local BI-organization (Operative Unit [OPU] or by a Contract Research Organization [CRO]) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial. For each OPU participating in this study, a CML will be appointed responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU.

Tasks and functions assigned in order to organize, 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.

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

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

10.1.1 Physician's Global Assessment for Generalized Pustular Psoriasis (GPPGA)

Erythema

☐ 0 = Clear:	Normal or postinflammatory hyperpigmentation
☐ 1 = Almost Clear:	Faint, diffuse pink or slight red
☐ 2 = Mild:	Light red
☐ 3 = Moderate:	Bright red
☐ 4 = Severe:	Deep fiery red

Pustules

☐ 0 = Clear:	No visible pustules
☐ 1 = Almost Clear:	Low density occasional small discrete (non coalescent) pustules
☐ 2 = Mild:	Moderate density grouped discrete small pustules (non coalescent)
☐ 3 = Moderate:	High density pustules with some coalescence
☐ 4 = Severe:	Very high density pustules with pustular lakes

Scaling/crusting

☐ 0 = Clear:	No scaling and no crusting
☐ 1 = Almost Clear:	Superficial focal scaling or crusting restricted to periphery of lesions
☐ 2 = Mild:	Predominantly fine scaling or crusting
☐ 3 = Moderate:	Moderate scaling or crusting covering most or all of lesions
☐ 4 = Severe:	Severe scaling or crusting covering most or all lesions

PGA Score for GPP

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

Source: (R15-5200)

10.1.2 Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI)

Severity

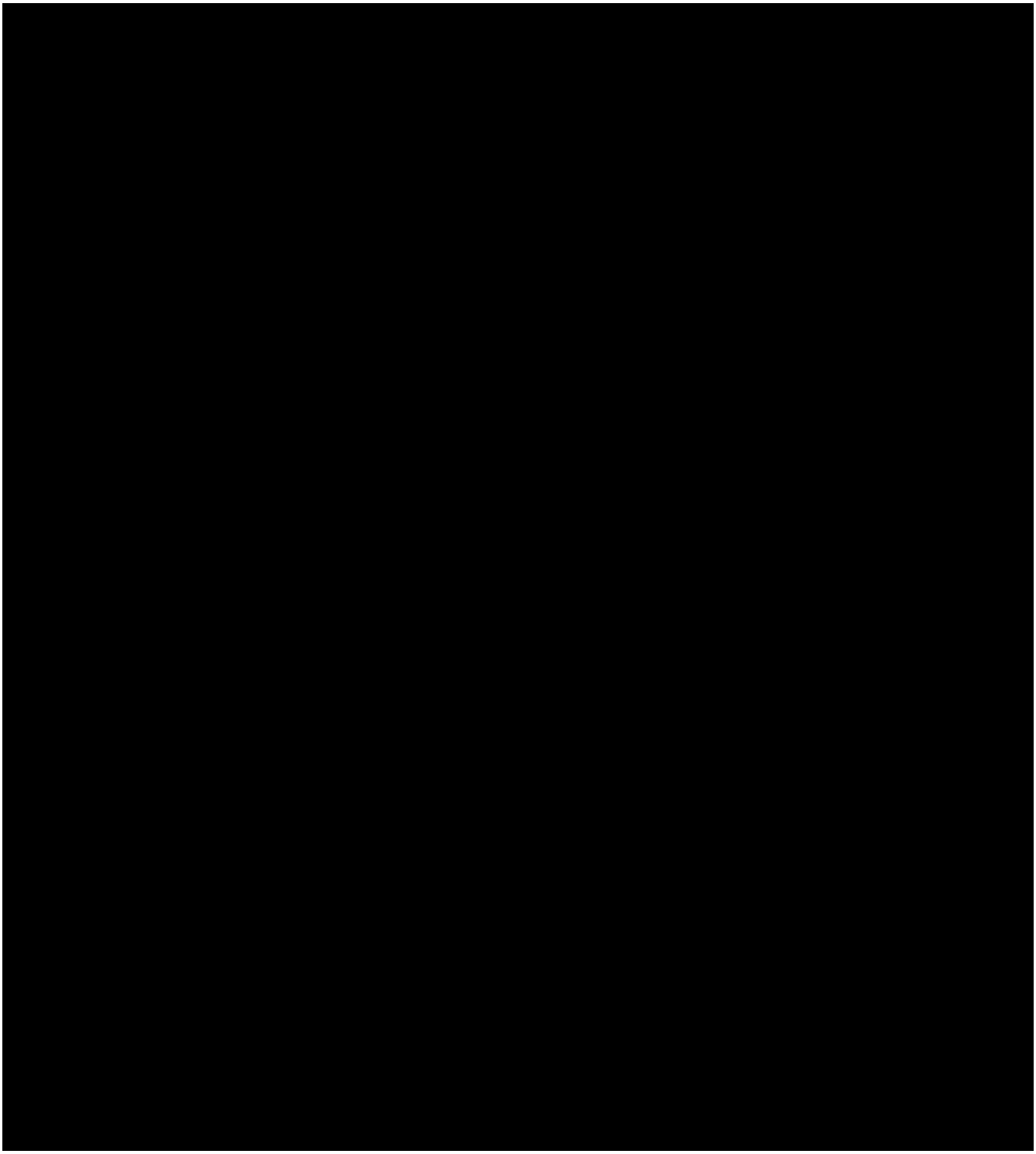
Erythema					
Head	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Trunk	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Upper Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Lower Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Pustules					
Head	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Trunk	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Upper Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Lower Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Scaling					
Head	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Trunk	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Upper Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe
Lower Limb	☐ 0=Clear	☐ 1=Almost clear	☐ 2=Mild	☐ 3=Moderate	☐ 4=Severe

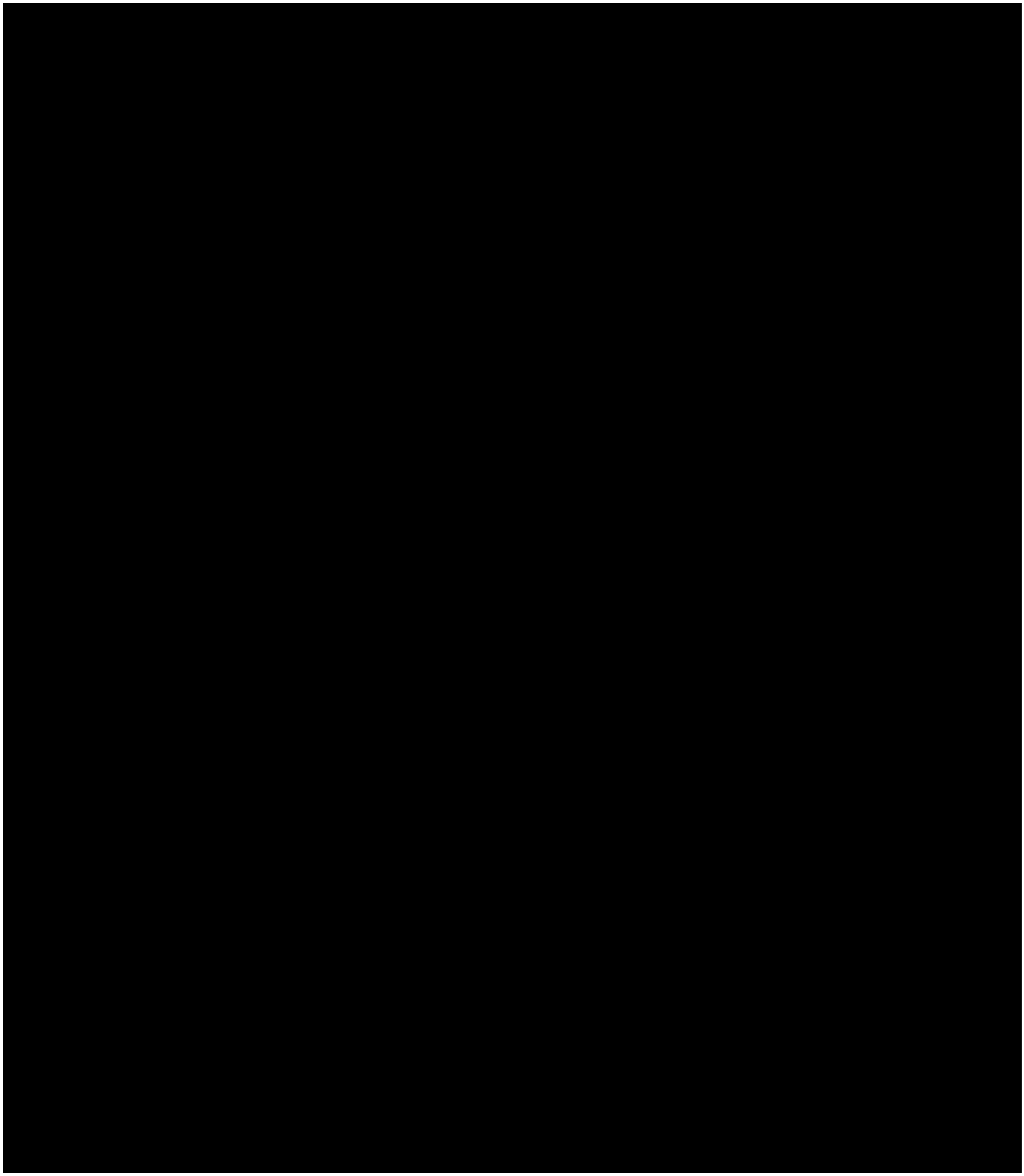
AREA OF INVOLVEMENT

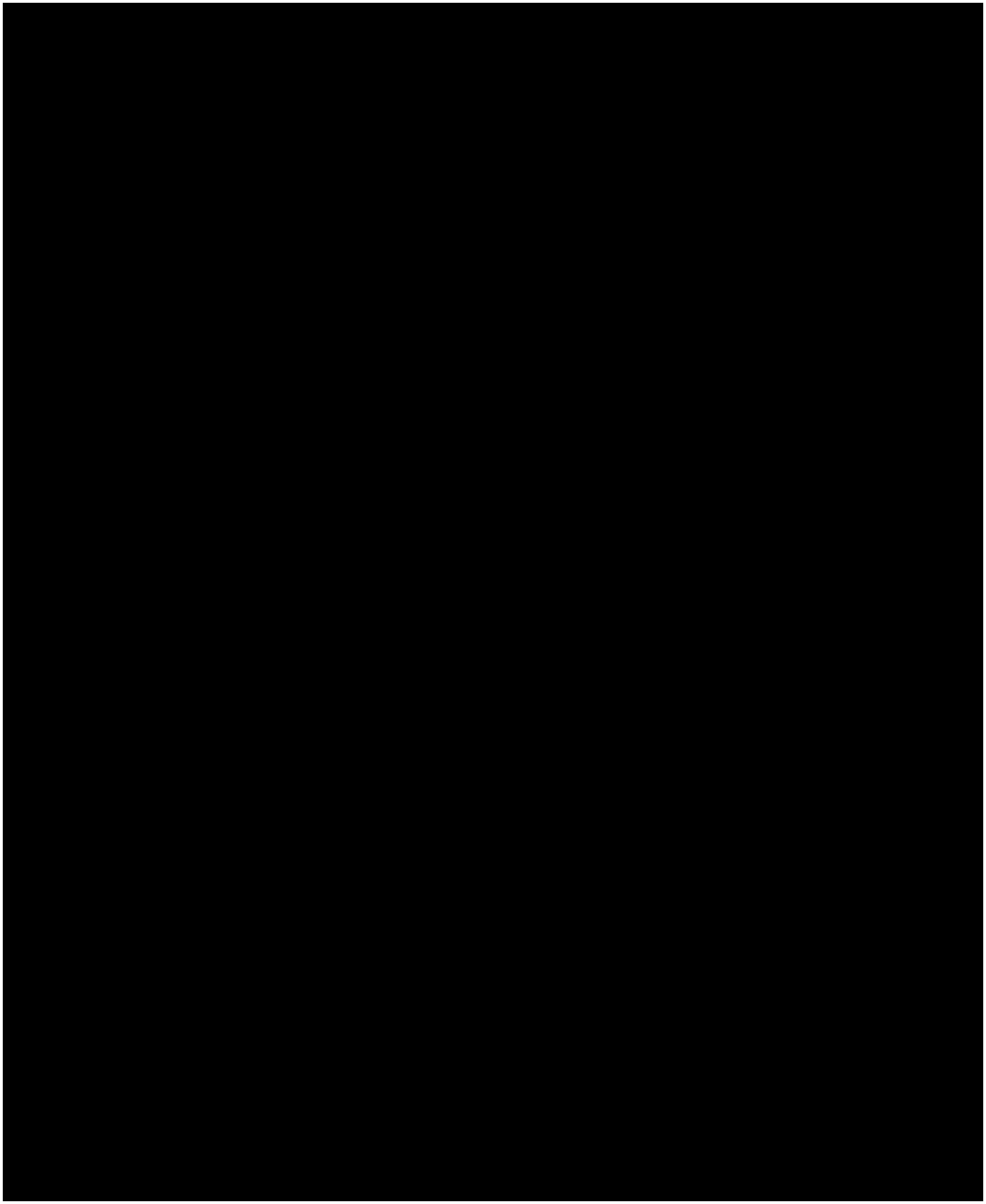
Provide the percentage of involved area in each body region (=area affected by pustules scaling [not the area for each component separately])

Head	☐ 0=0%	☐ 1=1 to < 10%	☐ 2=10 to < 30%	☐ 3=30 to < 50%	☐ 4=50 to < 70%
	☐ 5=70 to < 90%	☐ 6=90 to 100%			
Trunk	☐ 0=0%	☐ 1=1 to < 10%	☐ 2=10 to < 30%	☐ 3=30 to < 50%	☐ 4=50 to < 70%
	☐ 5=70 to < 90%	☐ 6=90 to 100%			
Upper Limb	☐ 0=0%	☐ 1=1 to < 10%	☐ 2=10 to < 30%	☐ 3=30 to < 50%	☐ 4=50 to < 70%
	☐ 5=70 to < 90%	☐ 6=90 to 100%			
Lower Limb	☐ 0=0%	☐ 1=1 to < 10%	☐ 2=10 to < 30%	☐ 3=30 to < 50%	☐ 4=50 to < 70%
	☐ 5=70 to < 90%	☐ 6=90 to 100%			

Source: (R96-3541, R16-3360)







10.1.4 FACIT Fatigue Scale (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued.....	0	1	2	3	4
HI12	I feel weak all over.....	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired.....	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired.....	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy.....	0	1	2	3	4
An7	I am able to do my usual activities.....	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat.....	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do.....	0	1	2	3	4
An16	I have to limit my social activity because I am tired.....	0	1	2	3	4

Source: (R16-0029)

English (Universal) 16 November 2007

10.1.5 Psoriasis Symptom Scale

Listed below are a set of problems that people with psoriasis have said are important. For each question, click on the circle that best describes the severity of your symptoms during the past 24 hours. Please answer every question.

1. How severe was your pain from your psoriasis during the past 24 hours?
   - None
   - Mild
   - Moderate
   - Severe
   - Very severe
2. How severe was the redness from your psoriasis during the past 24 hours?
   - None
   - Mild
   - Moderate
   - Severe
   - Very severe
3. How severe was your itching from your psoriasis during the past 24 hours?
   - None
   - Mild
   - Moderate
   - Severe
   - Very severe
4. How severe was your burning from your psoriasis during the past 24 hours?
   - None
   - Mild
   - Moderate
   - Severe
   - Very severe

Source: (R18-1990)

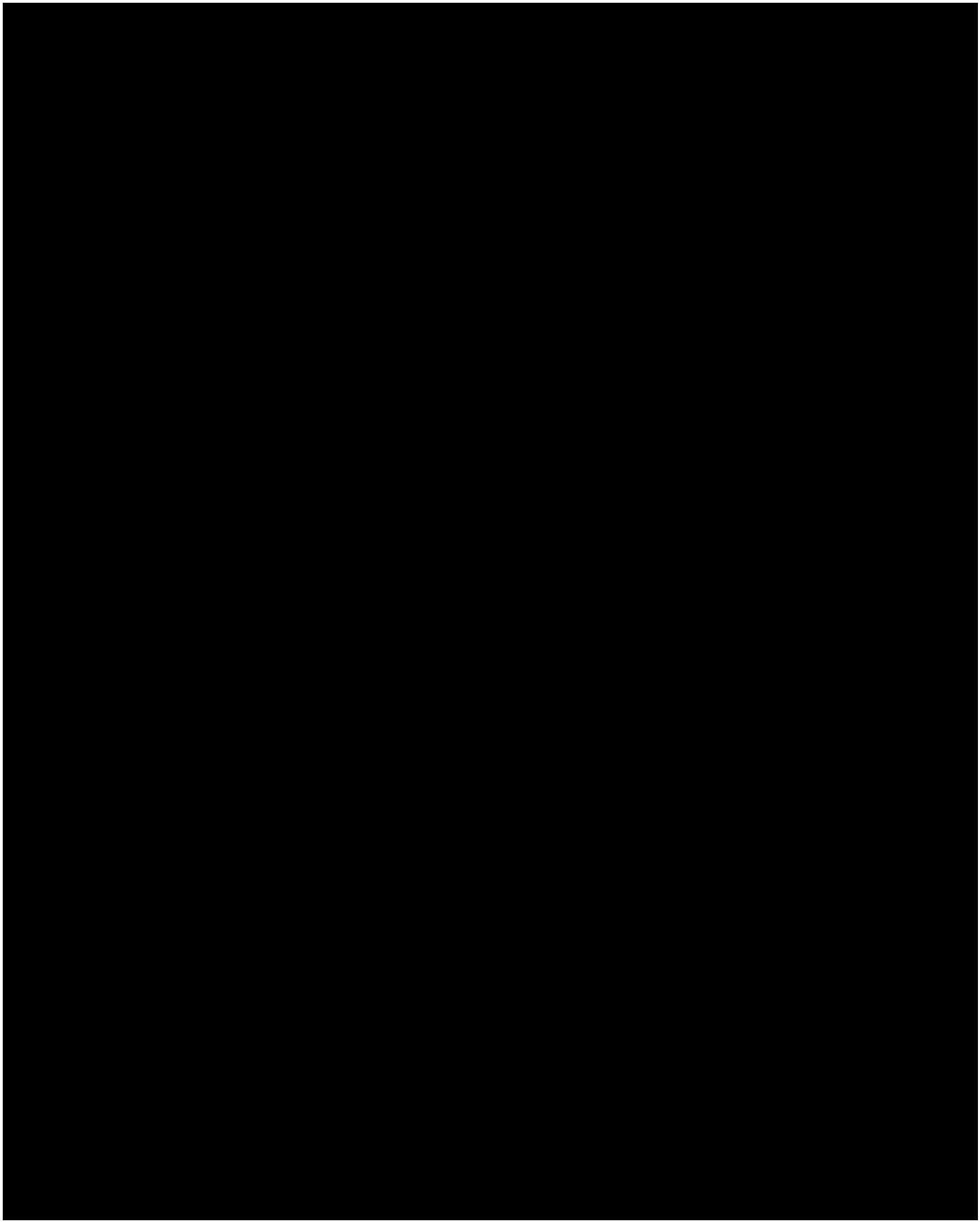
10.1.6 Diagnosis of Anaphylaxis

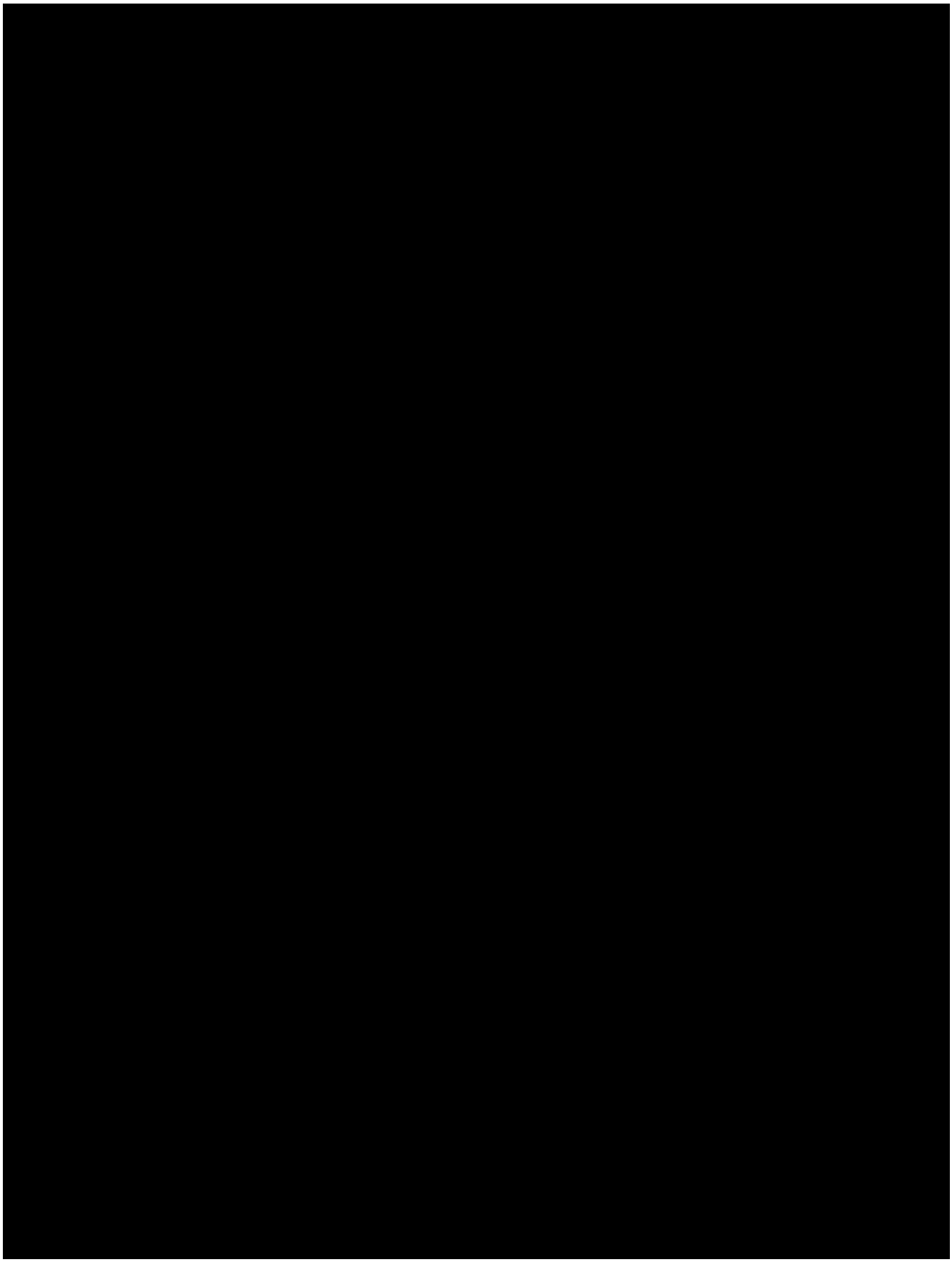
Clinical criteria for diagnosing anaphylaxis (R11-4890).

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 (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
AND AT LEAST ONE OF THE FOLLOWING
a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)
b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)
d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; BP, blood pressure.

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





10.1.9 Patient's assessment of Pain VAS

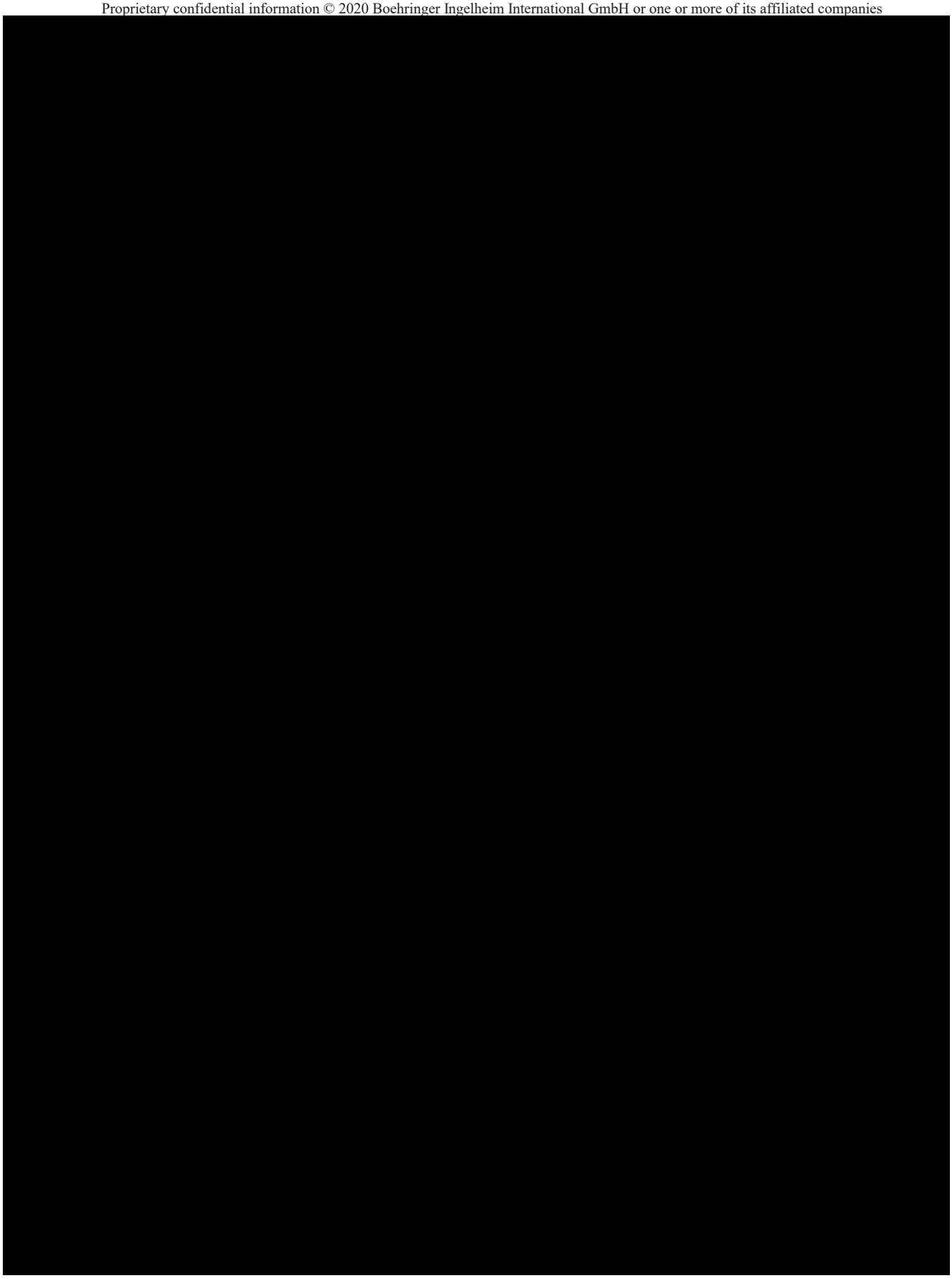
How much pain have you had because of your generalized pustular psoriasis (GPP) in the past week?

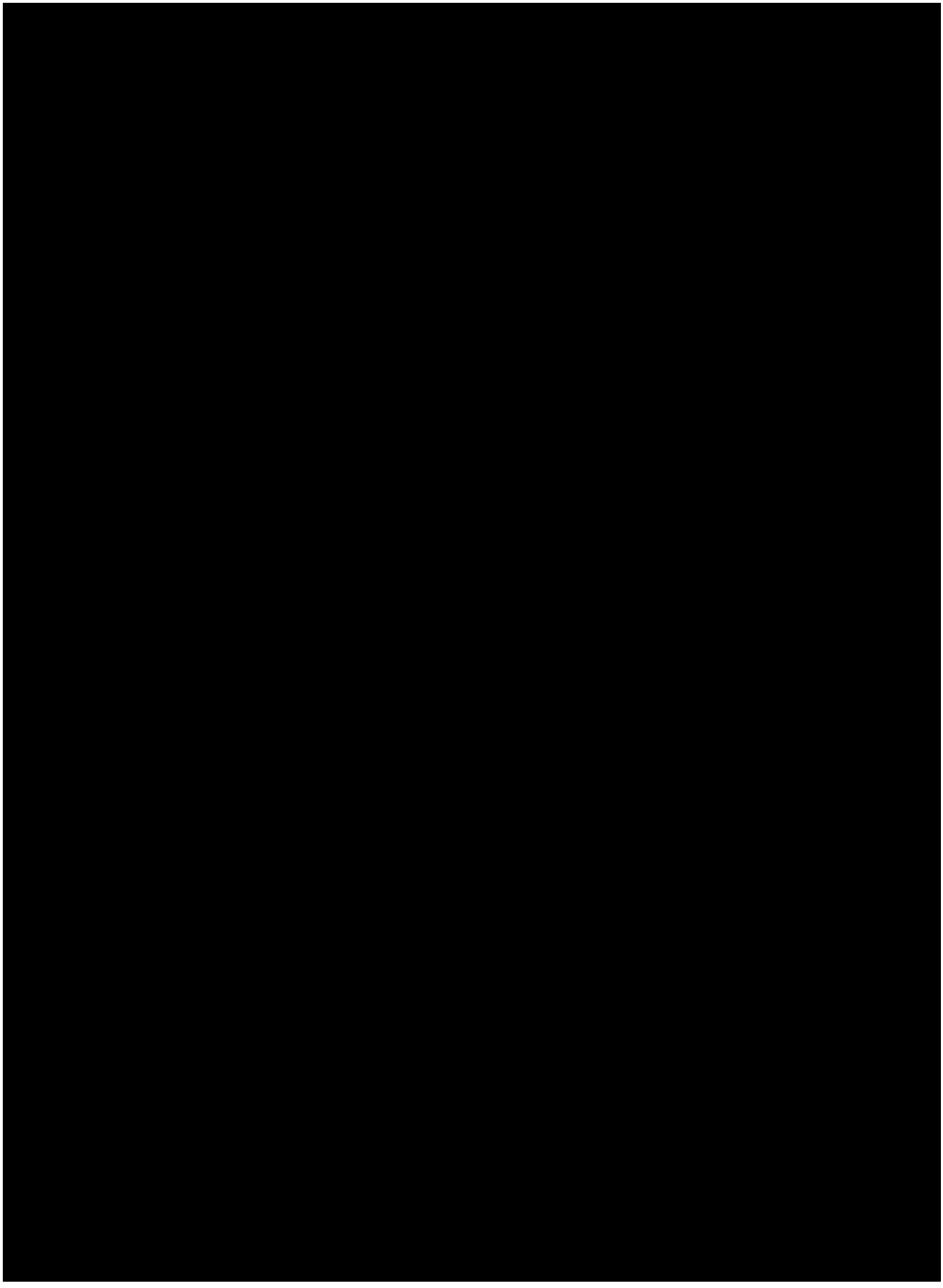
Place a vertical (|) mark on the line to indicate the severity of the pain.

No pain Severe pain

0 ——————————————————————— 100

Source: (R18-1989).





11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		19 Jul 2019
EudraCT number **EU number**		Spesolimab (BI 655130)
BI Trial number		1368-0013
BI Investigational Product(s)		Spesolimab (BI 655130)
Title of protocol		Effisayil™ 1: Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Title page: BI Investigational Medicinal Product Table 4.1.1:1 Study Compound
Description of change		Spesolimab (International Nonproprietary Name of BI 655130) was added.
Rationale for change		Updated information
Section to be changed		Title page and Synopsis
Description of change		Addition of Effisayil™ 1 to the trial title
Rationale for change		Administrative
Section to be changed		Clinical Trial Protocol Synopsis Table: Trial Site(s)
Description of change		Multi-center trial conducted in ~~8~~ **11** to ~~15~~ **20** countries.
Rationale for change		Updated Information. Since the sample size has increased, it is likely that we may have to recruit more countries to meet the recruitment goal.
Section to be changed		Clinical Trial Protocol Synopsis Table: Number of patients entered
Description of change		**51 patients**
Rationale for change		Updated information. Sample size has been increased from 27 patients to 51 patients. Per Health Authority recommendation, it is important that additional patients (i.e. beyond 27) be recruited into this trial in order to enhance the safety database in the acute GPP flare setting and, consequently, the assessment on benefit-risk. These additional patients also allow for a more robust assessment on the clinical efficacy, i.e. in a

		situation where the placebo rate is unexpectedly higher than the original estimate for both primary and key secondary endpoints.
Section to be changed		Clinical Trial Protocol Synopsis Table: Number of patients on each treatment
Description of change		**34 patients on BI 655130 and 17 patients on placebo**
Rationale for change		Updated information. Since the sample size increased from 27 patients to 51 patients the patients on each treatment arm also increased.
Section to be changed		Clinical Trial Protocol Synopsis Table: Endpoints
Description of change		Co-primary endpoints have been converted into primary endpoint and key secondary endpoint. **The primary endpoint of the study is:** • **A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) pustulation subscore of 0 indicating no visible pustules at Week 1.** **The Key secondary endpoint of the study is:** • **A GPPGA score of 0 or 1 at Week 1.**
Rationale for change		Updated Information. Per authority proposal, the co-primary endpoints have been adapted in this amended trial CTP to represent a primary endpoint reflecting the clearance of pustules at week 1, and a key secondary endpoint representing the overall improvement in GPP skin symptoms based on the achievement of a GPPGA score of 0 or 1 at week 1. The trial is still powered in order that success on both of these endpoints can be achieved.
Section to be changed		Clinical Trial Protocol Synopsis Table: Statistical Methods
Description of change		The trial is designed to demonstrate superiority of BI 655130 in ~~each of~~ the ~~two co-~~primary endpoint~~s~~, achievement of pustule clearance at week 1 and **the key secondary endpoint** GPPGA (0, 1) at Week 1, relative to placebo. The primary analysis, on each of the ~~co-~~primary **and key secondary** endpoints, will use a Suissa-Shuster test (~~un~~pooled method) to compare the proportion of patients who achieve a response on BI 655130 versus placebo at week 1. ~~Confirmation of efficacy is then given only if the~~

		~~proportion of patients with a response on BI 655130 is statistically significantly higher than the placebo for both of the co-primary endpoints.~~ A further hypothesis on the secondary endpoints, GPPASI 75 at Week 4, Pain VAS score at Week 4, PSS score at Week 4 and FACIT Fatigue Score at Week 4, will be tested in a hierarchical manner if the test of the null hypotheses for both ~~primary co-endpoints~~ **and key secondary endpoints** has previously been rejected.
Rationale for change		Updated information to reflect the change from co-primary endpoints to primary and secondary endpoints.
Section to be changed		Flow Chart
Description of change		Removed Alcohol History
Rationale for change		Updated Information
Section to be changed		Flow Chart
Description of change		Moved footnote 3 from Wk 2, 3, 4, 8 and 12 and moved it to the corresponding visit numbers V10, V11, V12 and V13.
Rationale for change		Clarification
Section to be changed		Flow Chart
Description of change		Removed pregnancy test from V3 through V8 (non dosing days)
Rationale for change		Updated Information. Removed requirement of pregnancy test from V3 through V8 as these are non-dosing days and therefore pregnancy tests is not required.
Section to be changed		Flow Chart
Description of change		Moved Pain VAS and FACIT-fatigue to group together with DLQI for (at best) weekly measurement.
Rationale for change		Correction
Section to be changed		Flow Chart and Footnote # 28

[redacted]

[redacted]

Section to be changed		Flow Chart
Description of change		Neutrophils will not be analyzed by flow cytometry from the whole blood sample.
Rationale for change		Limited utility and technical feasibility.
Section to be changed		Flow Chart
Description of change		• Footnote #11 text was clarified to **Fever** ~~will be assessed at the day the patient presents to the clinic/hospital with GPP flare of moderate to severe intensity prior to receiving medication for fever treatment. Thereafter, fever must be assessed and recorded 2 times on that day, separated by intervals of 2 to 4 hours. At all other visits, fever will be assessed once a day prior to receiving medication for fever treatment (if applicable)~~**assessments will be recorded on dosing days at three time points. If the patient will receive medication for fever treatment, the fever assessment will be performed prior to taking the anti-fever treatment. These fever assessments must be taken whether or not the patient has an elevated temperature and whether or not the patient takes anti-fever treatment. The fever assessments times are to be separated by intervals of 2 to 4 hours on dosing days. At all other visits (non-dosing days), fever will be assessed once a day and will be completed prior to receiving medication for fever treatment, if anti-fever treatment is given.** • Footnote # 12 text was clarified: Only applicable for women of childbearing potential. S – serum pregnancy test (performed at screening). U – urine pregnancy tests will be performed **on-site and** ~~at all other visits~~ **only at study drug administration visits**. 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 pregnancy test, a serum

		pregnancy (S) test will be done.
Rationale for change		Clarification
Section to be changed		Flow Chart
Description of change		Footnote 23 has been clarified to Patients who achieved a clinical ~~response~~ **improvement** to study treatment (not including escape treatment) and show no flare symptoms of moderate/severe intensity at V14 or V15 will be offered to enter into an open label extension (OLE) trial (1368-0025), if they have completed this study (EoS/V14 or V15) and meet the inclusion criteria for the OLE trial.
Rationale for change		Clarified that as long as the patients show clinical improvement or benefit from BI 655130, the patient may qualify to enter OLE trial. The patient does not have to have clinical response of GPPGA of 0 or 1 to qualify to enter in OLE trial.
Section to be changed		Flow Chart
Description of change		Added footnote 29. If the date of EOS visit for this trial is not the same as the date of first dose of trial medication on the OLE trial (1368-0025), the investigator must continue to capture the AEs in this trial until the patient receives 1st dose in the OLE trial. Please refer to section 5.2.6.2 for further details.
Rationale for change		Updated information to emphasize that if the date of EOS visit for this trial is not the same as the date of first dose of trial medication on the OLE trial (1368-0025), the investigator must continue to capture the AEs in this trial until the patient receives 1st dose in the OLE trial.
Section to be changed		Section 1.1 Medical Background
Description of change		<u>Treatment options</u> Current treatment options for controlling acute GPP and maintenance of response are limited and do not provide sustained efficacy. No treatments are currently approved for GPP in the US ~~and~~**or centrally approved for GPP in the** EU, though retinoids, cyclosporine or methotrexate are being recommended. Secukinumab (Cosentyx®), infliximab (Remicade®), **ixekizumab (Taltz®), brodalumab (Lumicef®), adalimumab (Humira®),**

		guselkumab (Tremfya®) and Risankizumab are only registered in Japan for the treatment of GPP and plaque psoriasis.
Rationale for change		Clarified the GPP treatment approval status in the EU.
Section to be changed		Section 1.2.1 Mode of action
Description of change		BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signaling. Binding of 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 diseases including GPP, palmoplantar pustulosis (PPP), **Atopic Dermatitis (AD)** and inflammatory bowel disease (IBD).
Rationale for change		Updated the information from IB version 6
Section to be changed		Section 1.2.3 Clinical Experience
Description of change		Added clinical experience details of the placebo controlled Phase II study (1368-0015) palmoplantar pustulosis (PPP) patients.
Rationale for change		Updated the information from IB version 6
Section to be changed		Section 1.3 Rationale for Performing the Trial
Description of change		No treatments are currently approved for GPP in the US ~~and~~ **or centrally approved for GPP in the** EU, though a combination of retinoids, cyclosporine or methotrexate has been recommended as primary options for controlling worsening of chronic GPP.
Rationale for change		Clarified the GPP treatment approval status in the EU
Section to be changed		Section 1.4 Benefit-Risk Assessment
Description of change		Included the following text based on IB V 6.0. **As of September 2018, BI 655130 has been given to 212 subjects in ongoing and clinically completed trials. BI 655130 was well tolerated. Most reported adverse events were of mild or moderate intensity, but there have also been a small number of patients experiencing severe or serious adverse events in clinical trials. It is**

		unknown whether these adverse events were caused by BI 655130. Overall adverse events observed in subjects who received BI 655130 were comparable to adverse events observed in those who received placebo and no dose-limiting adverse effects were observed (for details refer to IB; (c03320877)). ~~A total of 148 healthy volunteers have been exposed in phase I studies to single or multiple doses of BI 655130 with 118 subjects receiving up to dose levels of 20 mg/kg i.v., given once weekly (qw) for 4 weeks and 30 subjects receiving single s.c. injections of 150 mg or 300 mg. BI 655130 was safe in 4 healthy volunteer trials at all dose groups up to the highest tested dose of 20 mg/kg body weight given once a week for up to 4 weeks (for details refer to IB; (c03320877)). Moreover, a total of 4 clinical studies are ongoing as of June 2018: 1 trial with multiple doses (1368.15) exploring efficacy and safety in patients with Palmoplantar Pustulosis (PPP; target n=59), and 3 (1368.4, 1368.5, 1368.10) clinical trials exploring efficacy and safety of BI 655130 in patients with Ulcerative Colitis (UC; participant target n=10, 550, and 30, respectively).~~
Rationale for change		Updated the information from IB version 6
Section to be changed		Section 1.4 Benefit-Risk Assessment
Description of change		During and following the i.v. infusion, the patients will be monitored for **systemic hypersensitivity including (See Section 4.2.1.1 for further details)** infusion reactions at the site according to Instructions for Preparation and Handling of BI 655130.
Rationale for change		Updated Information
Section to be changed		Section 2.1.2 Primary Endpoint
Description of change		The ~~co-~~primary endpoint of the study is: • ~~A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 1.~~ • A GPPGA pustulation sub-score of 0 indicating no visible pustules at Week 1. For the estimand concept on the above-defined ~~co-~~primary binary endpoint definition(s), ~~death or~~ any use of escape medication prior to Week 1 will be

		considered to represent a non-response at the Week 1 timepoint.
Rationale for change		Updated Information. Per authority proposal, the co-primary endpoints have been adapted to represent a primary endpoint reflecting the clearance of pustules at week 1, and a key secondary endpoint representing the overall improvement in GPP skin symptoms based on the achievement of a GPPGA score of 0 or 1 at week 1. The trial is still powered in order that success on both of these endpoints can be achieved. Also, death was deleted because given short term nature of primary and secondary endpoints at week 1 and 4 respectively, and the exclusion of patients with life-threatening flare of GPP, death is not expected to be a relevant outcome in this trial.
Section to be changed		Section 2.1.3 Key Secondary Endpoint
Description of change		**The key secondary endpoint of the study is:** • **A Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 at Week 1.** **For the estimand concept on the above-defined key secondary binary endpoint definition(s), any use of escape medication prior to Week 1 will be considered to represent a non-response at the Week 1 timepoint.**
Rationale for change		Updated Information. Per authority proposal, the co-primary endpoints have been adapted to represent a primary endpoint reflecting the clearance of pustules at week 1, and a key secondary endpoint representing the overall improvement in GPP skin symptoms based on the achievement of a GPPGA score of 0 or 1 at week 1. The trial is still powered in order that success on both of these endpoints can be achieved.
Section to be changed		Section 2.1.4 Secondary Endpoints
Description of change		Death has been removed from the estimand concept of the endpoints.
Rationale for change		Updated Information. Given short term nature of primary and secondary endpoints at week 1 and 4 respectively, and the exclusion of patients with life-threatening flare of GPP, death is not expected to be a relevant outcome in this trial

Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Approximately ~~8~~ **11** to ~~15~~ **20** countries will participate by using sites/centers experienced in the management of GPP.
Rationale for change		Updated Information. Since the sample size has increased, it is likely that we may have to recruit more countries to meet the recruitment goal.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Added the following updated text: **Fifty-one patients with generalized pustular psoriasis (GPP) presenting with an acute flare of moderate to severe intensity are required to be randomized to receive BI 655130/ placebo (2:1) into this trial.**
Rationale for change		Updated Information reflecting the increase in sample size and/or recruitment period. Also, per Health Authority recommendation, it is important that additional patients (i.e. beyond 27) be recruited into this trial in order to enhance the safety database in the acute GPP flare setting and, consequently, the assessment on benefit-risk. These additional patients also allow for a more robust assessment on the clinical efficacy, i.e. in a situation where the placebo rate is unexpectedly higher than the original estimate for both primary and key secondary endpoints.
Section to be changed		Section 3.1 Overall Trial Design and Plan
Description of change		Updated as following: Patients who achieved a clinical ~~response~~ **improvement** to BI 655130 and who show no flare symptoms of moderate/severe intensity at V14 or V15 visit will be offered to enter into an open label extension (OLE) trial (1368-0025), if they have completed this study (EoS/V14 or V15 visit, see below) and meet the ~~inclusion~~ **eligibility** criteria for the OLE trial.
Rationale for change		Clarified that as long as the patients show clinical improvement or benefit from BI 655130, the patient may qualify to enter OLE trial. The patient does not have to have clinical response of GPPGA of 0 or 1 to qualify to enter in OLE trial.
Section to be changed		Table 3.1:1 Study Definitions (For Disease Worsening)
Description of change		Disease worsening is defined as worsening of

		clinical status or GPP skin and/or systemic symptoms as defined by the investigator. **Escape treatment is the Standard of Care (physician's choice) in the investigator's opinion to treat the disease worsening of GPP.** **Note**: The SoC options are multiple dose extended duration treatments. Wk1/D2-D7: If the severity and progression of the disease worsens within the first week a**nd requires immediate treatment, then** the investigator can treat the patient with ~~a Standard of care treatment~~ the escape medication of his/her choice ~~(escape medication)~~. However, if the disease condition is stable, it is recommended to wait until the primary endpoint visit (Wk1/D8) before prescribing an escape medication ~~(SoC)~~ since there will be an option to administer OL BI 655130 instead at this time. After D8: • Patients who do not achieve a clinical response (GPPGA 0 or 1) **but have disease worsening subsequent to D8 can receive an escape treatment chosen by the investigator.** ~~(GPPGA 0 or 1) at D8 and who do not qualify for treatment with OL BI 655130 at D8 OR who have a subsequent flare after receiving one rescue dose of OL BI 655130 can receive an escape treatment chosen by the investigator.~~ • **Patients who have achieved a clinical response and later have disease worsening that is not severe enough to meet the criteria for recurrence for GPP flare can receive the escape medication. However, it is recommended to wait until the patient meets the criteria for recurrence of GPP flare since there will be an option to administer rescue medication with OL BI 655130 instead at this time.** **Note: Only one rescue dose with BI 655130 is permitted if a patient experiences a recurrence of a GPP flare. Subsequent flares are to be treated with**

		Standard of Care (SoC) per physician's discretion.
Rationale for change		Clarified definition of disease worsening and scenarios when escape treatment may be given in case of disease worsening.
Section to be changed		Figure 3.1:1 Study Design
Description of change		Study design figure was updated to include **51** patients for sample size.
Rationale for change		Updated Information
Section to be changed		Section 3.2 Discussion of trial design, including the choice of control group (s)
Description of change		No active control group is included in this trial as there is currently no drug approved for the induction treatment of acute flares of moderate to severe GPP. Secukinumab (Cosentyx®), infliximab (Remicade®), **ixekizumab (Taltz®), brodalumab (Lumicef®), adalimumab (Humira®), guselkumab (Tremfya®) and Risankizumab** are only registered in Japan for the treatment of GPP and plaque psoriasis.
Rationale for change		Updated information
Section to be changed		Section 3.3 Selection of Trial Population
Description of change		~~Eight~~ **Eleven** to ~~15~~ **20** countries have been invited to participate in order to minimize the risk of under recruiting and to meet the goal of ~~27~~ **51**patients entered. Recruitment will be very challenging due to the rareness of the disease and because GPP patients must have an acute flare of moderate to severe intensity in order to be randomized on the trial.
Rationale for change		Updated Information. Since the sample size has increased, it is likely that we may have to recruit more countries to meet the recruitment goal.
Section to be changed		Section 3.3.3 Exclusion Criteria
Description of change		Exclusion criteria # 14: Active or Latent TB: QuantiFERON® **(or if applicable, T-Spot®)** TB test will be performed at screening.
Rationale for change		Updated Information to allow TSPOT test to be performed in applicable country (i.e. Japan) instead of QuantiFERON.
Section to be changed		Section 3.3.3 Exclusion Criteria

Description of change		Exclusion criteria # 16 has been deleted ~~Patients who have previously undergone allergy immunotherapy for prevention of anaphylactic reaction.~~
Rationale for change		This was removed from the exclusion criteria as it was felt that allergy immunotherapy is poorly defined (could be a desensitization to just anything) and would exclude a good number of patients unnecessarily.
Section to be changed		Section 4.1.2 Selection of doses in the trial
Description of change		**The intended dose for treatment of a moderate to severe flare which can be life-threatening is the maximum practical dose to deliver at one time. Experience with biologics has consistently led to concern about under-dosing leading to inadequate response. In this trial those who have inadequate response at 1 week are allowed to receive a dose of BI 655130. Thus, there will be a test of a second dose at an appropriate interval to evaluate under-dosing as the explanation for treatment failure.** Given (i) the rarity of the disease and in particular due to the rareness of flaring events precluding typical dose finding strategies, (ii) the serious and potentially life threatening nature of moderate/severe GPP and (iii) the favorable efficacy, safety and tolerability profile of BI 655130, exploration of ~~other~~ **lower** doses in GPP patients presenting with a flare (trial 1368-0013) is considered to be not feasible ~~and is not planned~~ **or worthwhile**.
Rationale for change		Provided additional details on the dose selected for this trial.
Section to be changed		Section 4.1.4 Drug assignment and administration of doses for each patient
Description of change		In all patients, the infusion solution is intended to be intravenously administered over a period of 90 minutes. In case of safety concerns, e.g. due to **systemic hypersensitivity including (See Section 4.2.1.1 for further details)** infusion reactions, it is at the discretion of the investigator or his/her designee to adapt the infusion scheme, including but not limited to slowing down the infusion rate, stopping the infusion, and provided no further safety concern exists, restarting at a slower rate.

		The administration of the trial medication will be done under the supervision of the investigating physician or a designee. The so-called four-eye principle (two-person rule) ~~should be applied~~ **is recommended** for administration of trial medication and – if applicable – its preparation, if correct dosage cannot be ensured otherwise.
Rationale for change		Updated information and added clarification. Previous trials with BI 655130 predominantly used intravenous route of administration. Sponsor decided to update the AESI term to expand the (previous) "infusion reaction including anaphylactic reaction" to include systemic hypersensitivity reactions that are not due to an infusion since there will be more trials which employ intravenous AND subcutaneous routes of administration of BI 655130.
Section to be changed		Section 4.1.7 Storage Conditions
Description of change		~~The medication may only be dispensed to trial patients according to the Clinical Trial Protocol (CTP) by authorized personnel as documented in the trial staff list~~ **The trial medication must be administered in the manner specified in the CTP and instructions for IMP preparation handling and administration of BI 655130 or Placebo.**
Rationale for change		Clarification
Section to be changed		Section 4.1.8 Drug Accountability
Description of change		~~Only authorized personnel as documented in the form 'Trial Staff List' may administer medication to trial patients. The trial medication must be administered in the manner specified in the CTP.~~
Rationale for change		Clarification. Removed the statement.
Section to be changed		Section 4.2.1.1 Emergency procedures
Description of change		**Systemic hypersensitivity** including Infusion reactions ~~including~~ **and** anaphylactic reaction In case of **Systemic hypersensitivity including** infusion reactions, ~~including~~ **and** anaphylactic reaction, emerging during or after infusion of trial medication, the investigator should consider in accordance with severity of the reaction and local standard of care to - Immediately interrupt the infusion

Rationale for change		Previous trials with BI 655130 predominantly used intravenous route of administration. Sponsor decided to update the AESI term to expand the (previous) "infusion reaction including anaphylactic reaction" to include systemic hypersensitivity reactions that are not due to an infusion since there will be more trials which employ intravenous AND subcutaneous routes of administration of BI 655130.
Section to be changed		Section 4.2.1.1 Emergency procedures
Description of change		QuantiFERON® **(or if applicable, TSPOT®)** TB test will be performed at screening.
Rationale for change		Adjustment of the text following the changes in Section 3.3.3 exclusion criterion 14.
Section to be changed		Table 4.2.2.1:1 Restricted Medications
Description of change		• Added **Risankizumab** as a restricted medication. • Reduced the washout period of all biologics to 2 months. • Corrected a typo **Na**talizumab • Updated footnote 1 as following: In case of worsening of the flare (disease worsening), **please refer to Section 4.2.1 for the details on** the use of escape treatment ~~i.e. standard of care (physician's choice) is left at the discretion of the investigator (refer to Section 4.2.1).~~
Rationale for change		Updated Information
Section to be changed		Section 5.2.2 Vital Signs
Description of change		In addition to the temperature being measured along with the vital signs at time points shown in the Flow Chart, ~~fever (temperature) will also be assessed at the day the patient presents to the clinic/hospital with GPP flare of moderate to severe intensity prior to receiving medication for fever treatment. Thereafter, fever must be assessed and recorded 2 times on that day, separated by intervals of 2 to 4 hours.~~ **additional fever assessments will be recorded on dosing days at three time points. If the patient will receive medication for fever treatment, the fever assessment will be performed prior to taking the anti-fever treatment. These fever assessments must be taken whether or not the patient has an elevated temperature and whether or not the**

		patient takes anti-fever treatment. The fever assessments times are to be separated by intervals of 2 to 4 hours on dosing days. At all other visits **(non-dosing days),** fever will be assessed once a day **and will be completed** prior to receiving medication for fever treatment, **if anti-fever treatment is given.**
Rationale for change		Clarification
Section to be changed		Section 5.2.3 Safety Laboratory Parameters
Description of change		However, local labs may be used for dosing decisions at visits involving i.v. administration of BI 655130 or placebo. The labs listed in Table 5.2.3: 2 are ~~recommended~~ to be collected and assessed by the investigator prior to study drug infusion to allow for immediate subject management; however, split or concurrent samples ~~will~~ **must** be drawn and sent to the central laboratory for analysis.
Rationale for change		Clarification
Section to be changed		Table 5.2.3:1 Safety Laboratory Tests (footnotes)
Description of change		Footnote 4: If the 1st QuantiFERON®**(or if applicable, T-Spot®)** TB test result is indeterminate, a retest should be performed. **<For Japan> T-Spot® TB test may be performed at local labs instead of QuantiFERON®TB test.** Footnote 5: In subjects with a negative QuantiFERON® **(or if applicable, T-Spot®)**TB test, the test should be repeated at EoS (V14 or V15 or V16 as applicable). **<For Japan> T-Spot® TB test may be performed at local labs instead of QuantiFERON®TB test**. Footnote 6: IgE will be taken in case of **systemic hypersensitivity including** infusion reaction together with ADA (anti-drug antibodies) sample.
Rationale for change		Updated Information.
Section to be changed		Table 5.2.3:2 Laboratory tests to be assessed prior to i.v. administration at V2, V9 or for any rescue treatment (Local Labs)
Description of change		For Substrates: C-Reactive Protein (CRP) , Serum albumin,

		Creatinine, Total bilirubin Direct bilirubin, eGFR (**preferably** estimated by CKD-EPI formula)
Rationale for change		Clarification
Section to be changed		Section 5.2.5 Local Tolerability
Description of change		**Grade the intensity of the local tolerability according to RCTC grading (cf. ISF).**
Rationale for change		Added Clarification as to what grading criteria should be used for grading local tolerability.
Section to be changed		Section 5.2.6.1 Definition of Adverse event
Description of change		Hepatic injury Hepatic Injury, is defined by the following alterations of hepatic laboratory parameters: • An elevation of AST and/or ALT and/or AP ≥3-fold ULN plus 2 times the baseline, combined with an elevation of total bilirubin ≥2-fold ULN plus 1.5 times the baseline, measured in the same blood **draw** sample, **or** • **aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN**
Rationale for change		Correction. To be consistent with the hepatic laboratory parameters to define hepatic injury in the preceding BI 655130 studies.
Section to be changed		Section 5.2.6.2 Adverse event collection and reporting
Description of change		AE collection period has been updated as following: **For patients rolling over into open label extension trial (1368-0025):** • From signing the informed consent ~~onwards until the individual patient's end of trial~~ **of the parent trial onwards until the first dose of trial medication in the extension trial:** ▪ all AEs (non-serious and serious) and all AESIs. **For patients not rolling over into subsequent OLE trial (1368-0025):** • **From signing the informed consent onwards until the individual patient's end of trial:** ▪ **all AEs (serious and non-serious) and all AESIs.**

Rationale for change		Updated Information
Section to be changed		Section 5.4.1 Biochemical and Cellular Biomarker (s)
Description of change		Serum will be collected to assess changes in protein levels of **select IL-36 pathway and** disease specific **bio**markers ~~such as but not limited to CRP, IL-1β, IL-1RA, IL1a, IL6, IL8, TNF, LCN2, and S-100 proteins (A7, A8, A12), IL17A, IL17F, IL-10, IL-12p70, IL-18, IL-22, IFN γ and VEGF~~ pre and post treatment with BI 655130.
Rationale for change		To include analysis of all potential biomarkers of interest.
Section to be changed		Section 5.4.1 Biochemical and Cellular Biomarker (s)
Description of change		**The biomarker assay analysis of samples will be performed in a staged approach. The initial analysis will focus on selected time points and depending on these results a decision will be made about further analysis of all samples. This is due to the exploratory nature of the mechanism being tested and the timing of effect on candidate biomarkers in the study.** The ~~se biomarkers are considered exploratory biomarkers and~~ respective assays will need to be qualified to meet the required performance criteria.
Rationale for change		Staged analysis ensures optimal allocation of resources.
Section to be changed		Section 5.4.1 Biochemical and Cellular Biomarker (s)
Description of change		Cellular biomarkers will be assessed using flow cytometry and will include specific markers of cells such as but not limited to ~~Neutrophils,~~ Macrophages, and T lymphocytes in PBMC's isolated from whole blood.
Rationale for change		Neutrophils will not be analyzed by flow cytometry from the whole blood sample due to limited utility and technical feasibility.
Section to be changed		Section 5.4.2 Pharmacogenomics Biomarker (s)
Description of change		In addition, skin biopsies and whole blood samples will be taken at time points indicated at the flow chart and used for RNA extraction and subsequent gene expression analysis to identify genes involved in the drug's mechanism of action or the pathology

		of the disease. **The biomarker analysis of samples will be performed in a staged approach. The initial analysis will focus on selected time points and depending on these results a decision will be made about further analysis of all samples. This is due to the exploratory nature of the mechanism being tested and the timing of effect on candidate biomarkers in the study.**
Rationale for change		Staged analysis ensures optimal allocation of resources.
Section to be changed		Section 6.2 Details of trial procedures at selected visits
Description of change		• The patients' questionnaires (PSS, [redacted], pain VAS, FACIT-Fatigue, and [redacted]) are to be completed by the patient on ~~him~~his/her~~self~~ **own in a pre-specified order in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team, and,** without any help from or interpretation by other people. • At each applicable visit (see Flow Chart), the order of completion for PROs is **recommended to be** as follows: PSS, [redacted] Pain VAS, FACIT Fatigue, [redacted] • Separate from the PROs above, the evaluation of efficacy assessments (GPPGA, GPPASI, [redacted] **for a patient** are to be conducted ~~preferably~~ by the same physician throughout the study. [redacted] • **Re-screening:** If a patient results in a screen failure (i.e. does not meet the eligibility criteria,

		or does not flare within the 6 month screening period) the patient must be registered as a screen failure in IRT system. However, re-screening of a previously screen failed patient will be permitted once. **Upon re-screening, the patient will be assigned a new patient number.** Details of IRT procedures can be found in the IRT manual located in the Investigator Site File (ISF).
Rationale for change		Clarification and Updated Information
Section to be changed		Section 7.1 Statistical Design - Model
Description of change		The primary analysis, on each of the ~~co-~~binary, primary endpoint, achievement of a GPPGA pustulation subscore of 0 at Week 1, and **key secondary endpoint,** achievement of a GPPGA of (0, 1) at Week 1, where ~~death or~~ any use of escape medication prior to observing the endpoint is considered to be a non-response, will compare the proportion of patients who achieve a response on BI 655130 to Placebo. Given the small sample size proposed to be used in this trial, an exact statistical test, the Suissa-Shuster Z-~~unpooled~~ **pooled** test, will be used to perform the primary analysis. Confirmation of efficacy is then given if the proportion of patients achieving a response on ~~each~~ the ~~co-~~primary endpoint~~s~~ is statistically significantly higher for BI 655130 than for placebo. **The final analysis of the trial, which will include all randomized patients, will be performed once all patients have completed the trial.**
Rationale for change		Update of endpoints and clarification
Section to be changed		Section 7.2 Null and Alternative Hypothesis
Description of change		Test of the ~~Co-~~Primary Endpoint~~s~~ The null hypothesis for the ~~co-~~primary endpoint, the proportion of patients achieving a GPPGA pustulation subscore of 0, at Week 1 is H_{01}: Effect of BI 655130 on the proportion of patients achieving a GPPGA pustulation subscore of 0 at Week 1 (where ~~death or~~ any prior use of escape medication will be considered to represent a non-response) ≤ Placebo; versus the alternative hypothesis

H_{02}: Effect of BI 655130 on the proportion of patients achieving a GPPGA pustulation subscore of 0 at Week 1 (where ~~death or~~ any prior use of escape medication will be considered to represent a non-response) > Placebo.

Only if the null hypothesis, H_{01} of the primary endpoint is rejected, will the efficacy of BI 655130 in the treatment of acute GPP flares be confirmed.

Test of the Key Secondary Endpoint
Further hypothesis will be tested on the key secondary endpoint in a hierarchical manner if the null hypothesis of the primary endpoint H_{01} has been previously rejected.

The null hypothesis for the ~~co-primary~~**key secondary** endpoint, the proportion of patients achieving a GPPGA score of (0, 1), at Week 1 is

H_{11}: Effect of BI 655130 on the proportion of patients achieving a GPPGA of 0 or 1 at Week 1 (where ~~death or~~ any prior use of escape medication will be considered to represent a non-response) ≤ Placebo;

versus the alternative hypothesis

H_{12}: Effect of BI 655130 on the proportion of patients achieving a GPPGA of 0 or 1 at Week 1 (where ~~death or~~ any prior use of escape medication will be considered to represent a non-response) > Placebo.

~~Only if both of the null hypotheses, H_{01} and H_{11}, of the two co-primary endpoints are rejected, will the efficacy of BI 655130 in the treatment of acute GPP flares be confirmed.~~No adjustment of the 1-sided alpha-level of 0.025 is necessary.

Test of the Secondary Endpoints
Further hypotheses will be tested on the following secondary endpoints in a hierarchical manner if **both null hypotheses of** the ~~two co-~~primary

		endpoint ~~null hypotheses~~**and key secondary endpoint**, H_{01} and H_{11}, have been previously rejected. Note that the study is not further powered for the performance of these additional statistical comparisons. The null hypothesis for the secondary endpoint, the proportion of patients achieving a GPPASI 75 at Week 4 is H_{21}: Effect of BI 655130 on the proportion of patients achieving a GPPASI 75 at Week 4 (where ~~death or~~ any prior use of escape medication/OL BI 655130 at D8/rescue medication with BI 655130 will be considered to represent a non-response) ≤ Placebo; versus the alternative hypothesis H_{22}: Effect of BI 655130 on the proportion of patients achieving a GPPASI 75 at Week 4 (where ~~death or~~ any prior use of escape medication/OL BI 655130 at D8/rescue medication with BI 655130 will be considered to represent a non-response) > Placebo.
Rationale for change		Update of endpoints and tests
Section to be changed		Section 7.3.1 Primary Endpoint Analyses
Description of change		**The analysis for the primary endpoint includes** the evaluation of patients achieving a GPPGA pustulation subscore of 0 at Week 1 ~~and of patients achieving a GPPGA score 0 or 1 at Week 1 are the co-primary endpoints of this trial~~. ~~Death or~~ Any use of escape medication, e.g. use of restricted medication **for disease worsening** in Table 4.2.2.1: 1, prior to observing the primary endpoint is considered to reflect a failure to achieve the endpoint outcome, i.e. non-response (see primary endpoint definition in Section 2.1.2). Due to the small sample size of the trial, an exact statistical test will be used to assess the statistical significance of the treatment effect versus Placebo. Since the traditional Fisher's exact test may be

		unnecessarily conservative, an alternative test, the Suissa-Shuster Z-~~unpooled~~ **pooled** test, will be implemented in this trial. The Suissa-Shuster Z-~~unpooled~~ **pooled** test always preserves the type I error level and is usually more powerful than the Fisher's exact test. ~~Each of the co-~~**The** primary **endpoint**~~s~~ will be ~~separately~~ tested, for the RS, using the Suissa-Shuster Z-~~unpooled~~ **pooled** test at a 1-sided, alpha level of 0.025. ~~Confirmation of efficacy is then given only if the null hypotheses on both of the co-primary endpoints are simultaneously rejected.~~ Secondary analysis of ~~both co-~~**the** primary **endpoint**~~s~~ will include: • A sensitivity analysis utilizing the PPS; • Analysis of an additional estimand whereby ~~death or~~ any use of escape medication prior to week 1 ~~following onset of disease worsening~~ will be considered to represent a non-response. For patients who use ~~escape~~ **other restricted** medication **but not for disease worsening** prior to Week 1, ~~without developing disease worsening,~~ data will be censored for further analysis following the ~~escape~~ use and imputed using the methods described in Section 7.5. • Sensitivity analyses which utilize alternative methods for the handling of missing data as described in Section 7.5. • **A subgroup assessment according to the Japan vs. non-Japan strata will be assessed descriptively.** Further analysis of the ~~co-~~primary **endpoint**~~s~~ will include: • Analysis of the time to first achievement of a response on ~~each of~~ the ~~co-~~primary **endpoint**~~s~~ via Kaplan-Meier methods.
Rationale for change		Update of endpoint and clarification
Section to be changed		Section 7.3.2 Key Secondary Endpoint Analysis
Description of change		• ~~There is no key secondary endpoint defined in the trial.~~ • **The analysis for the key secondary endpoint, for patients achieving a GPPGA**

		score 0 or 1 at Week 1, will be performed in the same manner as described for the analyses of the primary endpoint. • **Any use of escape medication, e.g. use of restricted medication for disease worsening in Table 4.2.2.1: 1, prior to observing the key secondary endpoint is considered to reflect a failure to achieve the endpoint outcome, i.e. non-response (see key secondary endpoint definition Section 2.1.3).**
Rationale for change		Update of endpoint
Section to be changed		Section 7.3.3 Secondary Endpoint Analysis
Description of change		• subsequent to the test of the **primary endpoint and key secondary endpoint,** which is defined in Section 7.2. • ~~death or~~ any use of escape medication… • Other secondary endpoints will be ~~descriptively displayed only.~~**presented in an exploratory manner using the methods described above**.
Rationale for change		Clarification
Section to be changed		Section 7.5 Handling of Missing Data
Description of change		• For primary and **key secondary and** secondary binary endpoints With regards to the handling of missing data on the primary**, key secondary** and secondary binary efficacy endpoints, a Non Response Imputation will be applied as the primary imputation approach that is, imputing as a failure to achieve a response, however:.. • Worst case ranks will be assigned to those with ~~death or~~ prior escape medication or OL BI 655130 at D8 or rescue medication with BI 655130, and for patients with missing data at Week 4 for **death or** other reasons.
Rationale for change		Information update
Section to be changed		Section 7.7 Determination of Sample Size
Description of change		• Update “co-primary endpoints” to “primary endpoint” and “key secondary endpoint”

		• The power estimates below for detecting the clinically relevant differences ~~statistically significant differences~~, for ~~both~~ the ~~co-~~primary endpoint, the proportion of patients with a GPPGA pustulation subscore of 0 at Week 1 **and the key secondary endpoint**, a GPPGA score of 0 or 1 at Week 1, were derived using R version 3.3.2, for a sample size of ~~27~~ **51 patients** (2:1 ratio), and a 1-sided type I error of 0.025. The results are as given in Table 7.7: 1~~Note that the power can be reduced if by chance we end up with 28 patients are randomized among which 19 patients are on BI 655130 treatment and 9 patients are on placebo. The resulting powers are also included in Table 7.7: 1.~~ • Updated Table 7.7: Power to achieve statistical significance for the ~~co-~~primary **endpoint~~s~~ and key secondary endpoint** on BI 655130 versus Placebo under various scenarios **for N=51 (2:1)** • Therefore, ~~for a total of 27 patients,~~ with an expected response rate of 0.6~~5~~ on BI 655130 and ~~0.05~~ **0.1** on placebo for **each of the ~~co-~~primary endpoint~~s~~ and key secondary endpoint and a type I error of <0.025 (1-sided), for a total sample size of 51 patients,** this trial will be able to detect an effect of BI 655130 relative to placebo, for **both primary endpoint and key secondary endpoint** simultaneously, ~~with a type I error of <0.025 (1-sided) and~~ **with an overall power of 93.9%.**
Rationale for change		Information update and clarification
Section to be changed		Appendix 10.1.2 Psoriasis Area and Severity Index for Generalized Pustular Psoriasis (GPPASI)
Description of change		GPPASI Scoring has been updated from "none, slight, moderate, severe and very severe" to "**clear, almost clear, mild, moderate, severe**".
Rationale for change		Correction
Section to be changed		[redacted]
Description of change		
Rationale for change		Correction

11.2 GLOBAL AMENDMENT 2

Date of amendment		26 Jun 2020
EudraCT number **EU number**		Spesolimab (BI 655130)
BI Trial number		1368-0013
BI Investigational Product(s)		Spesolimab (BI 655130)
Title of protocol		Effisayil™ 1: Multi-center, double-blind, randomized, placebo-controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Several sections
Description of change		Administrative
Rationale for change		Correction of spelling errors
Section to be changed		Title page: Clinical Trial Leader
Description of change		Change name of Clinical Trial Leader
Rationale for change		Updated Clinical Trial Leader
Section to be changed		Section 2.1.1 Main objectives
Description of change		Add wording to primary objective: **The primary objective of this trial is** to evaluate efficacy, safety, and tolerability of **one single i.v. dose of BI 655130** compared to placebo in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity.
Rationale for change		To clarify the primary objective
Section to be changed		[redacted]
Description of change		
Rationale for change		

Section to be changed	
Description of change	
Rationale for change	

Section to be changed	
Description of change	

		[redacted]
Rationale for change		[redacted]
Description of change		Add wording in Table 3.1: 1 for treatment of recurrence of GPP flare: **After Wk1/D8 and through week 12**, if there is ≥ 2 point increase in the GPPGA score and the pustular component of GPPGA ≥ 2 after achieving **a** clinical response (GPPGA 0 or 1) to **initial treatment** (either with BI 655130 at D1 or placebo at D1 or escape medication or OL BI 655130 at D8).
Rationale for change		Clarify treatment option in case of recurrent flare
Section to be changed		Table 4.1.5.1 Blinding
Description of change		Update the blinding plans for primary analysis and final analysis: ~~Patients, investigators, as well as sponsor personnel involved in the trial conduct or analysis, will remain blinded with regard to the randomized treatment assignments until after the database lock for the final analysis of the trial has been performed. Once the database lock has been performed, all parties will be officially unblinded to the randomization details~~ **Patients and investigators involved in the trial conduct will always remain blinded with regard to the randomized treatment assignments until after database lock for the final trial analysis.** **If the trial team agrees to perform the primary analysis and the final analysis separately (see Section 7.3), then, a database lock for the primary analysis will be done and treatment will be unblinded to trial and project team members.** **If the trial team agrees to perform the primary analysis and final analysis as one single analysis (at the time of trial completion), then patients, investigators, and sponsor personnel involved in the trial conduct, will unblinded to the randomized treatment assignments after the database lock has been performed.**
Rationale for change		To clarify the blinding plans of primary analysis and final analysis

Section to be changed		Table 4.1.5.2 Unblinding and breaking code
Description of change		Add wording: Treatment unblinding will be performed prior to each DMC meeting as a prerequisite for generation of the applicable DMC summaries required, as well as subsequent to the **primary analysis database lock (if applicable), and the** final trial database lock at which time the final trial analyses will be performed. Treatment unblind for the study will be officially released once database lock for the final trial analysis has been performed.
Rationale for change		To clarify the blinding plans of primary analysis and final analysis
Section to be changed		Section 5.2.3 Safety laboratory parameters
Description of change		Change wording: However, local labs ~~may~~ **are to** be used for dosing decisions at visits involving i.v. administration of BI 655130 or placebo.
Rationale for change		To clarify local labs results are required for dosing decision at visits involving i.v. administration of BI 655130 or placebo.
Section to be changed		Section 5.2.3 Safety laboratory parameters
Description of change		Add wording: **A positive HBV-DNA test at screening will exclude the patient.**
Rationale for change		For clarification.
Section to be changed		Section 5.2.6.2 Adverse event collection and reporting
Description of change		Removal of figure 5.2.6.2:1
Rationale for change		Since there are different AE collection scenarios as described in paragraph 5.2.6.2 (with or without roll-over to extension trial), the figure did not cover the different scenarios and therefore it was removed.
Section to be changed		Section 7.1 Statistical Design - model
Description of change		Add wording: The primary objective of this trial is to evaluate the efficacy, safety and tolerability of a single i.v. dose of BI 655130 in comparison to placebo **at Day 1**.
Rationale for change		To specify wording for primary objective.
Section to be changed		Section 7.1 Statistical Design - model

Description of change		Delete wording: ~~The final analysis of the trial, which will include all randomized patients, will be performed once all patients have completed the trial.~~
Rationale for change		Information for primary/final analysis are described in Section 7.3.
Section to be changed		Section 7.3 Planned analyses
Description of change		Add the analysis timelines for primary analysis and final analysis: **The primary analysis of this trial is planned to be performed once all randomized patients have completed the 12 week period or early discontinued from the trial: a database lock for the primary analysis will then be performed. Final analysis is planned to be performed at the end of the trial once all randomized patients have completed the trial (including any follow-up period) if applicable.** **The primary analysis and final analysis may be performed as a single analysis (at the time of trial completion), if, prior to the time of the primary analysis, the trial team agrees that the expected time interval between the planned analyses is insufficient to justify the performance of separate analyses.** **Details of treatment unblinding for the primary analysis and final analysis are described in Section 4.1.5.1. Details of the analysis to be performed will be described in the TSAP.** Delete wording: ~~The final trial analysis is planned to be performed at the end of the study once all randomized patients have completed the study (including any applicable follow-up period). The final analysis will include all trial data. Details of the analysis to be performed will be described in the TSAP.~~
Rationale for change		Clarify the time points of primary analysis and final analysis
Section to be changed		Section 7.3 Planned analyses
Description of change		Reference to CTR removed ~~A Clinical Trial Report will be prepared at the end~~

		~~of the trial.~~
Rationale for change		Administrative.
Section to be changed		Section 7.3.1 Primary endpoint analyses
Description of change		Add sensitivity analysis: **Sensitivity analyses to adjust for the covariates, IL36R mutation status (Yes vs No) and baseline GPPGA total score (3 vs 4) respectively using logistic regression.**
Rationale for change		It is of interest to check whether IL36R mutation status and baseline GPPGA total score are related to primary efficacy endpoints.
Section to be changed		Section 7.3.3 Secondary endpoint analyses
Description of change		Add primary estimand: For the analysis of the continuous secondary endpoints which are included in the statistical testing strategy, the following **estimand and testing** approach will be ~~done~~ **implemented**: **Any use of escape medication or OL BI 655130 at Day 8 or rescue medication with BI 655130 prior to an assessment time point will be considered as a non-response at this time point and assigned worst treatment outcomes in the analysis.**
Rationale for change		T clarify primary estimand for continuous endpoints
Section to be changed		
Description of change		

		[redacted]
Rationale for change		
Section to be changed		Section 7.3.5 Safety analyses
Description of change		Update that for patients who continue into the extension trial, TEAE up to the first dose in the extension trial will be available for display in the current study. Note that for patients who continue into the extension trial, ~~only~~ TEAE up to **the first dose in the extension trial** will be available for display in the current study. 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 **for patients who will not be rolled over to OLE study, the first dose of OLE study for patients who will be rolled over to OLE study**, drug stop date + 112 days, date of Day 8 if OL BI 655130 is given, date of rescue medication if BI 655130 is given).
Rationale for change		Correct the wording for AE collection
Section to be changed		Section 7.5 Handling of missing data
Description of change		Remove "Multiple Imputation" method for analysis: ~~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 for patients who will not be rolled over to OLE study, the first dose of OLE study for patients who will be rolled over to OLE study, drug stop date + 112 days, date of Day 8 if OL BI~~

		~~655130 is given, date of rescue medication if BI 655130 is given).~~
Rationale for change		It is not needed for missing data imputation.
Section to be changed		Section 7.5 Handling of missing data
Description of change		LOCF method will be used for imputation of continuous endpoints: **In test**, worst case ranks will be assigned to those with prior escape medication or OL BI 655130 at D8 or rescue medication with BI 655130 **or death**, and for patients with missing data at Week 4 for ~~death or~~ other reasons, **LOCF method will be used for imputation.** The ~~imputation and~~ ranking rules are outlined in Table 7.5: 1. Table 7.5: 1 ~~Imputation~~ Ranking rules for ~~missing~~ secondary continuous endpoint ** ~~Imputed~~ Ranked values **in this table** are only for purpose of rank tests but not for any descriptive displays
Rationale for change		It has been mentioned in Table 7.5: 1. Further to clarify this method in contexts.

APPROVAL / SIGNATURE PAGE

Document Number: c15875404 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol-version-03

Title: Effisayil (TM) 1: Multi-center, double-blind, randomized, placebo controlled, Phase II study to evaluate efficacy, safety and tolerability of a single intravenous dose of BI 655130 in patients with Generalized Pustular Psoriasis (GPP) presenting with an acute flare of moderate to severe intensity

Signatures (obtained electronically)

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