Clinical Trial Protocol

	Document Number: **c28020464-04**
EudraCT No. **EU Trial No.**	2018-003081-14
BI Trial No.	1368-0027
BI Investigational Medicinal Product(s)	BI 655130 (Spesolimab)
Title	Effisayil™ 2: Multi-center, randomized, parallel group, double blind, placebo controlled, Phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (Spesolimab) compared to placebo in preventing generalized pustular psoriasis (GPP) flares in patients with history of GPP
Lay Title	A study to test whether BI 655130 (Spesolimab) prevents flare-ups in patients with Generalized Pustular Psoriasis
Clinical Phase	Phase IIb
Clinical Trial Leader	[redacted] Phone: [redacted]
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Current Version and Date	Version 4.0, 28 July 2022
Original Protocol Date	Version 1.0, 23 October 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Original Protocol date	23 October 2019
Revision date	28 July 2022
BI trial number	1368-0027
Title of trial	Effisayil™ 2: Multi-center, randomized, parallel group, double blind, placebo controlled, Phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (Spesolimab) compared to placebo in preventing generalized pustular psoriasis (GPP) flares in patients with history of GPP
Coordinating Investigator	[redacted]
Trial site(s)	Multi-center trial conducted globally
Clinical phase	Phase IIb
Trial rationale	Current treatment options for controlling acute flare of GPP, complete resolution of symptoms and prevention of reoccurrence of flares are limited and often do not provide sustained efficacy. Moreover, current therapeutic options are not suitable for life-long treatment due to their side effect profile and existing contraindications. The motivation of this study is to provide dose-ranging data for 3 dose regimens of BI 655130 compared to placebo and to evaluate efficacy, safety, and tolerability of BI 655130 at preventing GPP flares compared to placebo in patients with a history of GPP and currently (at screening and at randomization) presenting with a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score of 0 or 1 (clear or almost clear).
Trial objective(s)	The primary objective of the trial is to demonstrate a non-flat dose response curve and evaluate the dose-response relationship for 3 subcutaneous dosing regimens of BI 655130 (with each regimen consisting of a single loading dose and a separate maintenance subcutaneous dosing regimen) versus placebo, on the primary endpoint, the time to the first GPP flare onset up to week 48. The secondary objective is to demonstrate superiority versus placebo for each of BI 655130 high dose (300 mg q4w) and BI 655130 medium dose (300 mg q12w) on the primary endpoint, the time to the first GPP flare onset up to week 48, as well as the key secondary endpoint, the occurrence of at least one GPP flare up to week 48. Another objective is to evaluate safety and tolerability of multiple s.c.

	doses of BI 655130 in patients with history of GPP. The use of i.v. dose of BI 655130 for treating patients with onset of acute GPP flare will be evaluated for safety and efficacy as an additional objective.
Trial endpoints	Primary endpoint: • Time to first GPP flare (defined by increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) up to week 48. Key Secondary Endpoint (For the secondary objective only): The key secondary endpoint of the study which is included in the statistical testing strategy (see Section 7 for details) in a hierarchical manner subsequent to performance of the test on the primary endpoint in the formal analysis is: • The occurrence of at least one GPP flare (defined by increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) up to week 48. Secondary Endpoints: The below-defined secondary endpoints, for the secondary objective only, are included into the statistical testing strategy in a hierarchical manner subsequent to performance of the test on the key secondary endpoint in the formal analysis. The study is not powered for the performance of these additional statistical comparisons. • Time to first worsening of Psoriasis Symptom Scale (PSS) up to week 48 defined as a 4-point increase in total score from baseline. • Time to first worsening of Dermatology Quality of Life Index (DLQI) up to week 48 defined as a 4-point increase in total score from baseline. The below-defined secondary endpoints, for the secondary objective only, are not included in the statistical testing strategy of the formal analysis of the trial. • Sustained remission, defined as a patient with a GPPGA score of 0 or 1 (clear or almost clear) at all visits up to week 48, without intake of rescue medication, or investigator-prescribed SoC. • The occurrence of treatment emergent adverse events (TEAEs)

Trial design	This is a multicenter, randomized, parallel group, double-blind, placebo-controlled Phase IIb dose finding study to evaluate efficacy and safety compared to placebo with multiple subcutaneous (s.c.) doses of BI 655130/placebo in adolescents from 12 years to less than 18 years of age and adult patients with history of GPP and currently presenting (at screening and at randomization) with a GPPGA score of 0 or 1 (clear or almost clear). Patients will continue to receive randomized maintenance treatment until their last dose at Week 44 if no flare occurs. In the event of a flare, the patient will receive rescue treatment with i.v. open label dose of BI 655130. Upon response of the flare, the patient will continue receiving open label s.c. dose of BI 655130. These patients will receive open-label treatment until 44 weeks after randomization, when the patient will receive the last dose. The maintenance treatment period ends at week 48. The primary statistical analysis of the trial will be performed once all randomized patients have either completed or early discontinued from the 48 week maintenance treatment period.
Total number of patients randomized	120 including at least 8 adolescent patients aged 12 years to less than 18 years of age evaluable for the primary endpoint (at least 2 adolescents per treatment group)
Number of patients on each treatment	30 patients on BI 655130 300 mg s.c. q4 weeks (Arm 1) 30 patients on BI 655130 300 mg s.c. q12weeks (Arm 2) 30 patients on BI 655130 150 mg s.c. q12 weeks (Arm 3) 30 patients on placebo (Arm 4)
Diagnosis	Patients with history of Generalized Pustular Psoriasis (GPP) and currently with GPPGA score of 0 or 1 (clear/almost clear)
Main in- and exclusion criteria	**Inclusion Criteria:** Each patient must meet all of the following inclusion criteria to be included into the trial: • Patients with a known and documented history of GPP per ERASPEN criteria (see Section 3.3.1) regardless of IL36RN mutation status, with at least 2 presentations of moderate to severe GPP flares with fresh pustulation (new appearance or worsening) in the past. • Patients with a GPPGA score of 0 or 1 at screening and randomization. • Patients who are not on concomitant GPP treatment at time of randomization (V2) must have had at least two presentations of moderate to severe GPP flare in the past year, at least one of which had evidence of either fever and/or elevated CRP and/or elevated WBC and/or asthenia and/or myalgia.

	• Patients who are not on concomitant GPP treatment at time of randomization (V2) but who were on concomitant GPP treatment until shortly before randomization (V2) (≤ 12 weeks before randomization), these patients must have a history of flaring while on concomitant treatment for GPP or in case of dose reduction or discontinuation of their concomitant medication. • Patients who are on concomitant treatment regimen with retinoids and/or methotrexate and/or cyclosporine must stop at the day of randomization (V2). These patients must have a history of flaring while on concomitant treatment for GPP or in case of dose reduction or discontinuation of these concomitant medications. • Male or female patients, aged 12 to 75 years at screening. For all patients, a minimum weight of 40 kg is required. • Signed and dated written informed consent and assent in accordance with ICH-GCP and local legislation prior to admission in the trial. • Women of childbearing potential (WOCBP)[1] 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 the CTP as well as in the patient, parent(s) (or patient's legal guardian) information. **Exclusion Criteria:** • Patients with SAPHO (Synovitis–acne–pustulosis–hyperostosis–osteitis) syndrome. • Patients with primary erythrodermic psoriasis vulgaris. • 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. • Relevant chronic or acute infections including active tuberculosis, human immunodeficiency virus (HIV) infection or viral hepatitis at the time of randomization.
Test product(s)	Solution for injection (s.c. dose): BI 655130 150 mg/PFS (150 mg/mL), 1 mL fill volume Solution for infusion (i.v. dose): BI 655130 450 mg/vial (60 mg/mL), 7.5 mL fill volume
dose	Arm 1: 600 mg total loading dose at Week 1/Day1 followed by maintenance treatment 300 mg s.c. q4 weeks

	Arm 2: 600 mg total loading dose at Week 1/Day1 followed by maintenance treatment 300 mg s.c. q12 weeks Arm 3: 300 mg total loading dose at Week 1/Day1 followed by maintenance treatment 150 mg s.c. q12 weeks Rescue Treatment: 900 mg i.v. dose in the event of the first GPP flare
mode of administration	s.c. for maintenance treatment and i.v. for rescue treatment
Comparator product(s)	Placebo comparator
dose	Arm 4: Loading dose Placebo at Week 1/Day 1 followed by maintenance treatment placebo
mode of administration	s.c.
Duration of treatment	Patients will continue to receive randomized treatment until their last dose at Week 44 if no flare occurs. The maintenance treatment period ends at week 48.
Statistical methods	For the primary objective, proof of concept and evaluation of the dose-response relationship for the activity of BI 655130 on the primary endpoint will be determined using a multiple comparison procedure with modelling techniques (MCPMod) with respect to achieving a non-flat dose response curve at the 1-sided alpha level of 0.05. As a basis for the MCPMod analysis a Cox regression model on the time to first GPP flare up to week 48 is used. If the primary objective is successfully achieved, the secondary objective is then to perform formal testing on the superiority of BI 300mg q4w and/or BI 300 mg q12w versus placebo. A formal statistical hypothesis test will be performed, at an overall 1-sided alpha level of 0.025, on the primary endpoint of time to first GPP flare up to week 48. A stratified log-rank test will be implemented for each dose of BI 300 mg q4w and BI 300 mg q12w versus placebo, with stratification by the factor, concomitant use of systemic GPP medication at randomization (yes or no) with multiplicity being controlled by the truncated Hocherg procedure. Formal testing of all other endpoints included in the testing hierarchy (i.e. the key secondary, and secondary endpoints), will then be performed, if the analysis on the primary endpoint is successful. The remaining alpha to be used for the key secondary endpoint analysis will be 0.025 (1-sided) if both high and medium doses of BI 655130 are statistically significantly superior to placebo on the primary endpoint. The key secondary endpoint will be analyzed using a Cochran-Mantel Haenszel test, in a similar manner to the analysis performed on the primary endpoint, for each dose of BI 655130 300 mg q4w and BI 655130 300 mg q12w versus placebo and a truncated Hochberg procedure will be used to control for multiplicity. If only one (high or medium) dose of BI 655130 was statistically significant on the test of the primary endpoint, then the same dose will be tested

	on the key secondary endpoint with a 1-sided alpha of 0.00625. If neither dose is declared to be statistically significantly superior to placebo for the primary endpoint, then no further formal testing in the hierarchical sequence will be conducted. Descriptive comparison of adult versus paediatric data will be performed.

FLOW CHARTS

FLOW CHART 1

	Screening	Randomized Treatment Period												Follow-up
		Loading	Maintenance											
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14/ EoS1[14]**	**V15/ EoS2[15]**
Week	-12 to 0	**1**	4	8	12	16	20	24	28	32	36	40	44	48	16 wks after last dose
Day	-84 to -1	1	29	57	85	113	141	169	197	225	253	281	309	337	
Visit Window (days)	N.A.	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Informed consent	X														
Infection testing	X[1a,1b]													X[1a]	X[1a,18]
[redacted]	[redacted]														
Demographics	X														
Medical history	X														
Smoking history	X														
Physical examination[3]	X[C]	X[C,T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[,T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[5]	X[S]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]
12 lead-ECG[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Review of in-/exclusion criteria	X	X													
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]		[redacted]	[redacted]
[redacted]															
Photographs of skin/skin lesions[9]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Skin biopsies (optional)[16] prior to dose		X												X	

FLOW CHART 1 (cont.)

	Screening	Randomized Treatment Period													Follow-up
		Loading	Maintenance												
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14/ EoS1[14]**	**V15/ EoS2[15]**
Week	-12 to 0	**1**	4	8	12	16	20	24	28	32	36	40	44	48	16 wks after last dose
Day	-84 to -1	1	29	57	85	113	141	169	197	225	253	281	309	337	
Visit Window (days)	N.A.	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
[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
[redacted]															
PSS; [redacted]		X	X	X	X	X	X	X	X	X	X	X	X	X	
DLQI [redacted]		X	X	X	X			X			X			X	
[redacted]		[redacted]			[redacted]			[redacted]			[redacted]			[redacted]	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	

FLOW CHART 1 (cont.)

	Screening	Randomized Treatment Period													Follow-up
		Loading	Maintenance												
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14/ EoS1[14]**	**V15/ EoS2[15]**
Week	-12 to 0	**1**	4	8	12	16	20	24	28	32	36	40	44	48	16 wks after last dose
Day	-84 to -1	1	29	57	85	113	141	169	197	225	253	281	309	337	
Visit Window (days)	N.A.	0	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IRT call	X	X	X	X	X	X	X	X	X	X	X	X	X	X[21]	
Dispense/Administer study drug		X	X	X	X	X	X	X	X	X	X	X	X		
Local tolerability[13]		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	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion														X	X
Vital Status														X[19]	X[20]
Open Label Extension Trial														X	

[redacted] C, complete physical examination; CGI-I, Clinical Global Impression – Improvement; d, Day; DLQI, Dermatology Quality of Life Index; ECG, Electrocardiogram; EoS, end of study; EQ-5D-5L, EuroQoL 5 Dimension 5 Level 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; [redacted]; OLE, Open Label Extension, PRO, Patient Reported Outcome; PSS, Psoriatic Symptom Scale; [redacted]; S, serum; T, Targeted physical examination; [redacted] U, urine; V, Visit; [redacted];

[1] a) Infection testing includes tuberculosis, hepatitis B, hepatitis C, and HIV assessments. See Table 5.2.3: 1.; b) For patients who sign the informed consent ≥ 4 weeks prior to V2, infection testing must be repeated 2 to 4 weeks prior to V2.
[redacted].
[3]Physical examination: C=complete, T=targeted. Refer to Section 5.2.1

[4]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 predose (prior to blood sampling), 10 mins after the end of drug administration and at Visit 2 and Visit 3 additional measurements will be performed approximately 60 minutes after the end of drug administration (i.e. 60 minutes after last injection). Refer to Section 5.2.2.
[5]Only applicable for women of childbearing potential. S – serum pregnancy test (performed at screening). U – urine pregnancy tests will be performed at all other visits indicated. 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 (via central lab) and study drug administration will be postponed until negative result of serum pregnancy test is available.
[6]ECG measurements should always precede blood sampling and drug administration.
[7] [redacted]
[8]Safety laboratory tests include clinical chemistry, haematology, coagulation, and urinalysis, and will be performed centrally. See Section 5.2.3 and Table 5.2.3: 1.
[9]Photographs of skin/skin lesions are to precede skin biopsies and study drug administration.
[10]Collection of serum biobanking sample is optional. Participating patients are required to give informed consent specifically for biobanking. Samples will be stored at a Biobanking facility for future research.
[11] a) 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 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 following: PSS; DLQI: PainVAS; EQ-5D-5L; WPAI-GPP; SF-36; PGI-S and PGI-C.
[11] b) DLQI, EQ-5D-5L, PGI-S and PGI-C are to be completed at V2, V3, V4, V5, V8, V11 and V14/EoS1 visit only.
[redacted]
[11]d) For PRO completion by the adolescent patients, please refer to Section 6.2 for further guidance and details.
[redacted].
[13]Local tolerability at the administration site of BI 655130/placebo (s.c.) will be assessed during the study drug administration and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction (s), e.g. swelling, induration, heat, redness, pain, and other findings should be reported as an adverse event.
[14]V14 will be recorded as the End of Study visit (i.e., EoS1) for patients who qualify and agree to enter the OLE trial (1368-0025). V14 will also be recorded as End of Study Visit (EoS 1) for patients who prematurely discontinue with the last dose of treatment up to and including Day 232 and who agree to complete all remaining study visits up to Wk 48 from randomization. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. See section 3.3.4.1.
[15]EoS2 visit is applicable for patients who do not qualify or who do not agree to enter OLE trial (1368-0025) at Week 48. EoS2 is also applicable for patients who prematurely discontinue with the last dose of treatment after Day 232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial.
[16]Skin biopsy is optional and is only to be done for patients who have consented for this procedure. V2 and V14 skin biopsies (optional): 1 lesional or non lesional (if no lesions are present) skin biopsy of 5 mm punch (split into half for IHC and RNASeq) should be collected prior to study drug administration.
[redacted]
[18] Only applicable if infection testing was not done at V14/EoS1 visit.
[19] Vital Status will be collected at V14 for patients who prematurely discontinue with the last dose of treatment up to and including Day 232 and who agree to be contacted further but do not agree for physical visits. See Section 5.2.6.1 for further details.
[20] Vital Status will be collected at V15 for patients who prematurely discontinue with the last dose of treatment after Day 232 and who agree to be contacted further but do not agree for physical visits. See Section 5.2.6.1 for further details.
[21]IRT registration is expected once at End of Study visit (as applicable) for a patient.

FLOW CHART 2 (GPP FLARE IV RESCUE)

	Flare confirmation	Rescue Treatment Period (i.v.)							Open Label Maintenance Treatment Period (s.c.)			Follow-up
Visit	**F0**	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**Vx[13]**	**V>x[13]**	**V14/EoS1[14]**	**EoS2[15]**
Week*	0	1	1	1	2	3	4	8	12	Every 4 weeks prior to Week 48 of randomization per original maintenance treatment schedule in Flowchart 1	Week 48 of randomization per original maintenance treatment schedule in Flowchart 1	16 wks after last dose
Day relative to R1		1**	4	8	15	22	29	57	85			
Visit Window (days)					±3	±3	±3	±7	±3			
Criteria to receive rescue treatment		X										
Infection Testing											X	X[18]
Physical examination[1]		X[C,T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[T]	X[C,T]
Vital signs[2]		X	X	X	X	X	X	X	X	X	X	X
Fever Assessment[3]	X	X										
Pregnancy test[4]		X[U,(S)]		X[U,(S)21]					X[U,(S)]	X[U,(S)]	X[U,(S)]	X[U,(S)]
12 lead-ECG[5]		X		X[21]					X	X	X	X
Safety laboratory tests[6]		X	X	X	X	X	X	X	X	X	X	X
[redacted]												
Photographs of skin/skin lesions[7]	X	X	X	X	X	X	X	X	X	X	X	X
Skin biopsies (optional)[8] – prior to dose		X					X				X	
[redacted]												

FLOW CHART 2 (GPP Flare IV Rescue) (cont.)

	Flare confirmation	Rescue Treatment Period (i.v.)							Open Label Maintenance Treatment Period (s.c.)			Follow-up
Visit	**F0**	**R1**	**R2**	**R3**	**R4**	**R5**	**R6**	**R7**	**V_X[13]**	**$V_{>X}$[13]**	**V14/EoS1[14]**	**EoS2[15]**
Week*	0	1	1	1	2	3	4	8	12	Every 4 weeks prior to Week 48 of randomization per original maintenance treatment schedule in Flowchart 1	Week 48 of randomization per original maintenance treatment schedule in Flowchart 1	16 wks after last dose
Day relative to R1		1**	4	8	15	22	29	57	85			
Visit Window (days)					±3	±3	±3	±7	±3			
[redacted]		[redacted]		[redacted]			[redacted]				[redacted]	
GPPGA	X	X	X	X	X	X	X	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PSS: [redacted]		X	X	X	X	X	X	X	X	X	X	
[redacted]												
IRT call		X		X[21]					X	X[22]	X[23]	
Dispense/administration study drug		X		X[21]					X	X[17]		
Local tolerability[12]		X		X[21]					X	X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X
Study Completion											X	X
Vital Status											X[19]	X[20]
Open Label Extension Trial											X	

*Week in the flow chart represents the end of each week (e.g. End of Week1=D8, End of Week2 =D15, End of Week3 = D22, End of Week4 =D29, etc.).
**The day of administration of rescue treatment = Day 1. All subsequent study days are counted from this Day 1 in Flow Chart 2 if there is no additional specification.

[1]Physical examination: C=complete, T=targeted. Refer to Section 5.2.1
[2]Vital signs: a) On non-study–drug administration days, vital sign assessments are to be done prior to blood sampling; b) On (i.v.) study drug administration days, vital signs will be assessed at predose (prior to blood sampling), at approximately 5 mins after the end of infusion, and 1 hour after the end of infusion; c) On (s.c.) study drug administration days, vital signs will be assessed at pre-dose (prior to blood sampling) and 10 mins after the end of drug administration. Refer to Section 5.2.2.
[3]Fever will be assessed at the day the patient presents to the clinic/hospital with GPP flare and prior to IMP administration. If the patient will receive medication for fever treatment, the fever assessment will be performed prior to taking the anti-fever treatment. This fever assessment must be taken whether or not the patient has an elevated temperature and whether or not the patient will require anti-fever treatment.
[4]Only applicable for women of childbearing potential. S – serum pregnancy test. U – urine pregnancy tests will be performed at all other visits indicated. 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 (via central lab with the exception of R1 and R3 (if patient qualifies to receive i.v. dosing) visits where serum pregnancy test can be performed locally)) and study drug administration will be postponed until negative result of serum pregnancy test is available.
[5]ECG measurements should always precede blood sampling and drug administration
[6]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. For all other visits, central labs are to be used. . See Section 5.2.3 and Table 5.2.3: 1.
[7]Photographs of skin/skin lesions are to precede skin biopsies and study drug administration.
[8]Skin biopsy is optional and is only to be done for patients who have consented for this procedure. Skin biopsies (optional) will be collected for each of the three visits (R1, R6 and EoS1 visit): 1 lesional or non-lesional (if no lesions are present) skin biopsy of 5 mm punch (split into half for IHC and RNASeq) should be collected prior to study drug administration. [redacted].
[10]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 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 following: PSS; [redacted] For PRO completion by the adolescent patients, please refer to Section 6.2 for further guidance and details.
[11] HCRU (healthcare resource utilization) data include the number of hospitalizations and length of stay in days, as well as the number of outpatient visits and emergency room visits (If applicable). Data should be collected for the time period since the last visit.
[12] Local tolerability at the administration site of BI 655130 will be assessed during the study drug administration (i.v. or s.c.) and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. swelling, induration, heat, redness, pain, and other findings should be reported as an adverse event.
[13] If the first dose of OL s.c. maintenance treatment is outside of any scheduled visit window by ±7 days per Flow Chart 1, it needs to be assigned to one of the scheduled visits by extending each visit time window to -13/+14 days of the original planned visit date. See Table 3.1:1 for the detailed rules of visit assignment. Then the following OL s.c. maintenance doses (if applicable) will be administered within original visit window by ±7 days per Flow Chart 1. Note: Once the OL s.c. visit assignment is calculated by referring to Flow Chart 1, all study procedures scheduled for this first dose of OL s.c. maintenance treatment visit and subsequent OL maintenance treatment visits should be completed as per Flow Chart 2.
[14]Visit at Week 48 of randomization will be planned for all patients who receive rescue treatment with BI 655130. It will be recorded as the End of Study visit (i.e., EoS1) for patients who qualify and agree to enter the OLE trial (1368-0025). V14 will also be recorded as End of Study Visit (EoS1) for patients who prematurely discontinue with the last dose of treatment up to and including Day 232 and who agree to complete all remaining study visits up to Wk 48 from randomization. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. See section 3.3.4.1.
[15]EoS2 is applicable for patients who do not qualify or who do not agree to enter OLE trial (1368-0025) at Week 48. EoS2 is also applicable for patients who prematurely discontinue with the last dose of treatment after Day 232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. . [redacted]

[17]Actual dose is administered either every 4 weeks or every 12 weeks dependent upon the current maintenance dosing scheme the patient is following.
[18] Only applicable if infection testing was not done at V14/EoS1 visit.
[19] Vital Status will be collected at V14 for patients with the last dose of treatment up to and including Day 232 and who agree to be contacted further but do not agree for physical visits. See Section 5.2.6.1 for further details.
[20] Vital Status will be collected at V15 for patients with the last dose of treatment after Day 232 and who agree to be contacted further but do not agree for physical visits. See Section 5.2.6.1 for further details.
[21] Only applicable for patients meeting protocol specified criteria for receiving D8 dosing. See Table 3.1:3 for criteria for receiving D8 dosing.
[22] IRT call is applicable for dosing visits only (i.e. q12 weeks or q4 weeks in case a patient has been switched to intensified maintenance treatment schedule).
[23] IRT registration is expected once at End of Study visit (as applicable) for a patient.

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ABBREVIATIONS

ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
AD	Atopic Dermatitis
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
CA	Competent Authority
CI	Confidence Interval
C_{max}	Maximum Concentration
C_{min}	Minimum Plasma Concentration
CGI-I	Clinical Global Impression – Improvement
CRA	Clinical Research Associate
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CRP	C-reactive protein
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
DILI	Drug Induced Liver Injury
DLQI	Dermatology Quality of Life Index
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
(e)COA	(electronic) Clinical Outcome Assessment
eDC	Electronic Data Capture
EoS	End of Study
ERASPEN	European Rare And Severe Psoriasis Expert Network
EudraCT	European Clinical Trials Database

FC	Flow Chart
FUP	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPP	Generalized Pustular Psoriasis
[redacted]	[redacted]
GPPGA	Generalized Pustular Psoriasis Physician Global Assessment
HA	Health Authority
i.v.	intravenous
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INN	International Non-Proprietary Name
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
[redacted]	
LPLT	Last Patient Last Treatment
LPLV	Last Patient Last Visit
MedDRA	Medical Dictionary for Drug Regulatory Activities
Nab	Neutralizing Antibodies
OPU	Operative Unit
PD	Pharmacodynamics
PK	Pharmacokinetics
PoC	Proof of Concept
PPP	Palmoplantar Psoriasis
PPS	Per-Protocol set
PRO(s)	Patient Reports Outcome(s)
PSS	Psoriasis Symptom Scale
q.d.	quaque die (once a day)

RA	Regulatory Authority
REP	Residual Effect Period
s.c.	subcutaneous
SAE	Serious Adverse Event
SC	Steering Committee
SMC	Safety Monitoring Committee
SoC	Standard of Care
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
t1/2	Half Life Time
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
Tmax	Timepoint of maximum plasma concentration
[redacted]	[redacted]
TSAP	Trial statistical analysis plan
TST	Tuberculin Skin Test
ULN	Upper Level of Normal
[redacted]	[redacted]
WOCBP	Woman of childbearing potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Clinical Presentation of Generalized Pustular Psoriasis (GPP):

The severe skin and systemic auto inflammatory disease GPP is a rare, serious condition that presents as recurring episodes of severe flares affecting the skin and internal organs (R15-1421, R16-0933), representing a true medical emergency with potentially life threatening consequences. The seriousness of the condition is reflected in the many systemic complications of GPP and the associated mortality.

In order to adequately treat GPP, flares need to be treated, but maintenance therapy also needs to be given to prevent future flares.

Treatment of acute GPP flares aims at the rapid control of the serious condition via controlling the systemic signs (CRP, fever, neutrophilia) and pustulation (e.g. visible sign of the inflammation) to prevent infection and onset of other complications making the event life threatening. In addition, the rapid response to associated dermatologic lesions (response to at least almost clear) and symptoms is key and the sustained control of the signs and symptoms of the GPP flare.

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 persistence of residual skin symptoms such as erythema and scaling and minor pustulation.

Co-morbidities:

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.

Treatment options

Current treatment options for controlling acute flare of GPP and maintenance of response and prevention of future flares are limited and do not provide sustained efficacy (R16-0933). No treatments are currently approved for GPP in the US and no centrally approved treatments are available 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®), Risankizumab (Skyrizi™), and certolizumab (Cimzia®) 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 are commonly 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. GPP flares are a true medical emergency requiring urgent intervention to stop the inflammation. If the inflammation is not controlled quickly, there is sloughing of the skin leaving the body unprotected from external pathogens resulting in bacteremia, most commonly staph sepsis and unable to prevent the leakage of essential proteins and electrolytes. The consequence is hypoalbuminemia, peripheral edema, hypovolemic and/or

septic shock, with shut down of hepatic and renal function. The morbidity and mortality without supportive care is substantial.

The acute phase is associated with a mean duration of hospitalization of 10 days (range 3-44 days) (R16-0933). Patients with GPP are known to be at an increased risk of death (R16-3932); (R16-0581). Six case series have published on deaths among patients with GPP (R16-2698);(R16-1463); (R16-0933); (R17-3898);(R17-3456); (R17-3605). Mortality estimates range from 2% in France (R16-2698) to 7% in Malaysia (R16-0933) and 7.7% in Thailand (R17-3456). In the US, Zelickson et al (R17-3605) conducted a case series on hospitalized patients with GPP at the Mayo clinic from 1961 to 1989 and reported a mortality rate of 3.2%. The most commonly reported causes of death in GPP patients were related to sepsis.

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 for prevention of the occurrence of flares that 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, concluding 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

Mode of action

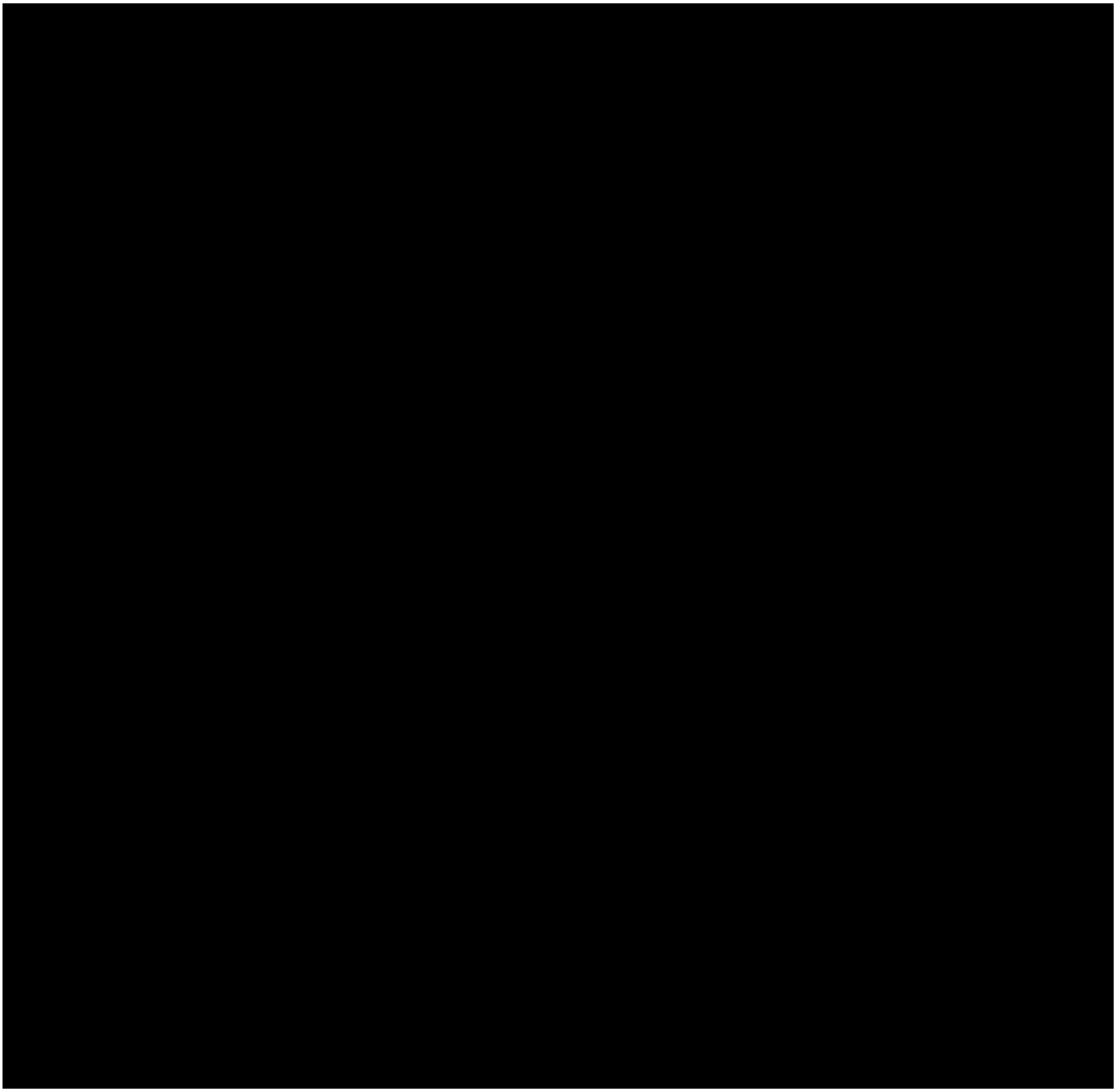
BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signaling. Binding of BI 655130 to IL36R is anticipated to prevent the subsequent activation of IL36R by cognate ligands (IL36 α, β and γ) and downstream activation of pro-inflammatory and pro-fibrotic pathways with 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), Hidradenitis Suppurativa (HS) and inflammatory bowel disease (IBD).

Key pharmacokinetic characteristics

BI 655130 has been characterized by typical IgG1 monoclonal antibody pharmacokinetics. PK data showed that exposure increased with increasing dose in a dose proportional manner from 0.3 mg/kg to 20 mg/kg following IV administration of BI 655130 to healthy volunteers. The half-life of BI 655130 was approximately 4 weeks in the linear dose range in healthy volunteers and approximately 3 weeks in GPP patients. PK data suggests target-mediated drug disposition (TMDD) kinetics for BI 655130 at doses lower than 0.3 mg/kg. Comparing the exposures between the 300 mg SC dose and 300 mg IV dose, a SC bioavailability of ~70% was determined. No differences in PK were observed between Caucasians and Japanese subjects.

Residual Effect Period

The Residual Effect Period (REP) of BI 655130 is 16 weeks. This is the period after the last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present.



Data from clinical studies

For a more detailed description of the BI 655130 profile, please refer to the current Investigator's Brochure (IB; c03320877).

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.

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

[redacted]

In a multiple rising dose trial, 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).

Study 1368.3 explored pharmacokinetics as well as safety and tolerability of a subcutaneous formulation of BI 655130 at two different dose strengths of 150 mg (1 mL) and 300 mg (2 mL) using an open-label, single dose, parallel group, matched pair design to determine the relative bioavailability of the 300 mg s.c. compared to one single 300 mg i.v. dose of BI 655130. In this study, 36 healthy male and female subjects have been treated with BI 655130, with 12 subjects per dose group. 35 subjects completed the study per protocol, one subject discontinued for logistical reasons (work-related issues).

No important protocol violations occurred. Pharmacokinetic data from 34 subjects (94.4%) were analysed for the primary and secondary endpoints. The minimum number of 11 subjects per treatment group was considered sufficient for the exploratory assessment of the primary objective. The precision and accuracy of the analytic methods used for the determination of PK parameters were adequate to achieve the trial aims. Matching was only performed for the 300 mg BI 655130 IV and 300 mg BI 655130 SC groups; however, the demographics were comparable across all treatment groups.

Safety

Single doses of BI 655130 given as SC injection or IV infusion were safe and well tolerated by the healthy subjects included in this trial. No AEs of severe intensity, protocol-specified AESIs, deaths, or other serious AEs were reported. One subject discontinued trial medication due to an AE (panic attack) beginning shortly after the start of the infusion, which was considered possibly related to trial drug administration. The overall incidence of AEs was higher in the 300 mg dose groups (both IV and SC) than the 150 mg SC group (300 mg BI IV: 11 subjects, 91.7%; 300 mg BI SC: 11 subjects, 91.7%; 150 mg BI SC: 8 subjects, 66.7%). This difference was mainly driven by the AE dermatitis acneiform. Since AUC and Cmax were substantially lower for 300 mg BI SC than for 300 mg BI IV, there was no clear exposure /AE relationship. The incidence of AEs assessed as possibly drug-related by the investigator was higher in the SC groups than in the IV group (150 mg BI SC: 5 subjects, 41.7%; 300 mg BI SC: 5 subjects, 41.7%; 300 mg BI IV: 3 subjects, 25.0%).

Safety laboratory tests and the evaluation of vital signs, oral body temperature, local tolerability, and electrocardiogram recordings revealed no clinically relevant findings.

[redacted]

In 1368.9 trial, 32 healthy Japanese male subjects were enrolled in 4 dose groups comprising 8 subjects per group. The study consisted of three dose groups receiving single rising intravenous doses of BI 655130 (300 mg, 600 mg, and 1200 mg) and one dose group receiving single subcutaneous doses of BI 655130 (300 mg). In each dose group, 6 subjects received BI 655130 and 2 subjects placebo.

Treatments were administered in a double-blind fashion within dose groups. In total, 24 subjects received BI 655130 and 8 subjects placebo. Three subjects in the 600 mg i.v. group (1 of them allocate to placebo) and 1 subject in the 1200 mg i.v. group discontinued the trial prematurely due to personal reasons.

A total of 3 out of 18 subjects (16.7%) on intravenous doses of BI 655130 (1 subject per i.v. dose level) were reported with an AE compared with 2 out of 8 subjects (25%) on placebo. No subject was reported with an AE following subcutaneous administration of BI 655130. Adverse events by preferred term reported on placebo were vomiting, chest discomfort, and allergic rhinitis, while AEs reported on BI 655130 were upper respiratory infection (300 mg i.v.), contusion (600 mg i.v.), gastroenteritis (1200 mg i.v.), and temporomandibular joint syndrome (1200 mg i.v.). None of the observed AEs were judged by the investigator as related to the trial medication.

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. Based on the PK results in GPP patients, the elimination half-life of BI 655130 was approximately 3 weeks in GPP patients. 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 by 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 79.8% (15.6), 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 letter 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 the overall population, the proportion of patients achieving ppPASI50 at Week 16 was not statistically different between the BI 655130 groups (900 mg and 300 mg: each 31.6% [95% CI 15.4%, 54.0%]) and the placebo group (23.8% [95% CI 10.6%, 45.1%]). Thus, the primary endpoint was not met. 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 pronounced reduction in pustule severity.

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 up to 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.

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

1.3 RATIONALE FOR PERFORMING THE TRIAL

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 (Spesolimab) would be beneficial in treatment of GPP flares as well as in prevention of flares. 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).

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 controlling acute flare of 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 option for controlling worsening of chronic GPP (R17-3600). The use of these for treatment or prevention of GPP flare 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. Preventing GPP flares with a safe and effective treatment will meet a high unmet need to have a proven treatment available for patients with frequent recurrence of this disruptive condition with high morbidity and associated mortality.

An open-label, single arm study trial (1368.11) has been conducted and demonstrates the proof-of-concept of a single dose of BI 655130 in patients with a moderate to severe flare of GPP. In total, seven patients have been treated with a single IV administration of 10mg/kg of BI 655130. A single dose of BI 655130 resulted in the rapid and sustained remission of clinical symptoms, with a good safety and tolerability profile. For further details and most recent results refer to the current IB (c03320877) and published letter in the New England Journal of Medicine (P19-01888). A follow-up randomized, double-blinded and placebo controlled Phase II study has been designed and is ongoing to confirm the efficacy and safety in this population (1368-0013). Also, an open-label, long term extension study (1368-0025) is ongoing to assess the safety and efficacy of BI 655130 treatment in patients with Generalized Pustular Psoriasis (GPP), who have completed the previous BI 655130 GPP trials.

The primary objective of this Phase IIb GPP trial is to provide dose-ranging data for 3 dose regimens of BI 655130 (with each regimen consisting of a loading dose and a separate maintenance subcutaneous dose) compared to placebo and to evaluate efficacy, safety, and tolerability of BI 655130 at preventing GPP flares compared to placebo in patients with a history of recurrent GPP and currently (at screening and at randomization) presenting with a GPPGA score of 0 or 1 (clear or almost clear). Three subcutaneous (s.c.) doses will be used in order to establish benefit/risk of prevention across a wide range of exposure, and i.v. treatment will be used to treat patients having onset of acute GPP flare, thereby gathering further data regarding the treatment of flares.

GPP is being extremely rare in general and especially in the paediatric population. It is anticipated that only a subset of available paediatric GPP patients would meet the criteria for GPP trial inclusion, thus limiting the feasibility of clinical development in this patient

population. Thus, a separate clinical program in the paediatric population to sufficiently demonstrate efficacy and safety of BI 655130 is considered unfeasible. Therefore, adolescents from the age of 12 years and above will be included in the adult clinical program. Based on the similarity of disease pathophysiology and mechanism of action of BI 655130 between adolescents and adults and available data on extrapolation of safety and efficacy from adults to adolescents it is anticipated that adolescent patients aged 12 and < 18 years are expected to have a therapeutic benefit with an acceptable safety profile (see Section 4.1.2 for further details).

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). 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

1.4.1 Benefits

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 reduces the flare severity and clears pustules, the primary lesion in GPP, a disease closely linked to loss of function mutations in the natural IL36R antagonist. Please refer to IB for additional details (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).

A total of an estimated 378 subjects have been exposed to single or multiple i.v. doses of BI 655130 as of September 2019. For additional details please refer to IB (c03320877). BI 655130 was safe and well tolerated in four healthy volunteers trials evaluating the i.v. and s.c. formulation.

1.4.2 Risks

There are no identified or potential risks for BI 655130, based on the toxicology program or any clinical trials conducted for this product to date (see also Section 1.2). No other IL-36 receptor antagonist is currently approved, providing information on identified risks in molecules of this class.

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

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

Table 1.4.2: 1 Risks

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

Table 1.4.2: 1 Risks (cont.)

Hypothetical risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Infections	Inhibition of the immune response with an immune-modulating biologic may increase the risk of infections. A recent characterisation of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signalling pathway inhibition does not compromise host defenses [R17-3632].	Screening procedures for infections will be established for this trial. Patients with any relevant chronic or acute infections including human immunodeficiency virus (HIV), viral hepatitis or tuberculosis are excluded from the trial. Treatment of infections should be initiated promptly according to standards of care. Severe infections and opportunistic infections are considered AESI for this trial. These conditions and serious infections are subject to close monitoring.
Malignancies	Inhibition of the immune response with an immune-modulating biologic may increase the risk of a decreased immune defence against malignancies. A recent characterisation of individuals with homozygous IL36R KO mutations revealed that normal immune function was broadly preserved suggesting that IL36 signalling pathway inhibition does not compromise host defences [R17-3632].	Patients with a recent history of malignancy within 5 years will be excluded from participation in this trial. In case of occurrence of malignant neoplasm other than appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix, the investigator should discontinue treatment with BI 655130. Diagnostics and treatment have to be initiated according to local standard of care. Malignancies represent always serious adverse events and are subject to close monitoring.
Peripheral Neuropathy	Three cases reported by the investigator as Guillain-Barré	Timely detection, evaluation, and follow-up of suspected

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

Table 1.4.2: 1 Risks (cont.)

Hypothetical risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Trial procedures		
Blood Sampling	As with all blood sampling, there is a risk of mild pain, local irritation, or bruising (a black or blue mark) at the puncture site. Furthermore, there is a small	These risks will be addressed by careful safety monitoring and risk mitigation measures such as (a) close clinical monitoring for

Hypothetical risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
	risk of light-headedness and/or fainting. In rare cases, the puncture site can also become infected or nerves may be damaged, inducing long-lasting abnormal sensations (paresthesia), impaired sensation of touch and persistent pain.	AEs; (b) selection of experienced sites and site staff; (c) training.
Skin Biopsy	Can cause local bruising, inflammation, nerve damage and pain.	These risks will be addressed by careful monitoring and risk mitigation measures such as (a) close clinical monitoring for AEs; (b) selection of sites with experienced site staff; (c) training.
Other risks		
Withdrawal of Standard of Care and Administration of Placebo/ BI 655130	If the standard therapy is withdrawn and the patient is randomized to receive a placebo/BI 655130, the patient´s condition could get worse during the course of the trial.	In the event of a GPP flare, the option of rescue treatment with open label BI 655130 is available for patients on placebo. Also, in an event of disease worsening, treatment with standard of care is always an option per physician discretion for all randomized patients

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

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

A thorough assessment based on the data available as of 18 May 2020 has been conducted to evaluate whether spesolimab may pose a higher risk associated with COVID-19 infection. Additionally, the general risk of COVID-19 infection in context of the trial population's

underlying disease and common co-morbidities was assessed. The key aspects of the assessment are summarized below.

Spesolimab is an immune-modulating humanized monoclonal antibody that blocks the human IL-36 receptor and thereby the pro-inflammatory IL-36 pathway. Available non-clinical and clinical data in 378 subjects (see Investigators Brochure Version 7) have not shown an increased risk of infections with spesolimab. However, as reflected in Table 1.4.2:1 above and the patient informed consent form, similar to other immune modulating biological treatments, spesolimab may hypothetically increase the risk of infections. Therefore, risk mitigation measures, such as exclusion of patients with increased risk of infections, close monitoring of adverse events, as well as guidance on treatment and handling of acute infections occurring during the trial have been included within this clinical trial protocol.

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

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

The benefit-risk assessment of spesolimab remains favourable in the context of the COVID-19 pandemic. Patients participating in trials with spesolimab are expected to benefit from trial treatment and interruption of treatment may worsen their disease. Published guidance for the use of biologics during the COVID-19 pandemic recommends to continue treatment with biologics (e.g. NICE COVID-19 rapid guideline: severe asthma [R20-2257], American College of Allergy, Asthma&Immunology [R20-2258], and National Psoriasis Foundation [R20-2256]). In line with this guidance no systematic testing for SARS-CoV-2 is required to be performed on the trial. However, the investigator may choose to perform the testing as per his/her discretion if useful based on individual medical consideration and in the case of suspected COVID-19 infection. Patients may receive COVID-19 vaccination in line with local recommendations/guidance and approved labels. However, it is not known whether there is any negative impact of spesolimab on the protective effect of COVID-19 vaccines.

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

Every subject or patient will be assessed thoroughly, and individual benefit-risk assessments are made prior to study entrance and during the study by the investigator in respect of SARS-CoV-2 infection. As any other acute infection a suspected or diagnosed COVID-19 infection

should be treated according to the standard of care and interruption of study medication should be considered. In case of a confirmed infection, trial treatment will be discontinued immediately and appropriate measures for monitoring, treatment and quarantine will be implemented. The investigators will take the totality of information related to each single patient and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. The patient may resume trial treatment following recovery from a SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.

1.4.3 Discussion

Considering the medical need of the development of an effective and well tolerated drug for preventing GPP flares and the demonstrated effectiveness of BI 655130 (Spesolimab) for treatment of incident flares, the benefit of this trial is considered to outweigh the potential risks for and justifies the administration of BI 655130 (Spesolimab) to patients with Generalized Pustular Psoriasis (GPP). 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 present trial will be performed to characterize the dose-response curve for BI 655130 in patients with a history of GPP (per European Rare and Severe Psoriasis Expert Network (ERASPEN) criteria) who are now (at screening and at randomization) presenting with a GPPGA score of 0 or 1 (clear, or almost clear).

The primary objective of the trial is to demonstrate a non-flat curve and evaluate the dose-response relationship for 3 subcutaneous dosing regimens of BI 655130 (with each regimen consisting of a single loading dose and a separate maintenance subcutaneous dosing regimen) versus placebo, on the primary endpoint, the time to the first GPP flare onset up to week 48.

The secondary objective is to demonstrate superiority versus placebo for each of BI 655130 300 mg q4 weeks and BI 655130 300 mg q12 weeks on the primary endpoint, the time to the first GPP flare onset up to week 48, as well as the key secondary endpoint, the occurrence of at least one GPP flare up to 48 weeks.

Treatment comparisons will be made for randomized patients regardless of treatment adherence or discontinuation, and any use of rescue medication or investigator-prescribed SoC prior to week 48 (see Section 3.1 for definition), will be considered to represent the onset of a GPP flare.

Another objective is to evaluate safety and tolerability of multiple s.c. doses of BI 655130 in patients with history of GPP.

The use of i.v. dose of BI 655130 for treating patients with onset of acute GPP flare will be evaluated for safety and efficacy as an additional objective.

2.1.2 Primary endpoint(s)

The primary endpoint of the study is:

- Time to first Generalized Pustular Psoriasis (GPP) flare (defined by increase in Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) up to week 48.

For the estimand concept on the above-defined primary endpoint definition, any use of rescue medication, or investigator-prescribed Standard of Care (SoC), will be considered to represent a GPP flare onset.

2.1.3 Secondary endpoint(s)

Key Secondary Endpoint:

For the secondary objective of the trial only, the key secondary endpoint which is included in the statistical testing strategy (see Section 7 for details) in a hierarchical manner subsequent to performance of the test on the primary endpoint is:

- The occurrence of at least one GPP flare (defined by increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) up to week 48.

For the estimand concept on the above-defined key secondary endpoint definition, any use of rescue medication, or investigator-prescribed SoC, prior to week 48 will be considered to represent the onset of a GPP flare.

For the primary objective (i.e., dose-finding analysis) of the trial, this endpoint will be considered as secondary in nature only instead of key secondary.

Secondary Endpoints:

The below-defined secondary endpoints, for the secondary objective of the trial only, are included into the statistical testing strategy in a hierarchical manner subsequent to performance of the test on the key secondary endpoint. The study is not powered for the performance of these additional statistical comparisons.

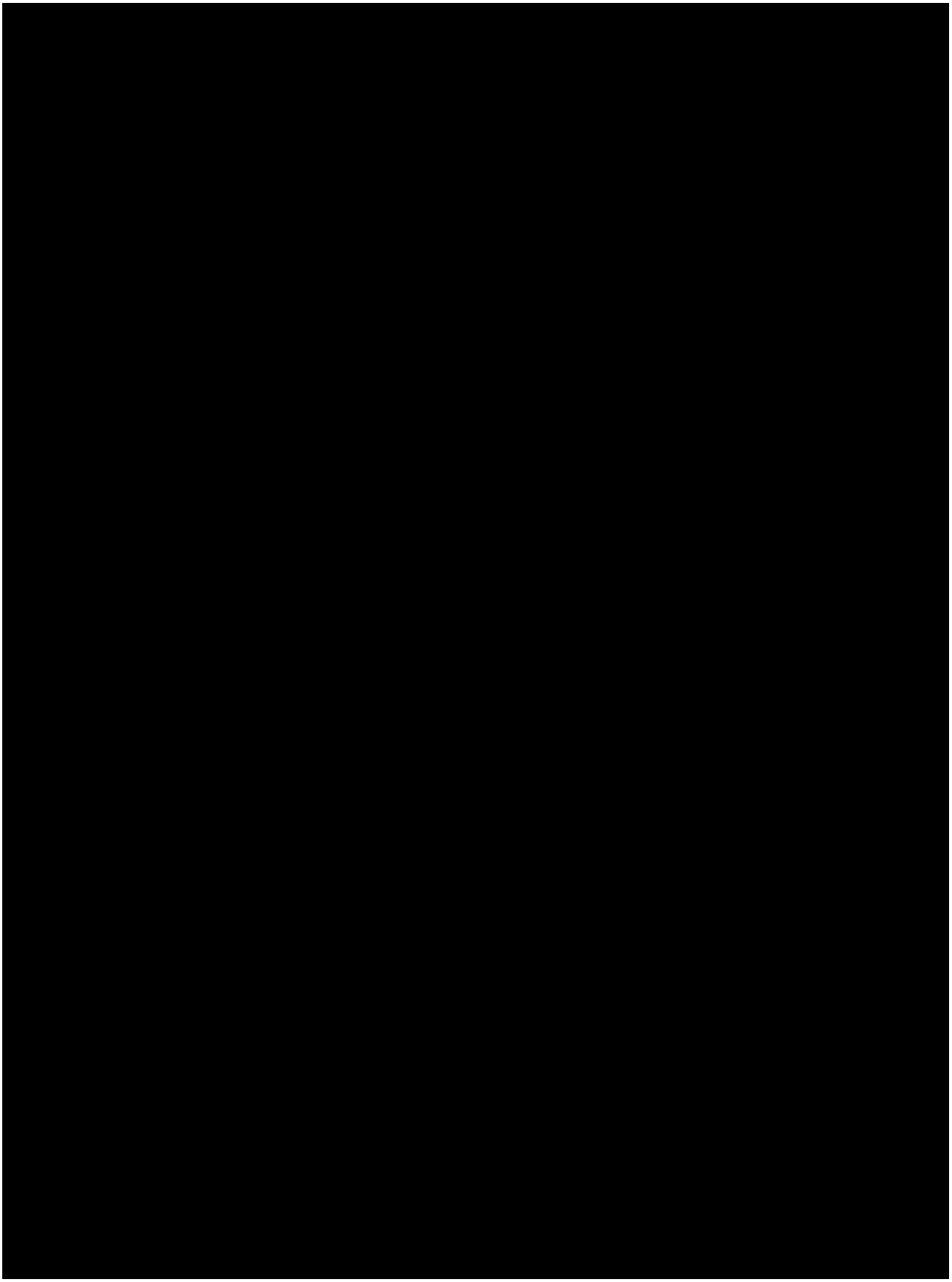
- Time to first worsening of Psoriasis Symptom Scale (PSS) up to week 48 defined as a 4-point increase in total score from baseline. Intake of rescue medication, or investigator-prescribed SoC, will be considered as onset of a worsening.
- Time to first worsening of Dermatology Quality of Life Index (DLQI) up to week 48 defined as a 4-point increase in total score from baseline. Intake of rescue medication, or investigator-prescribed SoC, will be considered as onset of a worsening.

The below-defined secondary endpoints, for the secondary objective of the trial only, are not included into the statistical testing strategy.

- Sustained remission, defined as a patient with a GPPGA score of 0 or 1 (clear or almost clear) at all visits up to week 48, without intake of rescue medication, or investigator-prescribed SoC.

Safety endpoint:

- The occurrence of treatment emergent adverse events (TEAEs)



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This is a multicenter, randomized, parallel group, double-blind, placebo-controlled Phase IIb study comprising of 3 active doses compared to placebo in adolescents from 12 years to less than 18 years of age and adult patients with history of GPP and currently presenting (at screening and at randomization) with a GPPGA score of 0 or 1 (clear or almost clear). Active treatment arms consist of active loading dose and active maintenance treatment. Please see Section 2.1.1 for details regarding the main objectives of the trial.

Approximately 120 eligible patients with generalized pustular psoriasis (GPP) will be randomized in a 1:1:1:1 ratio to one of the following treatment arms (See Figure 3.1: 1):

Arm 1: BI 655130	600 mg total loading dose at Week 1/Day1 followed by maintenance treatment 300 mg s.c. q4 weeks
Arm 2: BI 655130	600 mg total loading dose at Week 1/Day1 followed by maintenance treatment 300 mg s.c. q12 weeks
Arm 3: BI 655130	300 mg total loading dose at Week 1/Day1 followed by maintenance treatment 150 mg s.c. q12 weeks
Arm 4: Placebo	Loading dose Placebo at Week 1/Day 1 followed by maintenance treatment placebo

The randomization will be stratified accounting for the stratification factor, use of systemic GPP medications at randomization (yes versus no) (see Section 7.4), and the blocking factors, region (Japan versus Non-Japan) and population (Adults versus Adolescents) (see Section 7.4). A sufficient number of patients will be screened to meet the treatment goal of 120 patients including at least 8 adolescent patients. Patients are considered enrolled (screened) in the study once they have signed the informed consent. All patients will receive the first dose of study medication on Day 1.

Each randomized patient will receive 4 injections (loading dose) at Week 1/Day 1 followed by 2 injections (maintenance treatment) at subsequent visits until Week 44 if no flare occurs. This is required to keep the blinding. Please refer to Section 4.1.4 and Table 4.1.4: 1 for further details. The maintenance treatment period ends at Week 48.

The primary statistical analysis of the trial will be performed once all randomized patients have either completed or early discontinued from the 48 week maintenance treatment period.

Patients will be offered to enter into an open label extension (OLE) trial (1368-0025), if they have completed the treatment period in this study up to EoS1(i.e. without premature discontinuation of trial treatment), agree to participate in the OLE trial and meet the eligibility criteria for the OLE trial.

Patients who do not qualify to enter into the open label extension (OLE) trial or who may have qualified, but do not agree to participate in the OLE trial, will be followed as described in section 3.3.4.1 handling of patients with premature treatment discontinuation.

The primary analysis of this trial is planned to be performed once all randomized patients have completed or early discontinued from the 48 week treatment period; 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.

Handling of GPP Flares:

If a patient experiences the first GPP flare (increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) during the randomized maintenance treatment period, a rescue treatment with i.v. open label dose of 900 mg BI 655130 should be administered (R1/D1). The investigators should encourage the patient to inform them at the first signs of onset of a GPP flare. If a patient suspects that they have a GPP flare in between the protocol specified scheduled visits, they should contact the investigator to determine whether to make an unscheduled visit and return to the clinic/site for assessment. After confirming the onset of a GPP flare requiring treatment and subsequently receiving the i.v. dose of BI 655130, the patients will be seen at R2/D4 and R3/D8 of week1 (daily if hospitalized), week 2, week 3, week 4, and week 8 of the rescue treatment period (see Flow Chart 2). A patient may qualify to receive another rescue treatment with open label i.v. dose of 900 mg of BI 655130 at R3/D8, if either of the following criteria are met.

- **For patients with GPPGA score of ≥ 3 and a pustular component of GPPGA of ≥2 at R1**: the total GPPGA is ≥2 and the pustular component of GPPGA is ≥2 at R3/D8.
- **For patients with GPPGA score of 2 and a pustular component of GPPGA of ≥2 at R1:** the pustular component of GPPGA is ≥2 at R3/D8.

For patients who receive the administration of the first rescue treatment with open label i.v. (OL) BI 655130 for the first GPP flare up to Week 34 (Day 239) of randomization, after 12 weeks following the day of rescue i.v. treatment administration (R1 in Flow Chart 2) and response of the GPP flare, they will start the OL s.c. maintenance treatment period to receive the OL s.c. dose of 300 mg BI 655130 q12w. The visits of BI 655130 q12w during the OL s.c. maintenance treatment period should follow Flow Chart 1. Therefore, the visit of the first s.c. OL maintenance treatment should be assigned to a planned visit per Flow Chart 1 by comparing to the day of the first randomized treatment (V2/D1 in Flow Chart 1). If the first dose of OL s.c. maintenance treatment is outside of any scheduled visit window by ±7 days per Flow Chart 1, it needs to be assigned to one of the scheduled visits by extending each visit time window to -13/+14 days of the original CTP planned visit date, defined relative to

the day of first randomized treatment, Day 1. See Table 3.1: 1 for the detailed rules of visit assignment for the first dose of OL s.c. maintenance treatment. Then the following OL s.c. maintenance doses (if applicable) will be administered within original visit window by ±7 days per Flow Chart 1. Note that once the first dose of OL s.c. visit assignment referring to Flow Chart 1 is calculated (see Table 3.1:1), all study procedures scheduled for this visit and subsequent OL maintenance treatment visits should be completed as per open label maintenance treatment period in Flow Chart 2.

During the maintenance treatment with OL s.c. dose of 300 mg BI 655130 q12 weeks, if the patient's GPPGA total score increases by ≥ 1 (with or without the presence or new appearance of pustules), or if there is an increase in the pustular component of GPPGA ≥ 1 from any of the previous OL maintenance visit(s), then the investigator may treat the patient with intensified maintenance therapy with open label s.c. dose of 300 mg BI 655130 q4 weeks.

During the OL maintenance treatment period, the patients are to come q4 weeks irrespective of whether the patient is on q12 week dosing schedule or q4 week intensified maintenance dosing schedule.

Table 3.1: 1 Time windows for the visit assignment of the first OL s.c. maintenance treatment based on planned visit day in Flow Chart 1

Applicable for patients who receive the administration of the first rescue treatment with open label i.v. (OL) BI 655130 for the first GPP flare up to Week 34 (Day 239) of randomization

Time window for the day of the1st s.c. OL maintenance treatment with BI 655130 relative to the randomization day, Day 1[1]		Assigned Visit Number/Planned Week for the 1st s.c. OL maintenance treatment with BI 655130			
From	To	Visit Number	Planned Week	Planned Visit day	Based on the extended time window (only for the first dose[3])
Day 82	Day 99	*5*	Week 12	85	-3/+14 days
Day 100	Day 127	*6*	Week 16	113	-13/+14 days
Day 128	Day 155	*7*	Week 20	141	-13/+14 days
Day 156	Day 183	*8*	Week 24	169	-13/+14 days
Day 184	Day 211	*9*	Week 28	197	-13/+14 days
Day 212	Day 239	*10*	Week 32	225	-13/+14 days
Day 240	Day 267	*11*	Week 36	253	-13/+14 days
Day 268	Day 295	*12*	Week 40	281	-13/+14 days
Day 296	Day323[2]	*13*	Week 44	309	-13/+14 days

[1] The first dose of s.c. OL maintenance treatment is scheduled at 12 weeks after the 1st rescue i.v. treatment of BI 655130. This visit should be organized within the allowed time window relative to the day of the rescue treatment (per Flow Chart 2), and subsequently, by comparing to the day of the first randomized treatment (Day 1) and by applying the rules presented in this table, assigned to a scheduled OL maintenance dosing visit (per Flow Chart 1)
[2] The latest possible day to give the first dose of OL s.c. BI 655130 is Day 323 (i.e. the last day of Week 46), it will be assigned to Week 44 visit.
[3] The extended time window is only for the first dose of OL s.c. maintenance treatment, the time window for subsequent visits will be based on Flow Chart 1.

- For patients who receive the administration of the first rescue treatment with open label i.v. (OL) BI 655130 for the first GPP flare after Week 34 (Day 239) of randomization, they will not receive any further open label s.c. maintenance treatment of BI 655130 after the rescue treatment period. Depending on when the rescue i.v. treatment was administered these patients may not need to attend all scheduled visits in the rescue treatment period as described in Flow Chart 2 prior to Week 48 of randomization. Please refer to Table 3.1:2 for the follow up visits required based on the time of their administrations of rescue treatment with BI 655130. These patients will be rolled over into the open label extension (OLE) trial at week 48 (after randomization) if they agree to

and there is a clinical improvement (as per investigator judgement), otherwise, they will be followed for 16 weeks through EoS2.

Table 3.1: 2 Scheduled follow up visits (per Flow Chart 2) for patients who receive the first rescue treatment with BI 655130 for the first GPP flare after Week 34 of randomization and will not receive any open label maintenance treatment.

Time window for the first rescue i.v. treatment with BI 655130 for the 1st GPP Flare relative to the randomization day, Day 1		Required follow up visits[2]
Start	End	Visit Number
Day 240	Day 260	R1, R2, R3, R4, R5, R6, R7, V14/EoS1
Day 261	Day 295	R1, R2, R3, R4, R5, R6, V14/EoS1
Day 296	Day 302	R1, R2, R3, R4, R5, V14/EoS1
Day 303	Day 309	R1, R2, R3, R4, V14/EoS1
Day 310	Day 316	R1, R2, R3, V14/EoS1
Day 317	Day 337	R1, R2, R3,V14/EoS1[1]

[1]EoS1should be performed at least 7 days after the last rescue treatment with i.v. OL BI 655130 is given.
[2]If it was determined that a patient does not qualify or not agree to roll over to OLE, the patient still needs to attend the visits planned in the table if possible.

Handling of Investigator Prescribed Standard of Care (SoC) for GPP disease during Randomized Maintenance Treatment Period:

It is strongly recommended to avoid prescription of SoC to patients for GPP disease especially during the randomized maintenance treatment period.

If a patient on randomized (blinded) treatments experiences disease worsening but does not meet the GPP flare definition (See Table 3.1: 3), it is highly recommended that the investigator does not prescribe Standard of Care (SoC) but to wait until the patient meets the definition of a GPP flare in order that an OL i.v. dose of BI 655130 may be administered instead at this time. During the randomized maintenance treatment period, if a patient is given any investigator prescribed SoC for GPP disease worsening, the patient needs to discontinue from any further study drug. Please refer to section 3.3.4.1 for further details on handling of patients with premature treatment discontinuation.

Handling of Investigator Prescribed Standard of Care (SoC) for GPP disease during Rescue Treatment Period of the 1st GPP Flare:

Use of investigator prescribed SoC for GPP during the first 4 weeks of receiving i.v. rescue treatment with open label BI 655130 at R1/D1 is not allowed. The patient may be treated with SoC as per PI's discretion, but the patient needs to discontinue from any further study drug if SoC was given. In this case, the patient remains in the trial and, given his/her agreement, ideally should complete all the scheduled visits in rescue treatment period within Flow Chart 2 and as per Table 3.1:1 and then the remaining study visits in Flow Chart 1 as applicable up to Wk 48 from randomization. Please also refer to section 3.3.4.1 for further details on handling of patients with premature treatment discontinuation.

If a patient achieves at least a partial response (See Table 3.1: 1) to i.v. rescue treatment with open label BI 655130, then topical treatments/topical corticosteroids, methotrexate, cyclosporine and retinoids may be used after four weeks following i.v. rescue treatment with open label BI 655130 at R1/D1. These patients may continue on receiving open label s.c. BI 655130.

See section 4.2.2.2 for further details on the restricted medications list post visit 2 and exceptions.

Handling of Investigator Prescribed Standard of Care (SoC) for GPP disease during Open Label Maintenance Treatment Period:

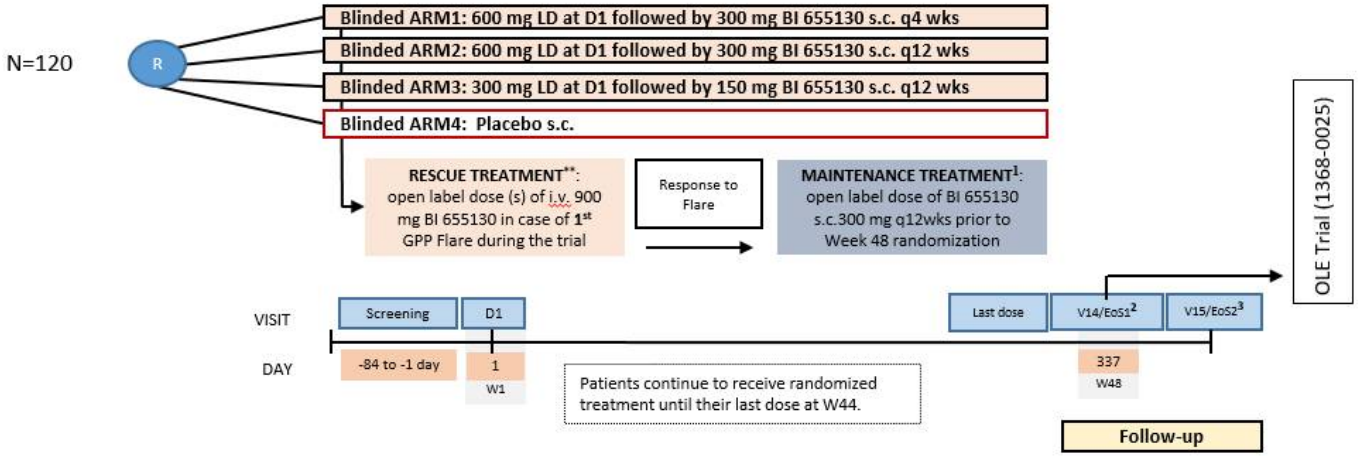
If the patient experiences any further disease worsening during the maintenance treatment with OL s.c. dose of 300 mg BI 655130 q12 weeks, investigator should treat the patient with intensified maintenance therapy with open label s.c. dose of 300 mg BI 655130 q4 weeks before prescribing any SoC. During the OL maintenance treatment period, if a patient is given any investigator prescribed SoC (with the exception of topical treatments/topical corticosteroids, methotrexate, cyclosporine and retinoids) for GPP disease worsening, the patient needs to discontinue from any further study drug. Please refer to section 3.3.4.1 for further details on handling of patients with premature treatment discontinuation.

Table 3.1: 3 Study definitions

GPP Disease Worsening	Disease worsening is defined as worsening of clinical status or GPP skin and systemic symptoms requiring treatment intervention in the investigator's opinion. In the case that rescue medication with BI 655130 has not been given before, it is recommended, however, to wait until a patient meets the definition of a GPP flare in order that rescue medication could be administered instead of SoC.
GPP Flare	Increase in GPPGA score by ≥ 2 from baseline* and the pustular component of GPPGA ≥ 2. *Baseline value for efficacy measurements is the last value measured before 1st IMP dose at V2.
Rescue Medication (OL i.v. dose of BI 655130)	Rescue with open label (OL) i.v. dose of BI 655130 to treat the first GPP flare during randomized treatment period. Rescue medication with OL i.v. dose of BI 655130 is only allowed for the first flare during the 48 week randomized treatment period.
Criteria to receive rescue treatment with Open Label (OL) i.v. dose of 900 mg BI 655130 **at R3/D8** of rescue treatment period	• **For patients with GPPGA score of ≥ 3 and a pustular component of GPPGA of ≥2 at R1**: the total GPPGA is ≥2 and the pustular component of GPPGA is ≥2 at R3/D8. • **For patients with GPPGA score of 2 and a pustular component of GPPGA of ≥2 at R1**: the pustular component of GPPGA is ≥2 at R3/D8
Response to GPP Flare Treatment	After rescue treatment with OL i.v. dose of BI 655130 (at R1/D1 or at R1/D1 and R3/D8), responders are patients who show no flare symptoms of moderate/severe intensity with a GPPGA score of <3 and a pustular component score of <2. In addition, the patient must have a decrease in GPPGA score by ≥ 1 from R1/D1.
Partial Response to GPP flare treatment	A GPPGA score 0 or 1 was not achieved, but a reduction in GPPGA score (to <3) **or** GPPGA pustule sub-score (to <2) was observed after receiving the rescue treatment with OL i.v. dose of BI 655130.
Criteria to switch the patient from OL s.c. dose of 300 mg BI 655130 q12 weeks to intensified maintenance therapy with open label s.c. dose of 300 mg BI 655130 q4 weeks	If patient's GPPGA total score increases by ≥ 1 (with or without the presence or new appearance of pustules), or if there is an increase in the pustular component of GPPGA ≥ 1 from any of the previous OL maintenance visit(s).

Table 3.1: 3 Study definitions (Contd.)

Investigator prescribed Standard of Care (SOC) for GPP Disease	• Medications used for treating worsening of GPP symptoms or clinical status (i.e. disease worsening) without GPP flare. It is recommended, however, to wait until a patient meets the definition of a GPP flare in order that rescue medication with BI 655130 could be administered instead in the case that rescue medication was never given before. Or • Medications used for treating patients without a response of a GPP flare after two weeks following i.v. dose rescue treatment with open label BI 655130 at R1/D1 (see also Response of a GPP Flare above). Or • Medications used for treating any new GPP flare (i.e. subsequent flares) after receiving rescue medication for the first GPP flare experienced by the patient on the trial. **Note:** Any use of Investigator Prescribed SoC for GPP disease during the trial will lead to the discontinuation of the trial treatment with the following exceptions. Use of topical treatment/topical corticosteroid, methotrexate, cyclosporine and retinoids is permitted after four weeks following i.v. dose rescue treatment with open label BI 655130 at R1/D1 and also during the OL maintenance treatment period. Refer to section 4.2.2.2 for further details.



** In an event a patient experiences 1st GPP flare, please refer to Figure 3.1:2 and Section 3.1 for further details.

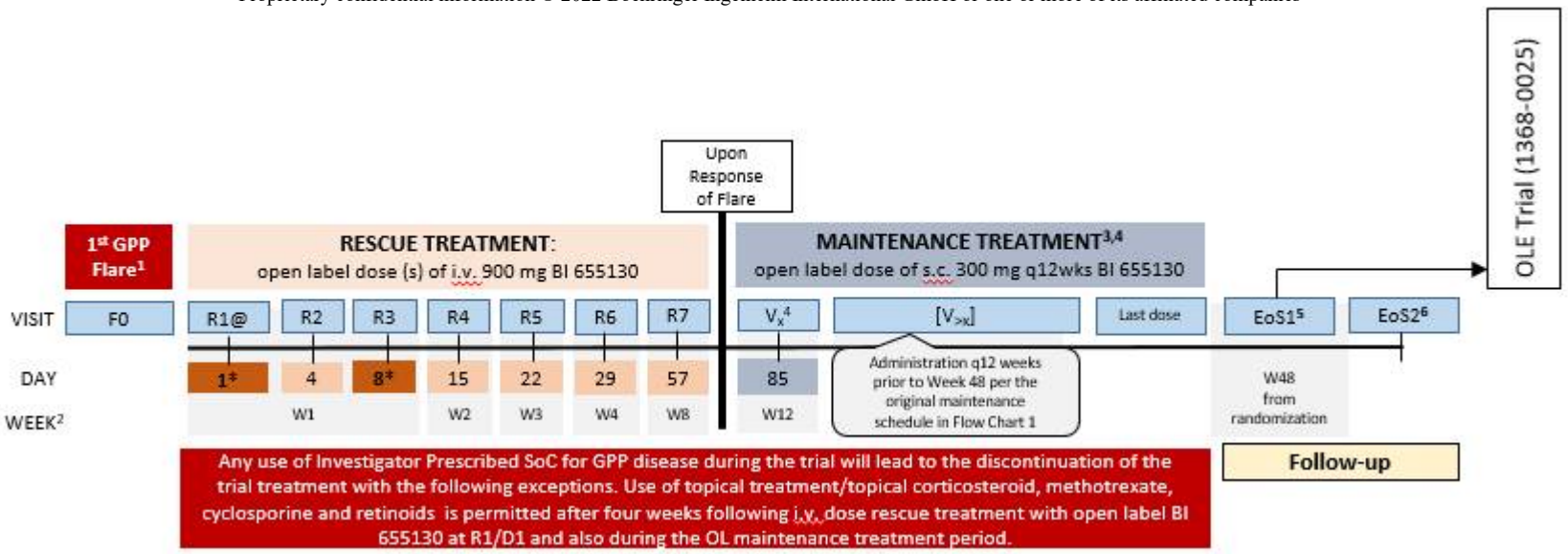
[1] If the patient's GPPGA total score increases by ≥ 1 (with or without the presence or new appearance of pustules), or if there is an increase in the pustular component of GPPGA ≥ 1, the investigator may treat the patient with intensified maintenance therapy of OL BI 655130 s.c. 300 mg q4weeks. Please refer to Section 3.1.

LD = Loading Dose; **EoS** = End of Study

[2]**EoS 1**: V14 will be recorded as the End of Study visit (i.e., EoS1) for patients who qualify and agree to enter the OLE trial (1368-0025). V14 will also be recorded as End of Study visit for patients who prematurely discontinue with the last dose of treatment up to and including Day 232 and who agree to complete all remaining study visits up to Wk 48 from randomization. Since these patients prematurely discontinued, they would not qualify to enter OLE trial.

[3]**EoS 2:** It is applicable to patients who do not qualify or who do not agree to enter into the OLE Trial (1368-0025) at Wk 48. EoS2 is also applicable for patients who prematurely discontinue with the last dose of treatment after Day 232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. EoS2 will be their End of Study visit for the trial.

Figure 3.1: 1 Overall study design



[1] increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2

[2] Week represents the end of each week (e.g. End of Week1=D8, End of Week2 =D15, End of Week3 = D22, End of Week4 =D29, etc.). w* represents * weeks after the rescue treatment .

[3] Investigator may treat the patient with intensified maintenance therapy of OL BI 655130 s.c. 300 mg q4 weeks if the patient meets protocol specified criteria. Please refer to Section 3.1.

[4] Patients who receive rescue treatment with BI 655130 up to Week 34 (Day 239) of randomization will start the OL s.c. maintenance treatment 12 weeks later following the response of the GPP flare. If the first dose of OL s.c. maintenance treatment is outside of any scheduled visit window by ±7 days per Flow Chart 1, it needs to be assigned to one of the scheduled visits following the rules in Table 3.1:1; Patients who receive rescue treatment with BI 655130 after Week 34 (Day 239) of randomization are to attend visits as described in Table 3.1:2.
@The day of administration of rescue treatment = Day 1. All subsequent study Days are counted from this Day 1 except for 'Last dose' for the maintenance treatment, EoS1 and EoS2.
***Dosing days**. Please refer to Section 3.1 for further details.

[5] **EoS1**, V14 will be recorded as the End of Study visit (i.e., EoS1) for patients who qualify and agree to enter the OLE trial (1368-0025). V14 will also be recorded as End of Study visit for patients who prematurely discontinue with the last dose of treatment up to and including Day 232 and who agree to complete all remaining study visits up to Wk 48 from randomization. Since these patients prematurely discontinued, they would not qualify to enter OLE trial.

[6] **EoS2** is applicable for patients who do not qualify or who do not agree to enter OLE trial (1368-0025) at Week 48. EoS2 is also applicable for patients who prematurely discontinue with the last dose of treatment after Day 232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial.

Figure 3.1: 2 Study design in the event a patient experiences 1st GPP flare

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

The rationale of this phase IIb trial is to provide dose-ranging data for 3 dose regimens of BI 655130 compared to placebo and demonstrate a non-flat dose response curve, as well as to provide statistical evidence regarding the superiority for BI dose vs. placebo on the primary and key secondary endpoint. This trial with BI 655130 and placebo is to be conducted in patients with a known history of frequent GPP flares and currently (at screening and at randomization) with GPPGA score of 0 or 1 (clear/almost clear). Patients with frequent flares (with at least 2 presentations/year, at least one of which had evidence of either fever and/or elevated CRP and / or elevated WBC.) of GPP without background medication or patients under treatment with background medications which is not adequately controlling the disease or not well tolerated are the primary group with an unmet need for a proven, safe treatment to prevent flares. Thus, these patients are proper study population to participate in this trial. In trial 1368.11 (PoCP trial in GPP), the patients had a treatment free period (no other concomitant GPP treatments) during which all flares were successfully treated with BI 655130. As all patients experiencing flares in that trial were successfully treated, treating with placebo in this trial (1368-0027) is a reasonable control to provide an estimate of the number of flares prevented by subcutaneous BI 655130. Treatment of the incident flares with intravenous BI 655130 will provide further evidence of the effectiveness in treating incident flares. For treatment of incident flares, a second randomization between BI 655130 and placebo is not justified due to the high IV exposure and long maintained effect seen in 1368.11, in addition, the placebo effect will have already been evaluated in trial 1368-0013.

Based on data from 1368.11 which demonstrated rapid treatment onset of control of flare symptoms and resolution including sustained response up to 20 weeks, a parallel group, randomized, double-blind and placebo controlled trial where GPP patients with GPPGA score of 0 or 1 (clear/almost clear) was considered most appropriate to evaluate the efficacy, safety and tolerability of BI 655130 at preventing GPP flares in patients with history of GPP. In the 1368-0027 trial, any randomized patient, who experiences a disease flare during the trial duration of sufficient severity to have a medical need to treat, will be offered rescue treatment with open label i.v. dose of BI 655130.

The incidence of flares in an untreated population is unknown, so a placebo regimen is essential for this trial. Demonstrating a high incidence is essential to demonstrating that patients benefit from preventive treatment. No active control group is included in this trial as there is currently no drug approved for the prevention of GPP flare. Secukinumab (Cosentyx®), infliximab (Remicade®), ixekizumab (Taltz®), brodalumab (Lumicef®), adalimumab (Humira®), guselkumab (Tremfya®), Risankizumab and certolizumab (Cimzia®) are only registered in Japan for the treatment of GPP. For secukinumab, authorization was granted because of long-term treatment data (52 weeks) derived from a single open label clinical trial conducted in 12 patients with chronic GPP symptoms and an endpoint at 16 weeks (R16-1462). In the absence of a treatment studied in controlled trials for prevention, the results of any active control would not be interpretable in comparison to Spesolimab. Moreover, due to the absence of approved drugs and a commonly accepted treatment algorithm, patients in this trial would have a very heterogenous pre-treatment

history as different SoC are preferentially used in different countries, which prevents the selection of suitable active comparator which is relevant for all patients.

Thus, study 1368-0027 will be a multicenter, randomized, double-blind, placebo-controlled Phase IIb dose finding study with multiple doses of BI 655130/placebo in patients with history of GPP flares and currently (at the time of screening and at randomization) with GPPGA score of 0 or 1 (clear/almost clear). The primary objectives of this trial are described in Section 2.1.1. It is planned that patients will continue to receive randomized treatments until the end of the treatment period.

For this trial, it is planned to include patients with history of GPP 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.
- Mutation status is only available for a subset of GPP patients.

Patients who show no flare symptoms of moderate/severe intensity at EoS1 and 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 once the patient completes EoS1 on this trial. See Section 3.1 for additional details on the trial design.

3.3 SELECTION OF TRIAL POPULATION

Screening of patients for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of patients have been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial. Patients already in screening and assessed as eligible will be allowed to continue to randomisation and treatment.

A suitable number of countries/sites will participate globally in order to minimize the risk of under recruiting and to meet the goal of 120 patients (including 8 adolescent patients) randomized. Due to the rareness of the disease, a high number of sites will participate relative to the number of patients required.

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

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

3.3.1 Main diagnosis for trial entry

This study will assess the treatment of patients with history of GPP flares with stable disease at the time of randomization.

At screening, the confirmation of history (diagnosis) of GPP is based on the consensus diagnostic criteria defined by the ERASPEN (R18-1705) and the patients must have had previous evidence (for past GPP flares) of either fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leukocytosis with peripheral blood neutrophilia (above ULN).

The ERASPEN diagnosis criteria are:

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 in- and exclusion criteria.

3.3.2 Inclusion criteria

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

1. Patients with a known and documented history of GPP per ERASPEN criteria (see Section 3.3.1) regardless of IL36RN mutation status, with at least 2 presentations of moderate to severe GPP flares with fresh pustulation (new appearance or worsening) in the past.

2. Patients with a GPPGA score of 0 or 1 at screening and randomization.

3. Patients who are not on concomitant GPP treatment at time of randomization (V2) must have had at least two presentations of moderate to severe GPP flare in the past year, at least one of which had evidence of either fever and/or elevated CRP and/or elevated WBC, and/or asthenia and/or myalgia.

4. Patients who are not on concomitant GPP treatment at time of randomization (V2) but who were on concomitant GPP treatment until shortly before randomization (V2) (≤ 12 weeks before randomization), these patients must have a history of flaring while on concomitant treatment for GPP or in case of dose reduction or discontinuation of their concomitant medication.

5. Patients who are on concomitant treatment regimen with retinoids and/or methotrexate and/or cyclosporine must stop at the day of randomization (V2). These patients must have

a history of flaring while on concomitant treatment for GPP or in case of dose reduction or discontinuation of these concomitant medications.

6. Male or female patients, aged 12 to 75 years at screening. For all patients, a minimum weight of 40 kg is required.

7. Signed and dated written informed consent and assent in accordance with ICH-GCP and local legislation prior to admission in the trial.

8. Women of childbearing potential (WOCBP)[1] 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 the CTP as well as in the patient, parent(s) (or patient's legal guardian) information.

[1]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 meeting any of these exclusion criteria must not be enrolled into the trial:

1. Patients with SAPHO (Synovitis–acne–pustulosis–hyperostosis–osteitis) syndrome.
2. Patients with primary erythrodermic psoriasis vulgaris.
3. 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.
4. Treatment with:
    a. Any restricted medication as specified in the CTP, 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 biologic.
5. 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.
6. Relevant chronic or acute infections including active tuberculosis, human immunodeficiency virus (HIV) infection or viral hepatitis at the time of randomization. A patient can be re-screened if the patient was treated and is cured from the acute infection.
7. Active or Latent TB:
    - Patients with active tuberculosis should be excluded
        - Patients with a positive QuantiFERON® (or if applicable, T-Spot®) TB test during screening are excluded, unless the patient had previous diagnosis of active or latent TB and has completed appropriate treatment per the discretion of the local

investigator within the last 3 years and at the latest at the time of screening (i.e. 2 to 4 weeks before study drug administration); patients may be re-screened once to meet this criterion)
- Patients with suspected false positive or indeterminate QuantiFERON® (or if applicable, T-Spot®) TB result may be re-tested once
- If QuantiFERON® (or if applicable, T-Spot®) TB testing is not available or provides indeterminate results after repeat testing, a tuberculin skin test (TST) or any alternative test/procedure (as per local standards) to rule out TB can be performed: A TST reaction of ≥10mm (≥5mm if receiving ≥15mg/d prednisone or its equivalent) is considered positive.

8. History of allergy/hypersensitivity to the systemically administered trial medication agent or its excipients.
9. Exclusion criteria removed in global amendment 1. Numbering of subsequent criteria was not changed.
10. 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.
11. 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). Exception: Patients on the 1368-0013 study who are in the screening period and who did not get a chance to get randomized on the 1368-0013 trial due to the study meeting target number of randomized patients or who did not qualify to get randomized into the 1368-0013 study can be enrolled on the 1368-0027 study if they meet all inclusion/exclusion criteria.
12. 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 for 16 weeks after the last study drug administration.
13. 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.
14. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse or congestive heart disease 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 Withdrawal of patients from treatment or assessments

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

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see sections 5.2.6.2.1 and 5.2.6.2.2).

3.3.4.1 Discontinuation of trial treatment

An individual patient will discontinue trial treatment if:

- The patient wants to discontinue trial treatment, without the need to justify the decision.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment.
- The patient can no longer receive trial treatment for medical reasons as per physician's discretion (such as surgery, adverse events, other diseases, or pregnancy).
- If a hepatic injury alert (as defined in Section 5.2.6.1.4) is detected without identification of an alternative cause in the work-up according to the "DILI checklist", the patient should not receive subsequent doses of trial medication.
- For individual stopping rules related to specific adverse events, please see Section 4.2.1 "Other treatments and emergency procedures."
- Worsening of clinical status or GPP symptoms requiring treatment with restricted medication (Section 4.2.2.1) in the investigator's opinion.
- The patient experiences an infection with SARS-CoV-2 (as confirmed by PCR test). The patient may resume trial treatment following recovery from SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.
- If peripheral neuropathy is suspected, treatment with spesolimab should be temporarily discontinued until a full neurological investigation has been conducted. After completion of the neurological investigation, treatment can be restarted based on medical judgement of the investigator.

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

Even if the trial treatment is discontinued, the patient remains in the trial and, given his/her agreement considering the GCP-guidelines, ideally should follow all of the remaining scheduled study visits and procedures as outlined in the Flow Chart 1 or Flow Chart 2 (as applicable) and Section 6.2.3 up to Wk 48 from randomization; If a patient is not willing to follow the whole visit schedule, the patient should at a minimum be followed for 16 weeks after last study drug administration (REP) and at least the scheduled visit at Week 48 (i.e. at the end of treatment period) should be conducted. Patients refusing to return to the study site should at least provide safety information by phone at the respective visits.

3.3.4.2 Withdrawal of consent to trial participation

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

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see Section 3.3.4.1 above. This discussion, as well as the patient's decision, should be well documented in the source.

3.3.4.3 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.

Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

Further follow up of patients affected will occur as described in Section 3.3.4.1.

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 monocloncal antibody heterodimer with a molecular weight of approximately 146 kDa.

BI 655130 solution for injection (s.c. administration) is formulated at 150mg/mL presented in a 1mL pre-filled syringe (150mg/syringe).

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 Test Product**:** BI 655130 (Spesolimab)

BI 655130 for Maintenance Treatment (including loading dose):

Substance:	BI 655130
Pharmaceutical formulation:	Solution for injection
Source:	BI Pharma GmbH & Co. KG, Biberach, Germany
Unit strength:	BI 655130 150 mg/PFS (150 mg/mL), 1 mL fill volume
Posology:	Arm 1: 600 mg total loading dose at Week 1/Day1 followed by maintenance treatment 300 mg s.c. q4 weeks Arm 2: 600 mg total loading dose at Week 1/Day1 followed by maintenance treatment 300 mg s.c. q12 weeks Arm 3: 300 mg total loading dose at Week 1/Day1 followed by maintenance treatment 150 mg s.c. q12 weeks
Mode of administration:	s.c. injection

Table 4.1.1: 1 (cont'd) Test Product**:** BI 655130 (Spesolimab)

BI 655130 for Rescue Treatment (at R1/D1 Or at R1/D1 & R3/D8):

Substance:	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 i.v. dose
Mode of administration:	i.v. infusion

Table 4.1.1: 2 **Placebo comparator**

Substance:	Placebo to match Solution for Injection(BI 655130)
Pharmaceutical formulation:	Solution for injection
Source:	BI Pharma GmbH & Co. KG, Biberach, Germany
Unit strength:	Placebo to match Solution for Injection (BI 655130), 1mL PFS
Posology:	Arm 4: Loading dose Placebo at Week 1/Day 1 followed by maintenance treatment placebo
Mode of administration:	s.c. injection

4.1.2 Selection of doses in the trial and dose modifications

In the proof-of-concept trial 1368.11 in GPP patients, a single intravenous dose of 10 mg/kg of BI 655130 was tested. The proof-of-concept (PoC) for IL36R inhibition in GPP was achieved in these patients who showed rapid clinical responses (for further detail, refer to Section 1.2). GPPASI score was measured at weeks 1, 4, 12 and 20 and the positive response was maintained up to week 20 following this single i.v. dose of BI 655130. Additionally, a 300 mg s.c dose of BI 655130 has been tested in healthy volunteers to obtain PK information following sub-cutaneous administration of BI 655130.

The aim of the current trial (1368-0027) is to provide dose-ranging data for 3 subcutaneous dosing regimens of BI 655130 with the proposed doses of 300 mg s.c. q4w and 300 mg s.c. q12w after a loading dose of 600 mg each and 150 mg q12w after a loading dose of 300 mg. These three doses/regimen were selected to test a wide range in exposure to thoroughly evaluate the exposure-response relationship of BI 655130 in GPP patients.

If a patient experiences a GPP flare (increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2) during the randomized maintenance treatment period, a rescue treatment with i.v. open label dose of 900 mg BI 655130 is to be administered at R1/D1. A patient may qualify to receive another dose of i.v. open label 900 mg BI 655130 at R3/D8 if protocol specified criteria are met (please refer to Table 3.1:1). The 900 mg BI 655130 i.v dose was selected based on positive data from 1368.11 and thus considered reasonable to continue with the dose of 10 mg/kg to maintain the PK exposures observed in the trial 1368.11. A fixed dose of 900 mg was selected to give the flexibility to recruit patients greater than 70 kg body weight. BI 655130 has been tested in healthy volunteers up to 20 mg/kg (given weekly in the MRD trial 1368.2) and was shown to be safe and tolerable. 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). Thus, the selected fixed dose (900 mg single i.v. dose) is anticipated to be within safety limits for patients with a lower weight as well.

Including adolescent patients with a minimum weight of 40 kg is not expected to pose any safety concern as the predicted exposures in adolescents with the doses planned are expected to be below the maximum exposures tested in healthy volunteer trials. Using the population PK model built from healthy volunteers and PK data from PPP patients, one thousand simulations were performed for a typical 40 kg subject taking into account inter-individual variability in model parameters.

Forty kilograms was chosen for the simulations as this represents the weight of the lightest subject that could be enrolled in this trial. Assuming the subjects receive the highest maintenance dose of 300 mg q4w until week 32 and then receives a 900 mg IV rescue dose at week 33 (worst case scenario for exposure, where the IV dose is administered 1 week after the last s.c. dose representing administration at t_{max}), the predicted median C_{max} following rescue dosing is 487,000 µg/L (314,000 – 756,000 µg/L (90% prediction interval)). This is well below the maximum observed concentration of 992,000 µg/L following the maximum tested dose of 20 mg/kg qw (x4 doses) in trial 1368.2.

Similarly, the model predicted median AUC over 12 weeks following rescue dosing is 9,620,000 µg/L *day (6,320,000 – 14,100,000 µg/L*day (90% prediction interval)) which is well below the model predicted AUC over 12 weeks of 31,900,000 µg/L*day (26,300,000 – 38,700,000 µg/L*day (90% prediction interval)) following the maximum tested dose of 20 mg/kg qw (x4 doses) in trial 1368.2.

The weight cutoff was chosen as 40 kg (median weight of a 12 year old subject) and not 30 kg (3rd percentile for a 12 year old subject) because the probability of exceeding the maximum observed concentration was calculated as 0.5% for subjects weighing 40 kg while the probability of exceeding the maximum observed concentration was 4.4% for subjects weighing 30 kg.

The expected exposure profile is shown in Figure 4.1.2:1. The blue line and shaded area represents the median and 90% prediction interval following 300 mg q4w maintenance dosing and then administration of a rescue dose at week 33 for a typical 40 kg adolescent, taking into account inter-individual variability in model parameters. The black line and shaded area represents the median and 90% prediction interval for the same scenario in

adults. The dashed blue line represents the maximum observed concentration of 992,000 ug/L following 20 mg/kg qw IV (4 doses) given in adults in trial 1368.2 which is the highest regimen tested to date in healthy volunteers.

The figure shows similar overlapping concentration time profiles for adults subjects (shown in grey) compared to an adolescent who meets the minimum weight requirement of 40 kg (shown in blue) although slightly higher exposure is expected in adolescents. Additionally, although the figure below demonstrates similarity in exposure between adults and adolescents for the highest dose to be tested, this similarity in exposure holds for all lower dose groups. Overall, the dosing regimens to be tested in adolescents is expected to be similar to adults and within the safe exposure range established for Spesolimab in adult patients.

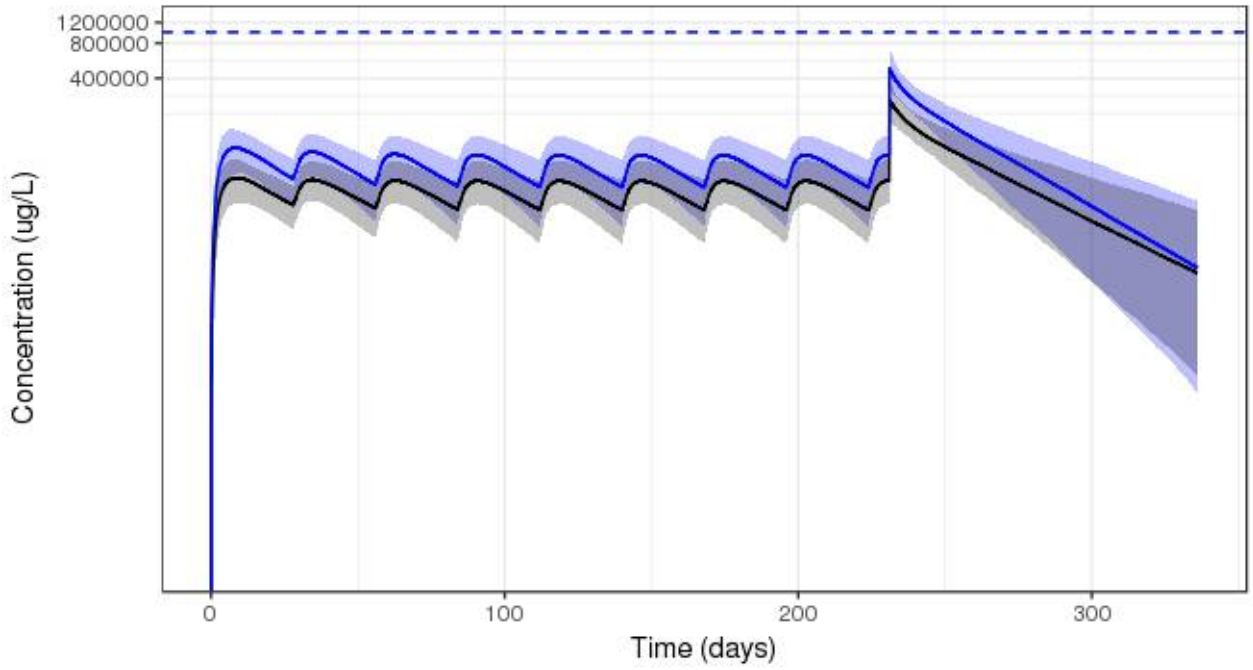


Figure 4.1.2:1 Expected exposure profile

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 is confirmed, patients will be randomized to blinded treatment arms according to a randomization plan in a 1:1:1:1 ratio. Randomization will be stratified by the stratification factor, concomitant use of systemic GPP medications at randomization (yes versus no) (see Section 7.4) and the blocking factors, region (Japan versus Non-Japan) and population (Adults versus Adolescents) (see Section 7.4). The assignment will occur in a blinded fashion via Interactive Response Technology (IRT).

At randomization as well as subsequent medication administration visits (including rescue treatment administration visit (s) with OL BI 655130 in the event that a patient experiences a GPP flare), IRT will assign medication numbers. Note that the medication number is different from the patient number (the latter is generated during screening via the IRT System). Each syringe and vial will have an individual medication number for dispensation.

4.1.4 Drug assignment and administration of doses for each patient

Prior to each administration of study drug, a urine pregnancy test will be performed on site. If this test has a positive result, the administration of study drug should not proceed and this urine test should be confirmed by a serum pregnancy test.

To maintain the treatment blind during the trial, all patients will receive 4 injections at Week 1/Day 1 for the loading dose followed by 2 injections at subsequent dosing visits in the every 4 weeks schedule.

Table 4.1.4: 1 Treatments used in this trial

	Randomized Maintenance Treatment Period	
Arm	**Loading Dose (Blinded) Week 1/Day 1**	**Maintenance Treatment (Blinded) Week 4 through Week 44**
Arm 1: 300 mg BI 655130 q 4 weeks	4 x BI 655130 150 mg/PFS	2 x BI 655130 150 mg/PFS s.c. q4 weeks
	Maintenance Treatment Period	
Arm	**Loading Dose (Blinded) Week 1/Day 1**	**Maintenance Treatment (Blinded) Week 4 through Week 44**
Arm 2: 300 mg BI 655130 q 12 weeks	4 x BI 655130 150 mg/PFS	2 x BI 655130 150 mg/PFS s.c. q12 weeks (i.e. at Week 12, Week 24, Week 36) 2 x Placebo to match Solution for Injection (BI 655130), 1mL PFS, at the intervening visits (i.e. at Week 4, Week 8, Week 16, Week 20, Week 28, Week 32, Week 40 and Week 44)

Table 4.1.4:1 (cont'd) Treatments used in this trial

	Maintenance Treatment Period	
Arm	**Loading Dose (Blinded) Week 1/Day 1**	**Maintenance Treatment (Blinded) Week 4 through Week 44**
Arm 3: 150 mg BI 655130 q 12 weeks	2 x BI 655130 150 mg/PFS 2 x Placebo BI 655130 150mg/ml, 1mL PFS, 0mg/syringe	1 x BI 655130 150 mg/PFS 150 mg s.c. + 1 x Placebo to match Solution for Injection (BI 655130), 1mL PFS s.c. q12 weeks (i.e. at Week 12, Week 24, Week 36) 2 x Placebo to match Solution for Injection (BI 655130), 1mL PFS at the intervening visits (i.e. at Week 4, Week 8, Week 16, Week 20, Week 28, Week 32, Week 40 and Week 44)
Arm 4: Placebo	4 x Placebo BI 655130 150mg/ml, 1mL PFS, 0mg/syringe	2 x Placebo to match Solution for Injection (BI 655130), 1mL PFS s.c. q4 weeks
	In case of a GPP Flare	
	Rescue Treatment (Open Label) at R1/Day 1 Or at R1/Day1 & R3/Day8	**Maintenance Treatment (Open Label)**
	2 x BI 655130 450 mg/vial (60 mg/mL)	2 x BI 655130 150 mg/PFS s.c. q12weeks Or 2 x BI 655130 150 mg/PFS s.c. q4weeks (intensified maintenance therapy)

During the randomized maintenance treatment period (Blinded) and maintenance treatment period (Open Label), the treatment will be administered subcutaneously. Injections during randomized maintenance treatment period will be given in a double blind fashion. Injections being given in the same area should be at least 2 cm apart and should not be close to a vein. The injection site should avoid sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses. Detailed instructions for administration of the s.c. injections are provided in the ISF.

OL 900 mg BI 655130 i.v. dose(s) will be used as GPP flare treatment, followed by a maintenance dosing schedule with OL 300 mg BI 655130 s.c. q12 weeks (and subsequently OL 300 mg BI 655130 s.c. q4 weeks, if needed). 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 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 (3 hours). Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for 1 hour following the end of i.v. study drug administration. Hypersensitivity reactions should be treated according to medical standards. Further based on his/her medical judgment the investigator will provide medications as needed. Detailed instructions for the preparation of the i.v. infusion solution, the volume to be administered and the infusion rate are provided in the ISF.

Subcutaneous administration of biologic agents may involve the risk of local (injection site) or systemic hypersensitivity reactions. Therefore, patients should be closely monitored for signs and symptoms of injection site or systemic hypersensitivity reactions following study drug administration. Study personnel should observe the injection site for signs of redness, swelling or hardness. They should also ask subjects about itching, dizziness or shortness of breath. Patients should be advised that if they experience redness, swelling or other changes at the injection site, they should notify site personnel. They should further be advised that if they experience itching all over or a feeling of being swollen, dizzy or short of breath, they should notify site personnel or their own healthcare provider immediately. Pre-medications for further injections might be considered and will be agreed on between investigator and BI clinical monitor (see also Section 6.2.2).

The administration of the study medication will be done under supervision of the investigating physician or a designee at the site.

Dose modifications or adjustments are not permitted. In exceptional cases of missed or delayed visits, if any of these visits has to be rescheduled, the date of subsequent visit should be calculated from Day 1. In case of missed visits (during the randomized treatment trial period), the patients should be given the assigned medication for both visits (i.e. up to 1 missed visit and the current visit) at the next scheduled visit.

During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient's safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and the administration of the study medication may be performed at patient's home under the supervision of the investigating physician or a designee. The trial medication may be shipped to the patient's home if acceptable according to local law and regulations. This must be approved by the sponsor's trial team.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

To maintain the treatment blind during the trial, all patients will receive the blinded treatments every 4 weeks. Please refer to Section 4.1.4 and Table 4.1.4: 1 for further details.

The sponsor will remain blinded with regard to the randomized treatment assignments until the last randomized patient has completed or early discontinued from the 48 week treatment period of the trial and the database is considered ready for unblinding to perform the primary analysis of the trial. Note that for the planned interim analysis of this trial (see details in Section 7.2.7), only clinical efficacy and safety data for the OL i.v. rescue treatment and OL s.c. maintenance treatment periods are intended to be reported; no unblinding of the initial randomized s.c. treatments is required..

With database lock for the primary trial analysis, the sponsor (including all trial personnel) will be officially unblinded to the randomization details; investigators and patients will remain blinded until the official end of the trial (final trial analysis) when the last patient has completed through 16 weeks of trial safety follow-up (if applicable).

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 bioanalytics prior to last patient out of the trial to allow for the exclusion from the analyses of PK samples taken from placebo patients. Bioanalytics will not disclose the randomization code or the results of individual measurements until the trial has been officially un-blinded to the sponsor. Sample drug levels and demographic data together with treatment assignments and dosing information may be made available to named individuals from the bioanalytics department for the purpose of PK dataset generation and analysis in accordance with the 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 / designee 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 eCRF 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 randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal 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). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the CT Manager, as provided in the list of contacts, must be contacted immediately.

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

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

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

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse /

drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

All concomitant medications should be carefully evaluated by the investigator and the Clinical Trial Manager (CTM) should be contacted when there are questions regarding concomitant medications.

The use of Investigator Prescribed SoC will lead to the discontinuation of the trial treatment except for the use of topical treatment/topical corticosteroids, methotrexate, cyclosporine and retinoids during OL rescue treatment period (4 weeks following i.v. dose rescue treatment with OL BI 655130 at R1/D1) and OL maintenance treatment period. Please refer to section 4.2.2.2 and section 3.1 for further details. Also, please refer to section 3.3.4.1 for further details on handling of patients with premature treatment discontinuation.

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/injection of study medication, the investigator should consider in accordance with severity of the reaction and local standard of care to

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

Also draw a plasma sample for IgE and ADA and a serum sample for neutralizing antibody (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] in ISF) 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 (3 hours).

In case of anaphylactic reactions based on published criteria (Appendix 10.1.6; R11-4890) that are suspected to be caused by the study 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, 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: refer to 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 study 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.

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 before randomization

The medications (or classes of medications) listed in Table 4.2.2.1: 1 must not be taken for the time periods as specified for washout.

Table 4.2.2.1: 1 Restricted medications

Medication or class of medications	Restriction duration
Biologic Treatments, e.g.: secukinumab (Cosentyx®), tildrakizumab (Ilumya™) , rituximab, ustekinumab (Stelara®), risankizumab (Skyrizi™) natalizumab, alemtuzumab, guselkumab (Tremfya®), ixekizumab (Taltz®), adalimumab (Humira®), brodalumab, efalizumab, visilizumab, briakinumab. infliximab (Remicade®), certolizumab (Cimzia®)	12 weeks or 5 half-lives, whichever is shorter, prior to Visit 2 (randomization)
Investigational products for psoriasis	12 weeks or 5 half-lives, whichever is shorter, prior to Visit 2 (randomization)
IL36R inhibitors	Not allowed
Etanercept (Enbrel®) live virus vaccinations[2]	6 weeks prior to Visit 2
Any investigational device or product (excludes psoriasis products) Other systemic immunomodulating treatments (e.g. corticosteroids[1], cyclophosphamide), tofacitinib (Xeljanz®), apremilast (Otezla®) Other systemic psoriasis treatments (e.g. fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g., PUVA).	4 weeks prior to Visit 2
GMA (Granulocytes and monocytes adsorptive apheresis)[2]	4 weeks prior to Visit 2

(Contd. See next Page)

Table 4.2.2.1: 1 Restricted medications (cont'd)

Medication or class of medications	Restriction duration
Topical corticosteroids	Must be stopped at the day of randomization.
Anakinra (Kineret®)	7 days prior to Visit 2
methotrexate, cyclosporine, retinoids	Must be stopped at the day of randomization. Patients can be on these background medications at screening visit (V1), however they can only be randomized (V2) into this trial on the day of their next scheduled dose for the background treatment (where the patient should not take the dose) but instead be randomized on the trial.

[1]No restriction on inhaled corticosteroids to treat asthma or corticosteroid drops administered in the eye or ear.
[2] Live virus vaccination and use of GMA should be restricted until the end of the trial.

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

4.2.2.2 Restrictions regarding concomitant treatment during the trial (Post V2)

The following listed medications are not permitted throughout the study participation unless they are prescribed by investigators to treat disease worsening of GPP. However it is strongly recommended not to prescribe SoC even for GPP disease especially when patients are on the randomized treatment (See details about investigator-prescribed SoC for GPP disease in Section 3.1 and Section 4.2.1). The use of Investigator Prescribed SoC for GPP will lead to the discontinuation of the trial treatment with some exceptions as described below.

Biologic Treatments:
Treatment with biologics are not allowed throughout the study.

Topical Treatments:
Topical treatment and any other therapies (e.g. Phototherapy) for GPP are not allowed throughout the study with the following exceptions:

- Topical treatment for other conditions (e.g. fungal infections, plaque psoriasis etc.) is allowed.
- Topical treatment is permitted for treatment of GPP after 4 weeks following i.v. dose rescue treatment with OL BI 655130 at R1/D1.
- Topical treatment is permitted for treatment of GPP during the OL maintenance treatment period.

Topical corticosteroids:

Topical corticosteroids for the treatment of GPP are not allowed throughout the study with the following exceptions:

- Topical corticosteroid for other conditions (e.g. fungal infections, plaque psoriasis etc.) may be initiated post visit 2 if needed.
- Topical corticosteroid is permitted for treatment of GPP after 4 weeks following i.v. dose rescue treatment with OL BI 655130 at R1/D1.
- Topical corticosteroid is permitted for treatment of GPP during the OL maintenance treatment period.

Systemic Immunomodulating Treatments:

Systemic immunomodulating treatments (e.g. corticosteroids, cyclophosphamide), tofacitinib (Xeljanz®), apremilast (Otezla®) and other systemic psoriasis treatments (e.g. fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g., PUVA) for the treatment of GPP are not allowed.

Methotrexate, Cyclosporine, Retinoids:

- **Randomized Treatment Period:** Treatment with Methotrexate, Cyclosporine, Retinoids are not allowed.
- **Rescue Treatment Period and Open Label Maintenance Treatment Period**: Methotrexate, Cyclosporine, or Retinoids may be allowed for the treatment of GPP only for those who have received a flare rescue treatment with i.v. dose of BI 655130 and have a partial response to the rescue treatment as following.

After at least 4 weeks from the rescue treatment at R1/D1, it is recommended to first initiate treatment with topical corticosteroids to manage skin symptoms, and then if further adjunctive treatment is required, then methotrexate, cyclosporine and/or retinoids may be initiated and continued with stable dosing until the patient achieves GPPGA score 0 or 1 or as per the investigator's judgement.

Other Medications/Products:

Treatment with the following medications/products are not allowed throughout the study.

- Investigational products for psoriasis
- IL36R inhibitors
- Etanercept
- Live virus vaccinations
- Any investigational device or product (excludes psoriasis products)
- Anakinra (Kineret®)
- GMA (Granulocytes and monocytes adsorptive apheresis)

4.2.2.3 Restrictions on diet and life style

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

4.2.2.4 Contraception requirements

Women of childbearing potential must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during the trial, and for a period of at least 16 weeks after the last study drug administration. A list of contraception methods meeting these criteria is provided in the patient, parent(s) (or patient's legal guardian) information.

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

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

4.3 TREATMENT COMPLIANCE

Administration of the study medication will be done in the study center (or at home in exceptional cases such as COVID-19 pandemic where physical visits to the clinic may not be possible. See section 4.1.4 and section 6.1 for additional details) 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, key secondary, secondary and further endpoints of the study are specified in Sections 2.1.2 and 2.1.3, and 2.2.2, respectively.

Skin condition will be assessed by using the Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) [redacted]

In addition to the above assessments, patient reported outcomes such as PSS, [redacted] DLQI, [redacted] will also be collected/assessed.

Additional details for efficacy assessments evaluated in this study 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 time points noted in the study Flow Chart 1 or Flow Chart 2 (as applicable).

[redacted]

PSS (Psoriasis Symptom Scale)

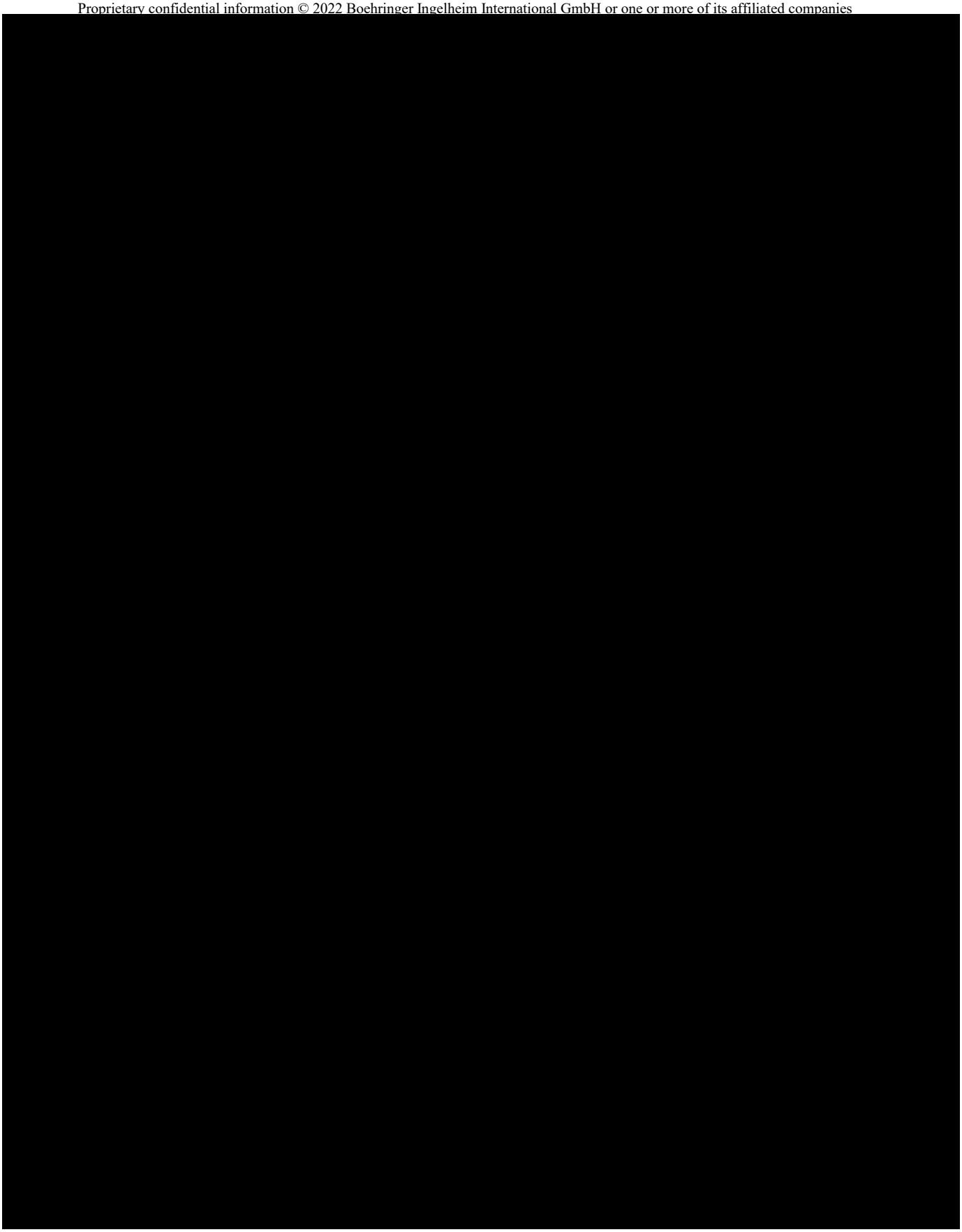
The PSS is a 4-item patient-reported outcome (PRO) instrument that was developed to assess the severity of psoriasis symptoms in patients with moderate to severe psoriasis (R18-1990). When completing this questionnaire, patients should report on symptoms experienced from their Generalized Pustular Psoriasis. 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; this will be measured at the timepoints noted in Flow Chart 1 or Flow Chart 2 (as applicable).

DLQI (Dermatology Life Quality Index)

The DLQI is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment (R05-2548). The DLQI has a one-week recall period. Response categories include “not relevant” (score of 0), “not at all” (score of 0), “a little” (score of 1), “a lot” (score of 2) and “very much” (score of 3). Question 7 is a “yes”/ “no” question where “yes” is scored as 3. DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0-1 = no effect on patient’s life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on patient’s life. The higher the score, the more the quality of life is impaired. A 4-point change from baseline is considered a clinically important difference (R18-1988).

The DLQI Instrument is provided in Appendix 10.1.10; this will be measured at the timepoints noted in Flow Chart 1.



[redacted]

5.2 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Treatment Emergent Adverse events
- Adverse events of special interest (AESI)
- Serious adverse events (SAEs)
- Clinical laboratory values (haematology, clinical chemistry, coagulation and urinalysis)
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to ISF for details)
- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-lead ECG
- Immunogenicity (ADA)

5.2.1 Physical examination

Complete and targeted physical examinations will be performed at visits as described Flow Chart 1 or Flow Chart 2 (as applicable). 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 1or Flow Chart 2 (as applicable), prior to blood sampling. 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 s.c. administration, vital signs will be assessed pre-dose and 10 minutes after the end of drug administration and at Visit 2 and Visit 3 additional measurements will be performed approximately 60 minutes post-dose (i.e. 60 min. after last injection).

At the visit with i.v. administration, vital signs will be assessed pre-dose, at approximately 5 minutes after the end of infusion and 1 hour after the end of infusion.

In addition to the temperature being measured along with the vital signs at time points shown in the Flow Chart 2, fever (temperature) will also be assessed at the day the patient presents to the clinic/hospital with GPP flare and prior to IMP administration. If the patient will receive medication for fever treatment, the fever assessment will be performed prior to taking the anti-fever treatment. This fever assessment must be taken whether or not the patient has an elevated temperature and whether or not the patient takes anti-fever treatment.

At the visit with i.v. study drug administration, patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 1 hour after the end of study drug administration. Hypersensitivity reactions should be treated according to medical standards.

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 1 or Flow Chart 2 (as applicable). Patients do not have to be fasted for the blood sampling for the safety laboratory.

The parameters that will be determined are listed in Table 5.2.3: 1. The laboratory tests will be performed at a central laboratory. Instructions regarding sample collection, sample handling/processing and sample shipping are included in the laboratory manual in ISF.

However, local labs are to be used at visit(s) involving i.v. administration of open label BI 655130 in the event a patient has a GPP flare. 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 will be drawn and sent to the central laboratory for analysis. It is highly encouraged to collect and assess the labs the day of i.v. administration; however in exceptional cases, labs may be collected one day prior to ensure lab results are available prior to dosing.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings (e.g. anemia, hypoproteinemia, hypoalbuminemia, hypocalcemia etc.) as judged by the investigator will be reported as adverse events (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1 and the DILI Checklist provided in the 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.

The central laboratory will transfer the results of the analysis to the sponsor.

Table 5.2.3: 1 Safety laboratory tests

Category	Test name
Haematology	Haematocrit 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 Glucose BUN (blood urea nitrogen) Uric acid eGFR (estimated by CKD-EPI formula for adults and Bedside Schwartz Equation for adolescents) (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 blood Urine leukocyte esterase Urine pH

Table 5.2.3: 1 Safety laboratory tests (cont'd.)

Category	Test name
Infection testing	Hepatitis B Surface Antigen (qualitative)[1] Hepatitis B core Antibody[1] HBV-DNA (quantitative) at baseline[1] and EoS Visit[2] QuantiFERON® (or if applicable, T-Spot®) TB[1,3,4,5] Hepatitis C Antibodies (qualitative) [1] HIV-1, and HIV-2 Antibody (qualitative) [1]
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. For patients who sign the informed consent ≥ 4 weeks prior to V2, infection testing must be repeated 2 to 4 weeks prior to V2.

[2]An HBV-DNA test should be conducted if Hepatitis B core Antibody is positive and Hepatitis B Surface Antigen is negative. These evaluations should be conducted at screening and EoS.

[3]There is a trial site option to perform a tuberculin skin test (i.e. PPD skin test) or any alternative test/procedure (as per local standards) to rule out TB if the retest QuantiFERON-TB test result is indeterminate (see footnote 4 below for details).

[4]If the 1st QuantiFERON® (or if applicable, T-Spot®) -TB test result is indeterminate, a retest should be performed. If the retest QuantiFERON-TB test result is indeterminate, a tuberculin skin test (i.e. PPD skin test) or any alternative test/procedure (as per local standards) to rule out TB should be performed at the site.

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

[5]In subjects with a negative QuantiFERON®-TB or tuberculin skin test (i.e. PPD skin test) or alternative test/procedure (as per local standards), the test should be repeated at EoS.

<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 1 or Flow Chart 2 (as applicable).

Table 5.2.3: 2 Laboratory tests to be assessed prior to i.v. rescue treatment with open label BI 655130 in an event of a GPP flare (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 for adults and Bedside Schwartz Equation for adolescents)
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 2.

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 Flow Chart 1 or Flow Chart 2 (as applicable). 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 Other safety parameters

Local tolerability at the administration site of BI 655130 /placebo will be assessed by the investigator during the study drug administration visit (i.v. or s.c.) and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. "swelling", "induration", "heat", "redness", "pain", and, "other findings" should be reported as adverse event.

Grade the intensity of the local tolerability according to RCTC grading (cf. ISF).

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 AEs

5.2.6.1.1 Adverse event

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

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

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

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

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

5.2.6.1.2 Serious adverse event

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

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

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

5.2.6.1.3 AEs considered "Always Serious"

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

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in Section 5.2.6.2.

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.2.6.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 Adverse events of special interest

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

The following are considered as AESIs:

Hepatic injury
A 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

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

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).

Peripheral Neuropathy

Any event suspected or diagnosed as Peripheral Neuropathy would be considered as an AESI. For the treatment interruption rules, please see Section 3.3.4.1.

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).

5.2.6.1.5 Intensity (severity) 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

5.2.6.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

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

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

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

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

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

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 study:
  - all AEs (serious and non-serious) and all AESIs.

- After the individual patient's end of study:
  - the investigator does not need to actively monitor the patient for AEs but should only report any occurrence of cancer and 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.

Vital Status Data Collection

Patients who discontinue trial medication prematurely and who agree to be contacted further but do not agree to physical visits, should be followed up as described in Section 3.3.4.1, withdrawal from trial treatment. From then on until the individual patient's end of the trial the investigator must report all deaths/fatal AEs regardless of relationship, and trial treatment related SAEs and trial treatment related AESIs the investigator becomes aware of.

Please refer to Flow Chart 1 or Flow Chart 2 (as applicable) for additional details on vital status collection time points.

5.2.6.2.2 AE reporting to the sponsor and timelines

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

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

5.2.6.2.3 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 1 or Flow Chart 2 (as applicable).

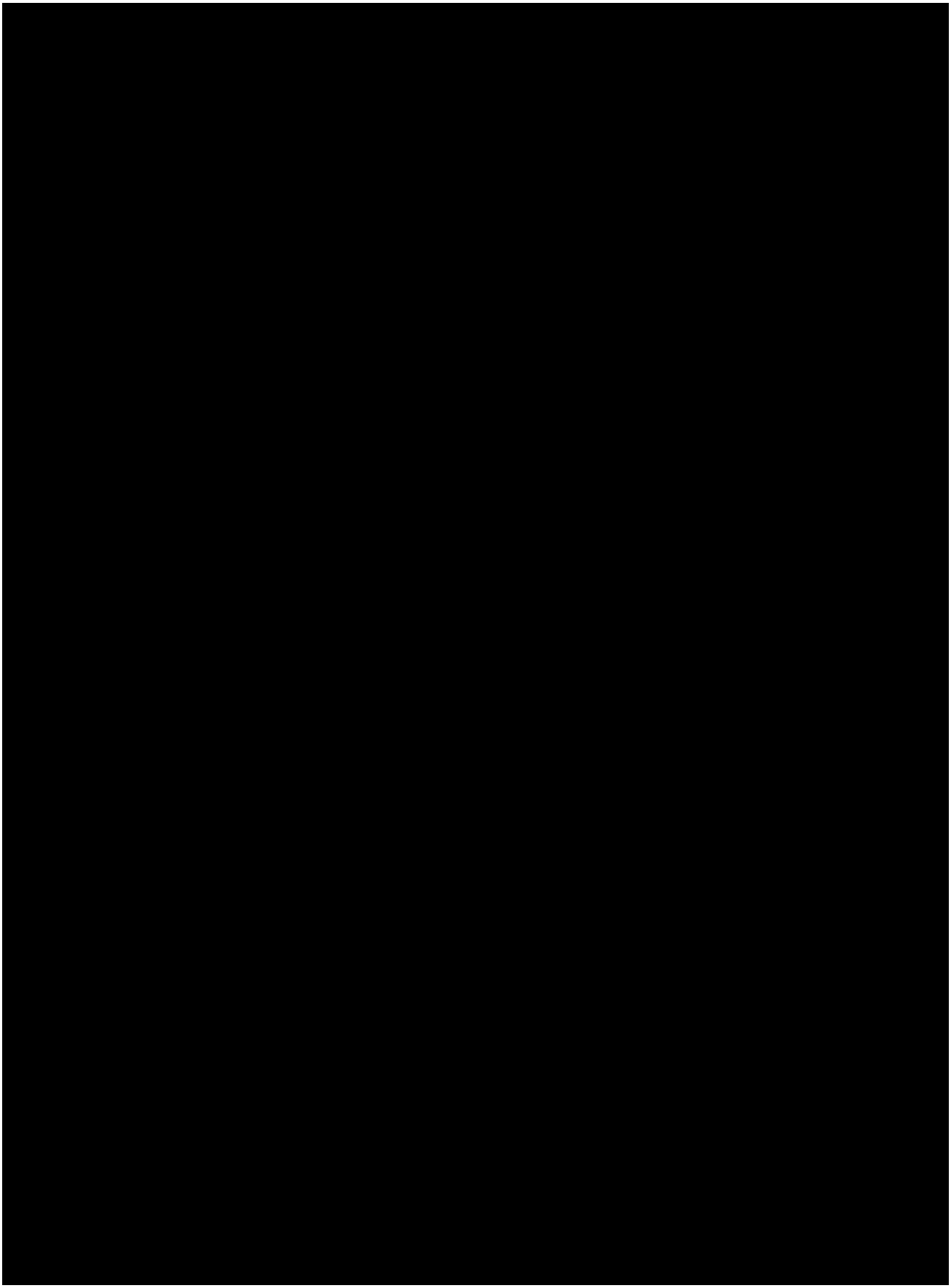
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring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

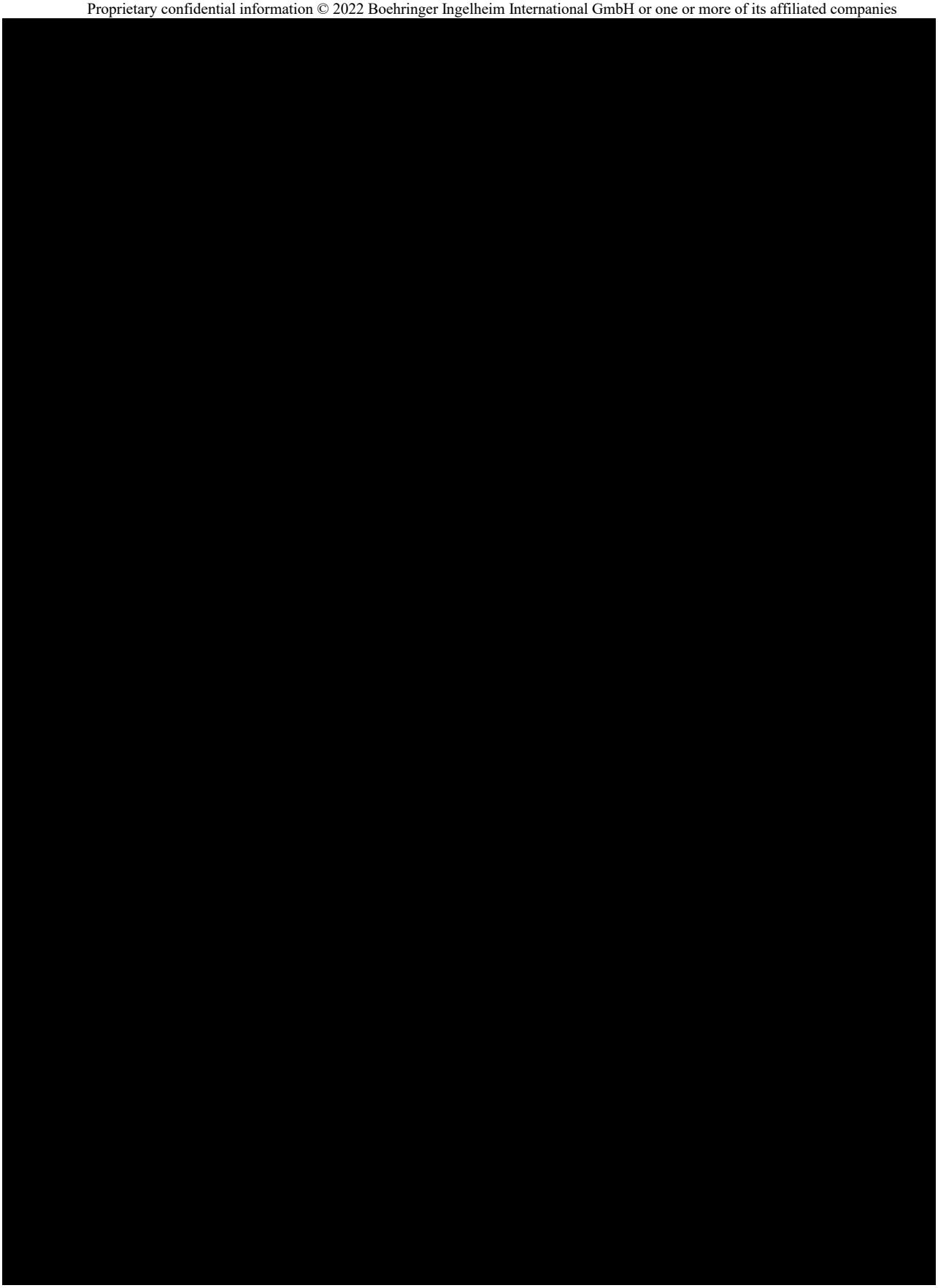
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).

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

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

[redacted]





5.6 OTHER ASSESSMENTS

Photography of skin/skin lesions (irrespective of presence of lesions or not) will be performed in all patients for additional documentation. Front and back trunk, legs and arms, as well as target lesions photographs will be taken preferably at the time points specified in the Flow Chart 1 and Flow Chart 2 per instructions in the ISF. Patients must be unrecognizable on the photos (refer to the procedure in the ISF).

5.7 APPROPRIATENESS OF MEASUREMENTS

The safety assessments are standard, are accepted for evaluation of safety and tolerability of both subcutaneous and 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 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

For investigational sites where patients below 18 years of age will be enrolled, trial visits should take place at a location within the clinical site that has a child-friendly infrastructure (e.g. an environment that is familiar to the patients, the setting is physically appropriate, if desired by the patient, parent(s)/legal guardian are allowed to stay with them during the trial procedures). Furthermore, site-personnel should be knowledgeable and skilled in dealing with the pediatric population and its age-appropriate needs.

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule specified in the Flow Chart 1 or Flow Chart 2 (as applicable).

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 !"#$"%$#&)(*+, *#-(+,./#&.+- 0.1.&23. 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 1 or Flow Chart 2 (as applicable).

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

In exceptional cases, if standard visits at the trial sites are impossible because of COVID-19 related safety risks or restrictions, the study visit may be performed at the patient's home or remotely (via telephone and/or internet based means of communication). The visit may also be performed as a combination of home and remote visit (via telephone and/or internet based means of communication). The study drug administration may be performed at patient's home under the supervision of the investigating physician or a designee. The trial medication may be shipped to the patient's home if acceptable according to local law and regulations.

All home/remote visits need to be discussed with and approved by the sponsor's trial team. Local regulatory and legal requirements of the participating country still apply.

All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart 1 or Flow Chart 2 and respective sections of this protocol. Refer to Section 5 for explanations of the specified assessments and procedural details.

The patients' questionnaires (PSS, DLQI, [redacted]) are to be completed 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 manner as possible. If this is not possible either, the questionnaires are not to be completed.

At each applicable visit (see Flow Chart 1 or Flow Chart 2 as applicable), the order of completion for PROs is recommended to be as follows:

[redacted]

PRO collection and completion for Adolescent Patients:
[redacted].
Adolescent patients below age 16 (i.e. 12 -15 years) do not have to complete DLQI and SF-36. All other PROs (PSS, [redacted] are to be completed by all adolescent patients. If adolescent patients do not feel comfortable answering any questionnaires, they may not be completed. For adolescent patients, PSS [redacted] are the most important questionnaires which may be prioritized over the others.

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

[redacted]

Safety laboratory tests
If blood sampling for central lab safety analyses at the trial site is not possible in exceptional cases (e.g., due to COVID-19 pandemic), these analyses can be performed at a local lab until central lab testing becomes available. The results of the local lab tests must be transferred to the investigator to ensure medical review and proper documentation of the lab results with clinical relevance for safety in the eCRF. For the minimum required safety lab parameters, follow Table 5.2.3: 2.

6.2.1 Screening and run-in period(s)

Screening Period

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. The importance of staying in the study until completion of all requirements is to be emphasized.

Screening (Visit 1) should normally take place no more than 84 days before Visit 2. Visit 1 procedures may be completed over multiple physical visits, if needed. For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to Flow Chart 1.

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).

Medical History:
Regarding the GPP, a detailed history of the previous flares (frequency, intensity etc.) in the past will be collected and reported in eCRF. Also, previous and concomitant treatment for GPP will be reported.

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.

[redacted]

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 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. Rescreening transaction must be registered in the IRT system. A new patient number will be provided which will be linked to the previous patient number in the IRT system. 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 1.

6.2.2 Treatment period(s)

The treatment period is lasting from V2 until V14/End of Study 1 (EoS1) visit. Study related procedures during treatment period will be performed as specified in the Flow Chart 1 or Flow Chart 2 (as applicable).

Upon completion of screening and confirmation of patient eligibility, patients will be randomized to receive one of four treatments. Please refer to Section 4.1.4 and Table 4.1.4:1 for further details.

Administration of the study drug should be the last activity at visits with study drug administration, with the exception of post dose vital signs assessments. Details relating to study drug administration are provided in Section 4.1.4.

Please refer to Section 3.1 for additional details on Handling of GPP flares and Handling of Investigator Prescribed Standard of Care (SoC) for GPP disease. For details of trial procedures please follow Flow Chart 1 or Flow Chart 2 (as applicable).

For information pertaining to laboratory tests, ECG, vital signs, local tolerability, and physical examination, see Section 5.2.

Skin/Skin lesion photographs will be taken on site at visits specified in Flow Chart 1 or Flow Chart 2 (as applicable) and are to be taken prior to study drug administration (for details see Section 5.6).

Pregnancy Testing
Urine pregnancy testing for all women of child-bearing potential will be conducted on-site at visits with study drug administration and must be negative to continue treatment. More frequent testing should be done if required by the local regulation and / or authority or per investigator judgment.

The pregnancy testing should be done **prior to** study drug administration. A positive urine test must be confirmed with a serum pregnancy test.

Blood Sampling
Blood sampling (e.g., for safety lab) should be done **prior to** study drug administration, if applicable. Fasting is not required for blood sampling.

For information pertaining to [redacted], ADA/Nab, [redacted], see Sections 5.3 and 5.4. Blood sampling for PK assessments should be done within **2 hours prior to** study drug administration**.**

Clinical monitoring after study drug administration:
At visits with s.c. study drug administration, vital signs will be assessed pre-dose and at approx. 10 minutes after the end of study drug administration(s) and at Visit 2 and Visit 3 additional measurements will be performed approximately 60 minutes post-dose (i.e. 60 min after last injection). Local tolerability at the administration site of BI 655130 /placebo will be assessed by the investigator during the study drug administration (i.v. or s.c.) visits [as noted in the Flow Chart 1 or Flow Chart 2 (as applicable)]. and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. “swelling”, “induration”, “heat”, “redness”, “pain”, and, “other findings” should be reported as adverse event.

They should also ask subjects about itching, dizziness or shortness of breath. Patients should be advised that if they experience redness, swelling or other changes at the injection site, they should notify site personnel. They should further be advised that if they experience itching all over or a feeling of being swollen, dizzy or short of breath, they should notify site personnel or their own healthcare provider immediately.

During i.v. drug administration, vital signs will be assessed pre-dose, at approximately 5 minutes after the end of infusion, and 1 hour after the end of infusion. Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 1 hour after the end of infusion. Hypersensitivity reactions should be treated according to medical standards.

Unscheduled visits
The investigator should encourage patients to return to the clinic/site at the first sign of onset of a GPP flare. If a patient suspects that they have a GPP flare in between the protocol specified scheduled visits, they should make an unscheduled visit and return to the clinic/site for assessment.

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

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

Concomitant medication review
Data concerning concomitant medications and procedures will be collected throughout the trial, as specified in the Flow Chart 1 or Flow Chart 2 (as applicable). These data will be obtained at scheduled or unscheduled trial visits based on information provided in the patient diaries, provided spontaneously by the patient or as a result of questioning the patient.

6.2.3 Follow-up period and trial completion

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

V14 will be recorded as the End of Study visit (i.e., EoS1) for patients who qualify and agree to enter the OLE trial (1368-0025). V14 will also be recorded as End of Study Visit for patients who prematurely discontinue with the last dose of treatment up to and including Day 232 and who agree to complete all remaining study visits up to Wk 48 from randomization. Since these patients prematurely discontinued, they would not qualify to enter OLE trial.

The EoS2 visit is applicable for patients who do not qualify or who do not agree to enter into the OLE trial (1368-0025) at Week 48. EoS2 is also applicable for patients who prematurely discontinue with the last dose of treatment after Day 232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial.

End of Study visit must be registered in IRT system for all randomized patients.

Please refer to Section 3.3.4.1 for further details on handling of patients with premature treatment discontinuation.

Early Randomized Treatment Discontinuation:

Patient who discontinue randomized study treatment early prior to week 44. These patients should be registered as withdrawn from randomized treatment in IRT.

Early Trial Discontinuation:

Patient who will not enter OLE trial and has not reached the end of study visit, EoS1 or EoS2 visit within the specified window per protocol (e.g. due to withdrawal of consent, lost to follow-up, death etc.).

Trial Completion
Trial completion for an individual patient is defined as a patient who has completed end of study visit per protocol. It could be EoS1 visit or EoS2 visit as defined above.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The trial is designed as a randomized, parallel group, double blind, placebo controlled, dose finding study to show superiority in the prevention of re-occurrence of flares for administration of BI 655130 300 mg q4w (high dose), 300 mg q12w (medium dose), and 150 mg q12w (low dose) respectively versus placebo in patients with a history of GPP (per ERASPEN criteria) and with a GPPGA score of 0 or 1 (clear, or almost clear) at screening and at randomization.

Primary Objective
The primary objective is to provide dose-ranging data for 3 dose regimens of BI 655130 compared to placebo on the primary endpoint of the time to the first GPP flare onset up to week 48. Proof of concept for the activity of BI 655130 will be determined using a multiple comparison procedure with modelling techniques (MCPMod) with respect to achieving a non-flat dose response curve, while keeping full control of the type I error at 0.05, one-sided. To achieve this, the log hazard ratio of each active dose vs. placebo is first obtained via a Cox regression model on the time to first GPP flare. These estimates are the basis then for the non-flat dose response MCPMod assessment.

Secondary Objective
If the primary objective regarding achievement of a non-flat dose response curve is successful, the secondary objective will then be performed, which is to perform formal testing on the superiority of BI 300 mg q4w and/or BI 300 mg q12w versus placebo, on the primary endpoint, the time to the first GPP flare onset up to week 48, and on the key secondary endpoint, the occurrence of at least one GPP flare during the 48 week maintenance treatment period. The target number of patients with GPP flare events in this trial is 27 but note that the actual number of events observed until primary analysis is driven by the time-point of the analysis.

A formal statistical hypothesis test will first be performed, at an overall 1-sided alpha level of 0.025, on the primary endpoint of time to first GPP flare up to week 48. A stratified log-rank test will be implemented for each dose of BI 300 mg q4w (high dose) and BI 300 mg q12w (medium dose) versus placebo, with stratification by the factor, concomitant use of systemic GPP medication at randomization (yes or no), and multiplicity will be controlled by the truncated Hochberg procedure (using a truncation fraction of 0.5). Subsequently, formal testing of all other endpoints included in the testing hierarchy (i.e. the key secondary, and then the secondary endpoints) will be performed, if the test on the primary endpoint is successful for at least one of the two doses (high or medium dose) of BI 655130.

The analysis of the key secondary endpoint for the proportion of patients with the occurrence of at least one GPP flare up to week 48 will be conducted subsequent to the test on the primary endpoint using a Cochran-Mantel Haenszel test, stratified by the factor concomitant use of systemic GPP medication at randomization (yes or no), for each of BI 655130 high and medium doses versus placebo. A truncated Hochberg procedure will be used to control for multiplicity on the tests of the key secondary endpoint, at an overall 1-sided alpha level of

0.025, if both doses were statistically significant on the test of the primary endpoint. If only one (high or medium) dose of BI 655130 was statistically significant on the test of the primary endpoint, then the same dose will be tested on the key secondary endpoint with a 1-sided alpha of 0.00625 (see Section 7.1 for further details). If neither dose is declared to be statistically significantly superior to placebo for the primary endpoint, then no further testing in the hierarchical sequence will be conducted. Subsequent tests on the secondary endpoints included in the testing strategy (i.e. the time to first worsening of PSS up to week 48, and then on the time to first worsening of DLQI up to week 48), as well as tests on the primary and key secondary endpoints for the lowest dose of BI 655130 150 mg q12w versus placebo, are described in detail in Section 7.1.

The primary analysis of the trial will be done once all patients randomized have either completed or discontinued from 48 weeks of treatment. The primary endpoint analysis may include more than the target number of patients with a GPP flare event. In this situation, it is not planned to perform an additional analysis of the primary endpoint whereby the exact number of target patients with a GPP event only are included.

To support a potential BI 655130 acute GPP flare treatment submission, an interim analysis of the clinical efficacy and safety data collected during the BI 655130 OL i.v rescue and s.c. maintenance treatment periods may be performed. For further details refer to Section 7.2.7.

The stratification factor, concomitant use of systemic GPP medications at randomization (yes or no) and the blocking factors, region (Japan or Non-Japan) and population (Adults versus Adolescents) will be included into the randomization of this trial. The blocking factors of region is implemented to ensure that sufficient patients per treatment group are recruited specifically to support individual country submission in Japan and the blocking factors of population is implemented to ensure there will be paediatric patients randomized to each treatment group to support paediatric investigational plan. The two blocking factors are not intended to be used as an adjustment factor in the primary and key secondary analyses of efficacy (See Section 7.2).

7.1 NULL AND ALTERNATIVE HYPOTHESES

The null and alternative hypotheses are described below. Statistical testing will be performed based on one-sided hypotheses with corresponding one-sided p-values. Note that for publication purposes also two sided p-values may be derived if needed. Details of this will be specified in the TSAP.

Primary objective: Dose Finding
The null hypothesis is that there is a flat dose response curve comparing the placebo and the BI 655130 dose groups. The alternative hypothesis is that there is a non-flat dose response curve indicating a benefit of BI 655130 over Placebo.

The MCPMod procedure allows for simultaneous evaluation of different potential dose response shapes, whilst protecting the false positive rate using a one-sided level α of 0.05. The pre-specified models and their parameters used for this test are outlined in Section 7.2.2.

Secondary objective: Formal Statistical Testing

If the primary objective regarding the achievement of a non-flat dose response curve is successful, the secondary objective will then be performed, which is to perform formal pairwise testing on the superiority of the high and medium doses of BI 655130 versus placebo, on each of the endpoints included in the statistical testing hierarchy as described below.

Formal testing of all trial endpoints in the testing hierarchy (primary, key secondary, and secondary endpoints) will be performed at a one-sided alpha level of 0.025. The overall testing strategy used to control the type I error for each of the endpoints and for each of the treatments is described below. Overall the testing strategy will follow a closed testing principle defining five families of endpoints/comparisons. The first family and the second family consist of the primary and key secondary endpoint comparisons for the high and medium doses of BI 655130 vs placebo respectively. The third family consists of the secondary endpoint comparisons on the time to first worsening of PSS for the high and medium dose of BI 655130 vs placebo. The fourth family consist of the secondary endpoint comparisons on the time to first worsening of DLQI for these same two doses of BI 655130 vs placebo. The fifth family includes the test of the BI 655130 low dose (BI 655130 300mg q12w) vs placebo on the primary and key secondary endpoints only.

First family: Test of the Primary Endpoint

The null and alternative hypothesis for each of the BI high and medium doses versus placebo on the primary endpoint, the time to first GPP flare up to week 48 (defined by an increase in GPPGA score by ≥ 2 from baseline and the pustular component of GPPGA ≥ 2), are:

(1) BI 655130 300 mg q4w vs. Placebo

$H_{0,11}$: Effect of BI 655130 300 mg q4w on prolonging the time to the first GPP flare up to week 48 ≤ Placebo;

versus the alternative hypothesis

$H_{A,11}$: Effect of BI 655130 300 mg q4w on prolonging the time to the first GPP flare up to week 48 > Placebo.

(2) BI 655130 300 mg q12w vs. Placebo

$H_{0,12}$: Effect of BI 655130 300 mg q12w on prolonging the time to the first GPP flare up to week 48 ≤ Placebo;

versus the alternative hypothesis

$H_{A,12}$: Effect of BI 655130 300 mg q12w on prolonging the time to the first GPP flare up to week 48 > Placebo.

Regarding the first family, to control the overall type I error rate at a one-sided alpha = 0.025 for the comparison of both high and medium doses of BI 655130 vs. Placebo on the primary endpoint, the truncated Hochberg method will be applied. The weight of the truncated Hochberg method is chosen as 0.5. If both primary endpoint p-values are ≤ 0.01875 (one-sided), then both comparisons involving the two BI 655130 dose regimens will be declared to be statistically significant. If the maximum of the p-values for the two dose comparisons is >0.01875 (one-sided), then the remaining p-value will be tested at the 0.0125 (one-sided level) and declared to be statistically significant only if that p-value is ≤ 0.0125 (one-sided).

The remaining alpha to be used in the second family will be 0.025 (one-sided) if both high and medium doses of BI 655130 are statistically significantly superior to Placebo on the primary endpoint. If only one comparison is successful then alpha will be 0.025/4=0.00625 according to the truncated Hochberg procedure with a weight of 0.5. If neither dose is declared to be statistically significantly superior to Placebo for the primary endpoint, then no further formal testing in the hierarchical sequence will be conducted.

Second family: Test of the Key Secondary Endpoint
Further hypotheses will be tested on the key secondary endpoint in a hierarchical manner if the test for at least one dose of BI 655130 on the first family is successful.

The null and alternative hypotheses for the key secondary endpoint, the occurrence of patients having developed a GPP flare up to week 48, are:

(3) BI 655130 300 mg q4w vs. Placebo

$H_{0,21}$: The proportion of patients who do not experience a GPP flare up to week 48 on BI 655130 300 mg q4w ≤ Placebo;

versus the alternative hypothesis

$H_{A,21}$: The proportion of patients who do not experience a GPP flare up to week 48 on BI 655130 300 mg q4w > Placebo

(4) BI 655130 300 mg q12w vs. Placebo

$H_{0,22}$: The proportion of patients who do not experience a GPP flare up to week 48 on BI 655130 300 mg q12w ≤ Placebo;

versus the alternative hypothesis

$H_{A,22}$: The proportion of patients who do not experience a GPP flare up to week 48 on BI 655130 300 mg q12w > Placebo

If both high and medium doses of BI 655130 on the primary endpoint are successful, then the truncated Hochberg procedure will be used to control for multiplicity on the key secondary endpoint in the second family. The weight of the truncated Hochberg method is chosen as

0.5. If both key secondary endpoint p-values are ≤ 0.01875 (one-sided), then both comparisons involving the two BI 655130 dose regimens will be declared to be statistically significant. If the maximum of the p-values for the two dose comparisons is >0.01875 (one-sided), then the remaining p-value will be tested at the 0.0125 (one-sided level) and declared to be statistically significant only if that p-value is ≤ 0.0125 (one-sided). The remaining alpha, α', to be used in the tests on the following secondary endpoints will be 0.025 (one-sided) if both doses of BI 655130 are statistically significantly superior to placebo on the key secondary endpoint. If only one comparison is successful then α' will be 0.025/4=0.00625 according to the truncated Hochberg procedure with a weight of 0.5. If neither dose is declared to be statistically significantly superior to placebo for the key secondary endpoint, then no further formal testing in the hierarchical sequence will be conducted.

If only one (high or medium) dose of BI 655130 on the primary endpoint is successful then the same dose will be tested on the key secondary endpoint with a one-sided alpha= 0.00625. If this comparison is successful, then further tests on this dose for the next secondary endpoint in the hierarchy will be performed with a one-sided alpha= 0.00625.

Third and fourth families: Test of the Secondary Endpoints
Further hypotheses will be tested on the two secondary endpoints, the time to first worsening of PSS up to week 48 and the time to first worsening of DLQI up to week 48 in a hierarchical manner if the test for at least one dose of BI 655130 on the second family is successful.

The null and alternative hypotheses for the secondary endpoint, the time to first worsening of PSS up to week 48, are:

(5) BI 655130 300 mg q4w vs. Placebo

$H_{0,31}$: Effect of BI 655130 300 mg q4w on prolonging the time to first worsening of PSS up to week 48 ≤ Placebo;

versus the alternative hypothesis

$H_{A,31}$: Effect of BI 655130 300 mg q4w on prolonging the time to first worsening of PSS up to week 48 > Placebo.

(6) BI 655130 300 mg q12w vs. Placebo

$H_{0,32}$: Effect of BI 655130 300 mg q12w on prolonging the time to first worsening of PSS up to week 48 ≤ Placebo;

versus the alternative hypothesis

$H_{A,32}$: Effect of BI 655130 300 mg q12w on prolonging the time to first worsening of PSS up to week 48 > Placebo

The null and alternative hypotheses for the secondary endpoint, time to first worsening of DLQI up to week 48, are:

(7) BI 655130 300 mg q4w vs. Placebo

$H_{0,41}$: Effect of BI 655130 300 mg q4w on prolonging the time to the first worsening of DLQI up to week 48 ≤ Placebo;

versus the alternative hypothesis

$H_{A,41}$: Effect of BI 655130 300 mg q4w on prolonging the time to the first worsening of DLQI up to week 48 > Placebo

(8) BI 655130 300 mg q12w vs. Placebo

$H_{0,42}$: Effect of BI 655130 300 mg q12w on prolonging the time to the first worsening of DLQI up to week 48 ≤ Placebo;

versus the alternative hypothesis

$H_{A,42}$: Effect of BI 655130 300 mg q12w on prolonging the time to the first worsening of DLQI up to week 48 > Placebo

If both doses of BI 655130 on the key secondary endpoints are declared to be statistically significant, then a graphical procedure as shown in the end of the section will be used to attribute the remaining α' to the testing of each of the (hierarchically-ordered) secondary endpoints.

If only one (high or medium) dose of BI 655130 on the key secondary endpoint is successful, then the same dose will be tested on the third family endpoint and then, if the dose is declared to be statistically significant in the third family, on the fourth family endpoint with a one-sided alpha= 0.00625 in a hierarchical order.

Fifth family: Test of the Low Dose BI 655130 vs Placebo
Further hypotheses for the low dose of BI 655130 (150 mg q12w) will be tested on the primary endpoint, and subsequently on the key secondary endpoint, in a hierarchical manner, if the test for at least one dose of BI 655130 (High or Medium) on the third and fourth family is successful.

The null and alternative hypotheses to be tested are:

(9) Primary endpoint for BI 655130 150 mg q12w vs. Placebo

$H_{0,13}$: Effect of BI 655130 150 mg q12w on prolonging the time to the first GPP flare up to week 48 ≤ Placebo;

versus the alternative hypothesis

$H_{A,13}$: Effect of BI 655130 150 mg q12w on prolonging the time to the first GPP flare up to week 48 > Placebo.

(10) Key Secondary endpoint for BI 655130 150 mg q12w vs. Placebo

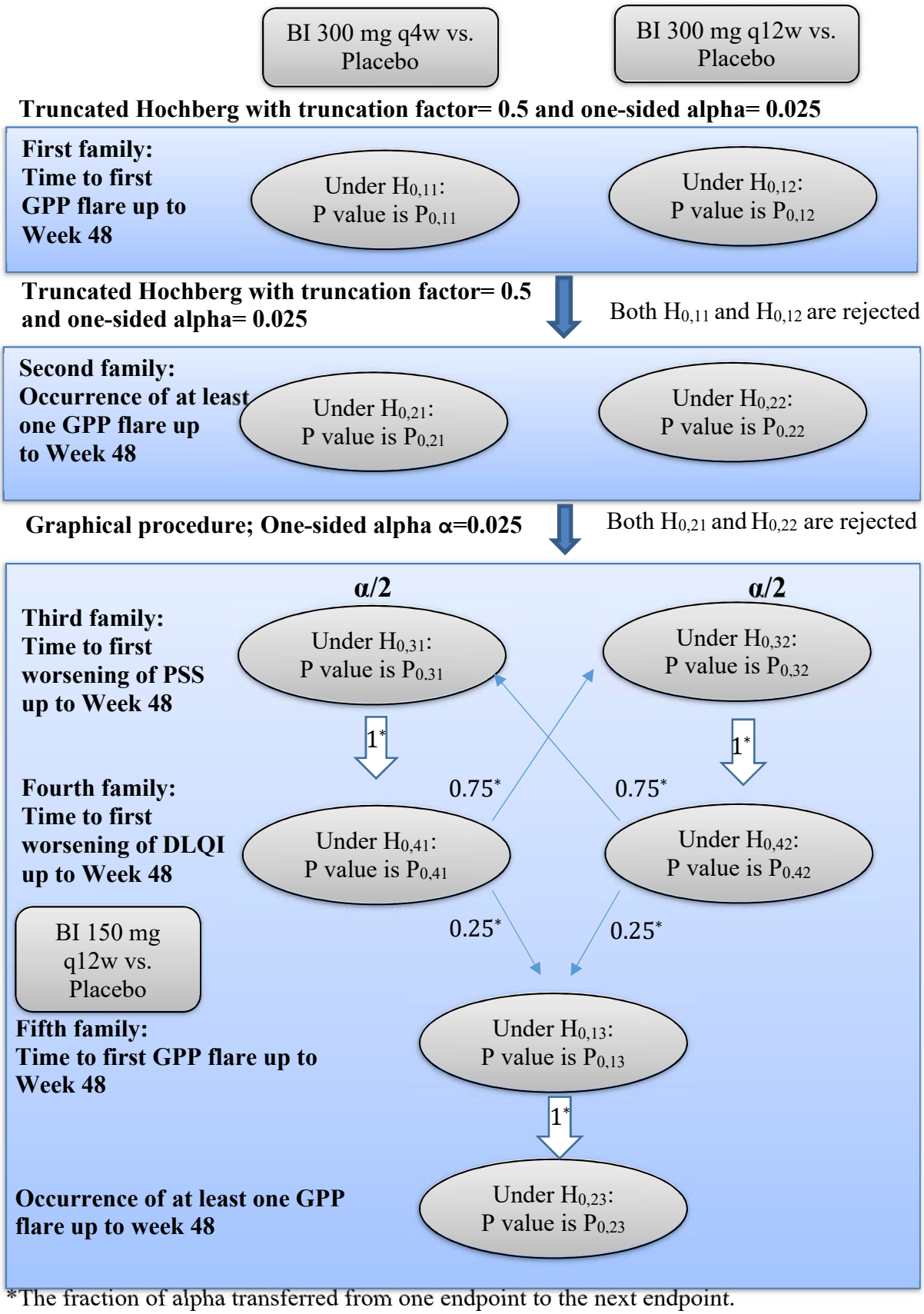
$H_{0,23}$: The proportion of patients who do not experience a GPP flare up to week 48 on BI 655130 150 mg q12w ≤ Placebo;

versus the alternative hypothesis

$H_{A,23}$: The proportion of patients who do not experience a GPP flare up to week 48 on BI 655130 150 mg q12w > Placebo

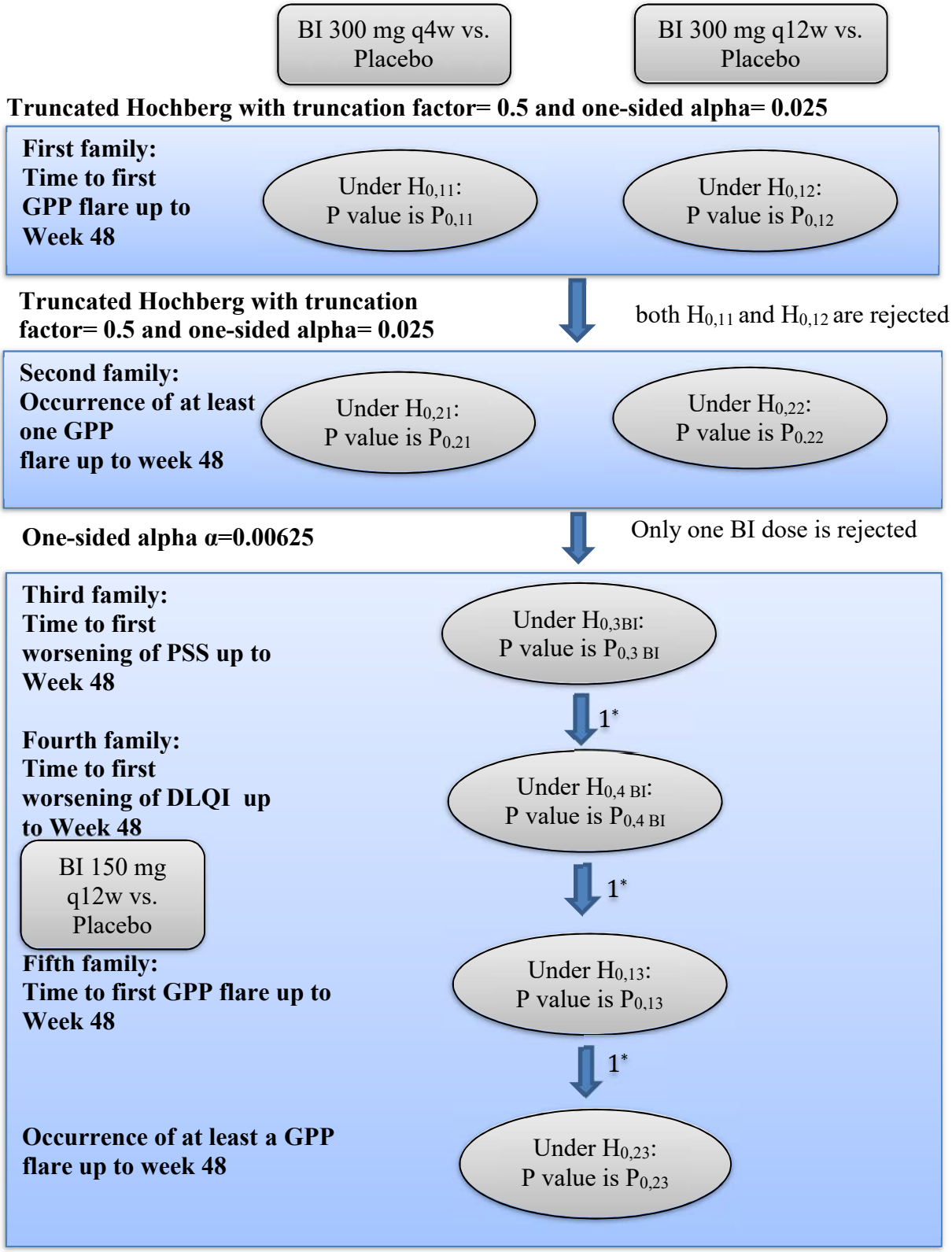
Tests on the fifth family for the BI low dose will be performed as shown below with alpha transferred only if successful testing has occurred previously on both of the two secondary endpoints of at least one dose (High or Medium) in the hierarchical chain.

The flowchart in the case that both high and medium doses of BI 655130 on the primary endpoint and key secondary endpoints are declared to be statistically significant, is as presented below:



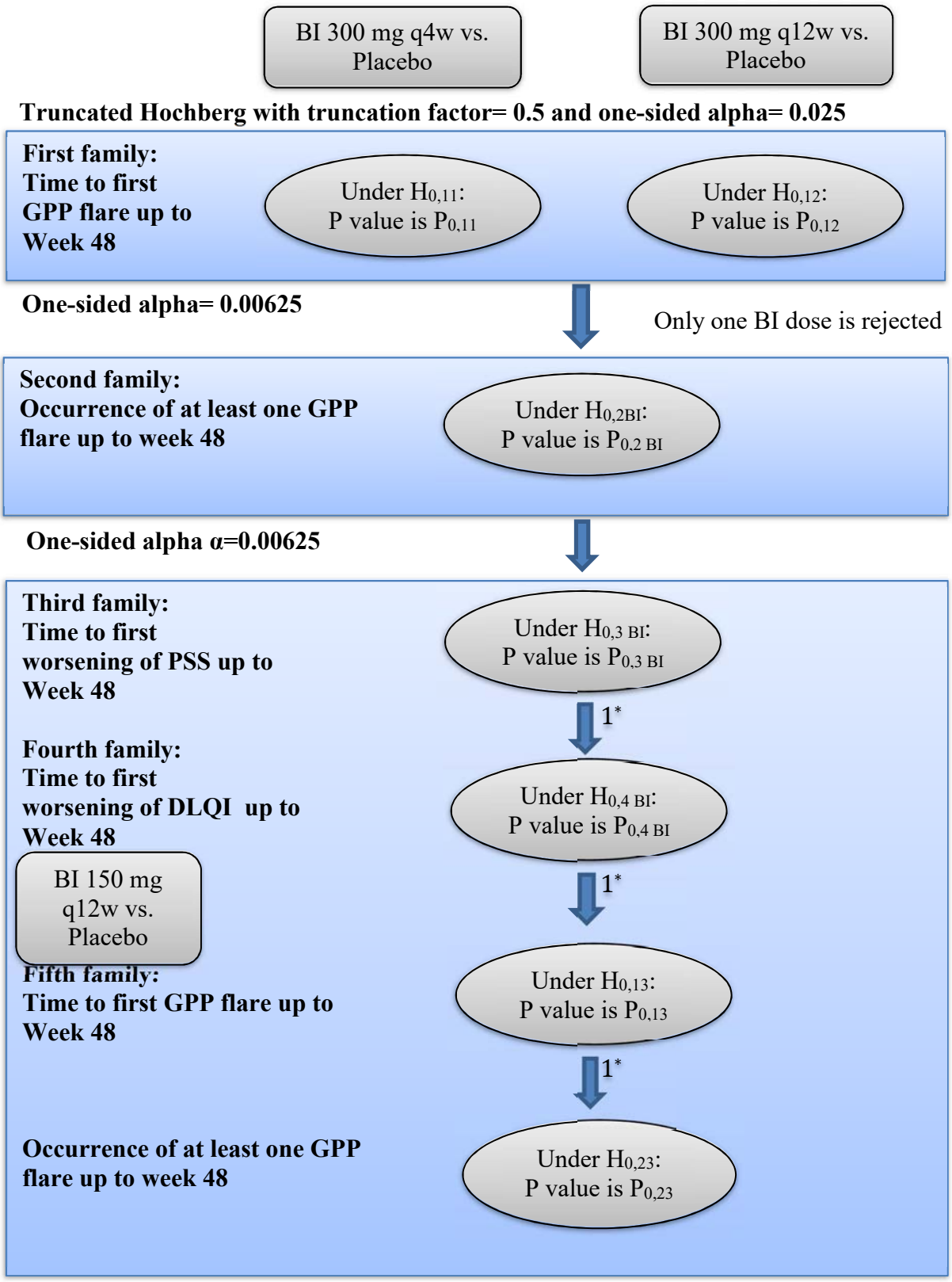
*The fraction of alpha transferred from one endpoint to the next endpoint.

If both high and medium doses of BI 655130 on the primary endpoint are statistically significant and only one of high and medium doses of BI 65510 on the key secondary endpoint is statistically significant, then the remaining α'=0.00625 will be used to test the following endpoints of the corresponding dose of BI 655130 and the low dose in a hierarchical order. The flowchart is as presented below:



Note: BI= the single dose that was successful on the key secondary endpoint (BI 300 mg q4w or BI 300 mg q12w)
*The fraction of alpha transferred from one endpoint to the next endpoint.

If only one of high and medium doses of BI 655130 on the primary endpoint is statistically significant, then the remaining alpha=0.00625 will be used to test the following endpoints of the corresponding dose of BI 655130 and then the low dose in a hierarchical order. The flowchart is as presented below:



Note: BI= the single dose that was successful on the primary endpoint (BI 300 mg q4w or BI 300 mg q12w)
*The fraction of alpha transferred from one endpoint to the next endpoint.

7.2 PLANNED ANALYSES

7.2.1 General considerations

There will be 3 main patient populations in this trial for analyses: the randomized set (RS), the safety set (SAF), 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 IPVs (potentially affecting the study outcome) which lead to exclusion from the PPS. This set will be used for sensitivity analysis on the primary and key secondary efficacy endpoints which are included in the testing hierarchy.

[redacted]

Important violations of the protocol will include violations of the key inclusion and exclusion criteria, incorrect medications taken, concomitant use of restricted medications, 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 primary trial analysis.

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

A Clinical Trial Report will be prepared for the primary analysis.

7.2.2 Primary endpoint analyses

The time to first GPP flare up to week 48, defined by an increase in GPPGA score from baseline by $\geqslant 2$ and a GPPGA pustulation subscore $\geqslant 2$, is the primary endpoint of this trial. Any use of rescue medication (see Section 3.1) or investigator-prescribed SoC prior to the first onset of a GPP flare is considered to indicate the onset of such a flare.

Primary Objective: Dose Finding
The primary analysis for the primary objective consists of a MCPMod-based testing (with respect to a non-flat dose response curve). MCPMod (multiple comparison and modelling

techniques) [R10-1424] is used to evaluate several possible dose response models (patterns), and to identify the best-fitting model or subset of models (while keeping full control of the type I error at 0.05, one-sided).

The generalized MCPMod procedure for time to event endpoints (Pinheiro et al. 2014 [R15-4293]) is based on the log hazard ratio of the active doses vs. placebo obtained via a Cox regression model on the time to first GPP flare. In detail the hazard function for patient i in stratum m (systemic concomitant use of GPP medications at randomization (yes or no)) is assumed to have the form

$$\Lambda_i(t) = \lambda_{mo}(t)\exp(\beta_1 X_{1i} + \beta_2 X_{2i} + \beta_3 X_{3i})$$

where

- $\Lambda_i(t)$is the hazard for patient i at time t
- $\lambda_{mo}(t)$ is the unspecified, non-negative, baseline hazard function that is assumed to be the same for all subjects in stratum m
- X_1, X_2, X_3 are indicator variables representing the treatment group with $X_{ki} = 1$ if patient belongs to the active treatment group i and 0 otherwise
- $\exp(\beta_k)$ with k=1,2,3 is the respective hazard ratio for the 3 active treatment groups

The MCPMod test is based on the estimated log hazard rates β_k (k=1, 2, 3) as well as the estimated variance-covariance matrix obtained from the Cox regression model fit. In particular the placebo adjusted version of MCPMod will be applied.

For the PoC testing and for the sample size calculation, the contrasts of each of the models to be tested must be pre-defined. The following cases has been selected to cover the plausible and a diverse range of potential dose response patterns.

Table 7.2.2: 1 Candidate case scenarios

	HR for each group vs Placebo in candidate cases*		
The response patterns	300 mg day1 150 mg q12w	600 mg day1 300 mg q12w	600 mg day1 300 mg q4w
Linear	0.64	0.41	0.10
Emax1	0.17	0.13	0.10
Emax2	0.11	0.10	0.10
Exponential	0.70	0.47	0.10

*The HRs are derived based on following models using planned total doses (i.e. the sum of all doses before Week 48): Linear; Emax1: assumes 70% of the maximum effect is achieved at low dose; Emax2: assumes 95% of the maximum effect is achieved at low dose; Exponential: assumes 35% of the maximum effect is achieved at medium dose. The scenarios in the table cover both the plausible and a diverse range of potential dose response patterns. For other HR combinations that is different but similar to the trend of the ones in the table, the primary analysis is robust and provide sufficient power. Hazard rates are rounded to two decimals.

The optimal contrasts corresponding to the candidate models are calculated and shown in Table 7.2.2: 2 (please note that no contrast for placebo is presented since placebo adjusted MCPMod test is applied). In the trial analysis stage, these optimal contrasts will be updated using the estimated variance-covariance matrix from the collected data (as suggested e.g. in [R15-4293]). The updated contrast coefficients will be described in the CTR.

Table 7.2.2: 2 Contrast coefficients

	Contrast coefficients for dose		
Model	300 mg day1 150 mg q12w	600 mg day1 300 mg q12w	600 mg day1 300 mg q4w
Linear	-0.177	-0.353	-0.919
Emax1	-0.492	-0.579	-0.650
Emax2	-0.565	-0.579	-0.588
Exponential	-0.146	-0.307	-0.940

A non-flat dose response is established if at least one contrast test (after adjusting for multiplicity using MCP step in MCPMod approach) is statistically significant, thereby rejecting the null hypothesis of a flat dose-response curve and indicating a benefit of BI 655130 over placebo. If a non-flat dose response is established, the statistically significant model(s) from the above candidate set are refitted to the data to generate new estimates for all model parameters.

If considered necessary and for the purpose of further model refinement, MCPMod might be repeated on the primary endpoint but with an extended set of shapes including the original candidates. Furthermore, covariates may be taken into account in further sensitivity analyses. Details of these analyses will be described in the TSAP.

Other analyses of the primary endpoint will include:

- Alternative PK metrics including model predicted metrics (e.g. cumulative AUC) for the dose regimens will be evaluated.

Secondary Objective: Formal Statistical Testing

Formal Statistical analysis
The primary analysis for the secondary objective on the time to first GPP flare up to week 48 for each dose of BI 655130 versus placebo will be tested using the stratified log-rank test stratified by the systemic concomitant use of GPP medications at randomization (yes or no) and based on the RS.

Kaplan-Meier (KM) estimates of the survival/failure probabilities at 1-monthly intervals, as well as the median time-to-event, will be provided by treatment. Confidence intervals will be based on two-sided $\alpha = 0.05$. A Kaplan-Meier graph will also be produced.

If a patient discontinues the treatment early, the follow-up of the patient will be still continued and the primary analysis will include patients' on- and off-treatment data up to Week 48. If a patient has no GPP flare event through 48 weeks of study, or is lost to follow-up or withdrawn from the trial prior to achieving such an event, then the primary endpoint will be censored at the day of the last visit upon which it was confirmed that no GPP flare had yet been observed.

The primary method for handling of missing data on the time to first flare is described in Section 7.3.

Secondary analysis of the primary endpoint will include:

- A sensitivity analysis utilizing the PPS to evaluate the impact on treatment outcomes of patients who may have relevant deviations from the conduct described in the CTP;
- Analysis of an additional estimand whereby for patients who used rescue medication or investigator-prescribed SoC prior to the first onset of a GPP flare is considered to indicate the onset of such a flare. For patients who use restricted medication for other disease and not for the onset of a GPP flare, data will be censored for further analysis following the use and imputed using the methods described in Section 7.3.
- Sensitivity analyses which utilize alternative methods for the handling of missing data as described in Section 7.3.
- Descriptive comparisons between the levels of each stratification (concomitant use of systemic GPP medications at randomization (yes or no)) and blocking factors (region (Japan or Rest of world) and population (adults versus adolescents)) will be performed.

7.2.3 Secondary endpoint analyses

Key Secondary Endpoint Analysis

Primary Objective: Dose Finding
For the dose finding analysis of the study, there are no key secondary endpoints defined.

Secondary Objective: Formal Statistical Testing
For the formal analysis of the study, the treatment effect on the key secondary endpoint, the occurrence of at least one GPP flare up to week 48, will be tested in a hierarchical manner as a part of the pre-specified testing strategy, subsequent to the test of the primary endpoint, which is defined in Section 7.1

The stratified Cochran-Mantel-Haenszel (CMH) test will be performed for each dose of BI 655130 versus placebo stratified by the concomitant use of systemic GPP medications at randomization (yes or no), and based on the RS. The difference in the proportion of patients who do not experience a GPP flare, and the associated confidence intervals will be presented for each active group versus the placebo group using the Mantel-Haenszel type weighted average of differences using weights as proposed by Greenland & Robins [R09-1299].

Any use of rescue medication or investigator-prescribed SoC prior to the onset of the first GPP flare is considered to represent a failure, i.e. the onset of a GPP flare event. Furthermore, as described for the primary endpoint analysis, the key secondary endpoint analysis will also include both on- and off-treatment data of all patients up to Week 48.

The primary method for handling of missing data on the occurrence of at least one GPP flare is described in Section 7.3.

Secondary analyses of the key secondary endpoint will be the same as those defined for the primary endpoint. In addition, a sensitivity analysis using a landmark test will be performed to evaluate treatment effects. This test will compare Kaplan Meier estimates at Week 48 between each dose of BI 655130 and placebo whereby the variance of each KM estimate is calculated by the Greenwood's formula. Further details for the landmark test will be described in the TSAP.

Secondary Endpoint Analysis:
For the formal analysis of the study, the treatment effect on the following secondary endpoints, 1) Time to first worsening of PSS up to week 48 (defined as a 4-point increase in total score from baseline), and, 2) Time to first worsening of DLQI up to week 48 (defined as a 4-point increase in total score from baseline), will be tested in a hierarchical manner as a part of the pre-specified testing strategy, subsequent to the test of the primary and key secondary endpoints, which is defined in Section 7.1.

The time to first worsening of PSS up to week 48, where any use of rescue medication or investigator-prescribed SoC prior to observing the endpoint is considered to represent a worsening of the PSS, will be tested for each dose of BI 655130 vs. placebo using the

stratified log rank test stratified by the factor, concomitant use of systemic GPP medications at randomization (yes or no) and based on the RS.

The time to first worsening of DLQI up to week 48, where any use of rescue medication or investigator-prescribed SoC will be considered to represent a worsening of the DLQI, will be analysed in the same manner as described for the time to first worsening of PSS.

Imputation rules of missing data for the above two secondary endpoints will be described in Section 7.3.

All secondary endpoints will be descriptively displayed. Descriptive comparison for adults versus adolescents will be performed for secondary endpoints in the hierarchical testing. Statistical tests on the remaining secondary binary endpoints will be performed as described for the key secondary endpoint.

[redacted]

7.2.5 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 (1368-0025), all TEAE up to the time-point of first dose of the trial medication 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 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 at database lock.

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, [for patients who didn't roll over to the extension trial] last contact date per EoS page, [for patients who roll over into the extension trial] date of first dose in extension trial – 1 day, drug stop date + 112 days, date of rescue medication of BI 655130). 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 analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be 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.

Immunogenicity data will be analysed in a descriptive way.

[redacted]

[redacted]

7.2.7 Interim analyses

To support a potential BI655130 acute flare treatment submission, an interim analysis of the clinical efficacy and safety data collected during the BI 655130 OL i.v rescue treatment and s.c. maintenance treatment periods for GPP flare may be performed. The interim data snapshot will include the data from the i.v. rescue treatment period and OL maintenance treatment period. The initial randomized s.c. treatments will remain blinded and these data will not be analysed as part of this interim analysis. The timing of the interim analysis is driven by the timing of the submission of the acute flare treatment. Further details on the specifications for this interim analysis will be presented in the trial statistical analysis plan.

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 un-blinded 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.

7.3 HANDLING OF MISSING DATA

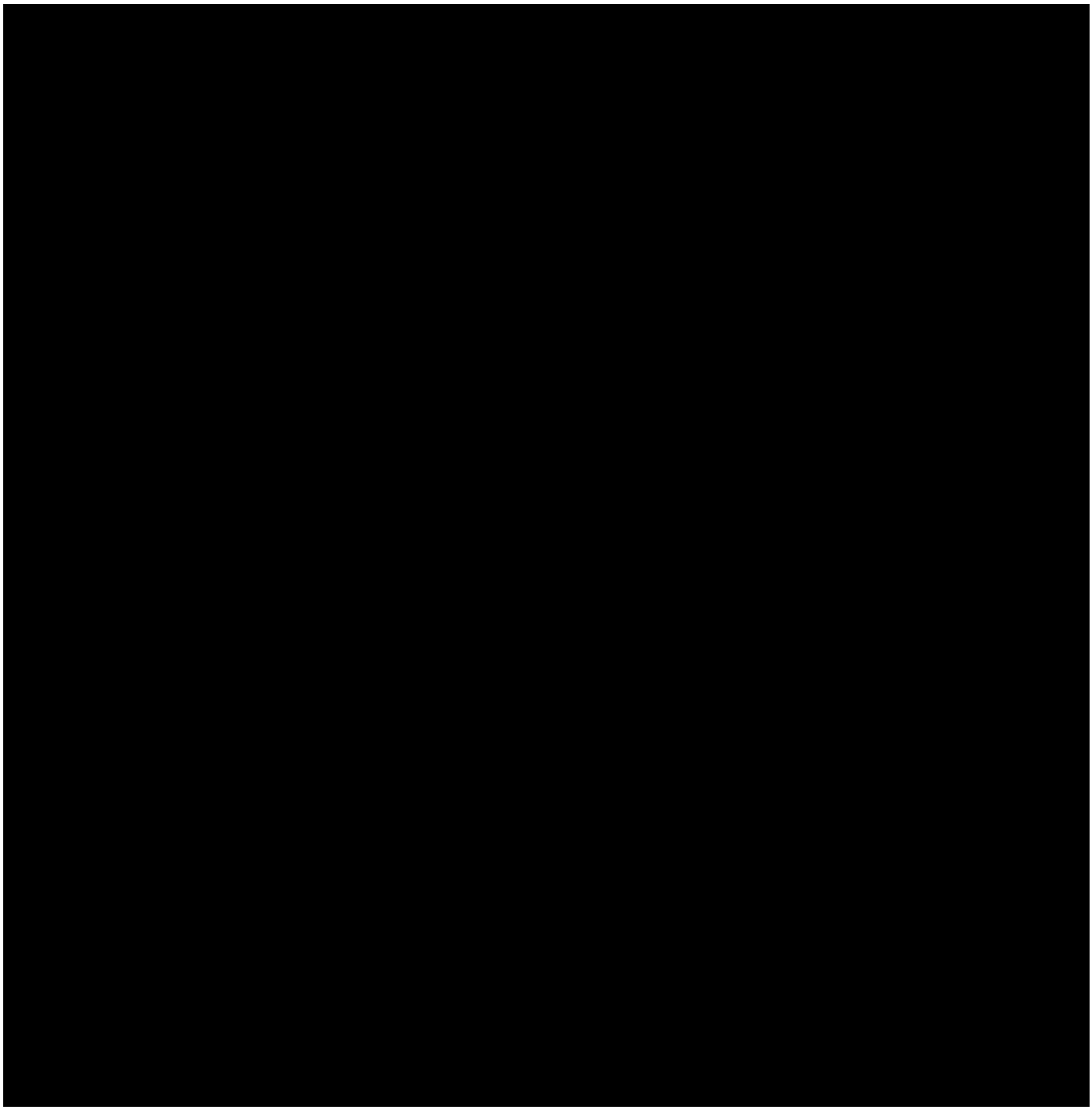
Every effort will be made to collect complete data at all visits. However, missing data will still occur and approaches to handle this are proposed below.

It is generally assumed that given the severity of a GPP flare, patients will always report to the investigator in a timely manner in order to ensure that proper treatment is received so that the developing flare can be rapidly treated. For the primary endpoint, only observed GPP flare events will be included in the primary analysis. No further imputation will be implemented on the missing values of GPPGA score and/or missing GPPGA pustule subscore. This will be the primary imputation method for the primary analysis. The same imputation strategy will be used for the two secondary endpoints, time to first worsening of PSS and time to first worsening of DLQI in the hierarchical testing procedure. The detailed censoring rules as outlined in Table 7.3: 1 will be used.

Table 7.3: 1 Primary Method: Description of censoring rules for primary endpoint, and two secondary endpoints in hierarchical testing procedure

Situation	Outcome (event or censored)	Date of outcome
Without post randomization assessment		
No use of rescue medication or investigator-prescribed SoC	Censored	Date of randomization
The first use of rescue medication or investigator-prescribed SoC	Event	Date of the first use of rescue medication or investigator-prescribed SoC whichever comes earlier
With post randomization assessment		
No event, and, no use of rescue medication or investigator-prescribed SoC	Censored	Date of last assessment with no event confirmed
The first event, or the first use of rescue medication or investigator-prescribed SoC	Event	Date of first event, or the date of first use of rescue medication or investigator-prescribed SoC whichever comes earlier

The sensitivity analysis (Sensitivity Method) will utilize different rules to deal with missing values in the above-defined endpoints. The alternative censoring rules for sensitivity analysis are defined in Table 7.3: 2.



For the primary analysis of the key secondary endpoint:
Missing GPPGA or GPPGA pustule subscores will not be imputed and only observed values will be utilized. If a patient is followed up to Week 48 and there is no flare, use of rescue medication or investigator-prescribed SoC reported, then this patient will be considered as a responder (i.e., no flare event) for the key secondary endpoint.

If for any reason, one or more patients are lost to follow-up or early discontinuation from the study before reaching the time-point of Week 48, then a sequential regression multiple imputation method will be implemented to impute the assessment of whether a flare event has

occurred by each visit at a binary level (Yes vs. No). This is a monotone increasing variable, so once a flare has occurred by a particular visit, all subsequent visits will also by definition have had a preceding flare. The imputation will include covariates, GPPGA subscore (pustules, scaling, erythema), as ordinal variables with values 0, 1, 2, 3 and 4. First, any non-monotone missing values will be imputed as the next observed value. Then the achieved monotone missing data will be imputed per the following steps:

1. *Multiple Imputation of Missing data:* A sequential logistic regression method is used to impute missing values of binary key secondary endpoint (Flare: Yes vs. No) at each visit.

   For Visit 2, the GPPGA subscores (pustules, scaling, erythema) at Visit 2 as well as treatment, may be included as variables in the imputation model. If the assessment of a patient at Visit 2 is observed or imputed as a flare event, then the assessments of all subsequent visits of this patient will be imputed as flare events.
   Visit 3 will be imputed in the same way but now including the GPPGA subscores (pustules, scaling, erythema) up to Visit 3, treatment and the response of patient at Visit 2 (Flare: Yes vs. No). All visits after an observed or imputed flare event with a flare event are again imputed as an event. Using the same approach, all visits will be imputed in order up to Visit 14 (Week 48).

2. *Analysis of Completed Datasets*: The imputed complete dataset will be used to perform the corresponding statistical analysis per permutation as specified in Section 7.2.3.

3. *Combine Results*: PROC MIANALYZE combines the analysis results from step 2 and generates valid statistical inferences by accounting for the variability introduced by the MI process using Rubin's rules (R12-2378).

Further imputation rules for secondary endpoints and further endpoints will be described in TSAP if necessary. With respect to safety evaluations, it is not planned to impute missing values.

7.4 RANDOMISATION

If applicable, 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 the concomitant use of systemic GPP medications at randomization (yes or no) will be done. If a patient received any GPP medication within 4 weeks prior to or at randomization, then this patient will be categorized as "yes" and otherwise, "no". Primary and key secondary efficacy analyses will be performed including an adjustment for this stratum.

Blocking for region (Japan versus Rest of World) will be done in order to ensure that sufficient patients per treatment group are recruited specifically to support individual country

submission in Japan; this factor will be treated as operational factor and will not be included into the analyses of efficacy endpoints.

Blocking for population (Adults versus Adolescents) will be done in order to ensure that there will be adolescent patients randomized in each treatment group for paediatric investigational plan; this factor will be treated as operational factor and will not be included into the analyses of efficacy endpoints.

The first twelve adolescent patients will be randomized in a 1:1:1:1 ratio to the four arms regardless of concomitant use of systemic GPP medications at randomization (yes vs. no) and blocking factor region (Japan vs. Rest of world). This is to ensure that within each randomized arm, there are at least 2 randomized adolescent patient. Any additional adolescent patients within each stratum (concomitant use of systemic GPP medications at randomization (yes vs. no) and each blocking factor region (Japan vs. Rest of world), will be randomized in a 1:1:1:1 ratio to the four arms.

The adult patients within each stratum (concomitant use of systemic GPP medications at randomization (yes vs. no) and each blocking factor region (Japan vs. Rest of world), will be randomized in a 1:1:1:1 ratio to the four arms.

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.

7.5 DETERMINATION OF SAMPLE SIZE

Based on an application of the defined testing strategy, a power calculation has been performed for sample size assessment on the dose finding analysis (primary objective) and on the formal analysis (secondary objective) of the trial.

The effect of each dose of BI 655130 on preventing a GPP flare in patients with a history of GPP will be compared relative to placebo where the high and medium doses of BI 655130 (300 mg q4w and 300 mg q12w) are assumed to be closely effective, while the lowest dose (150 mg q12w) is assumed to be a sub-therapeutic dose. Most patients will withdraw from their prior GPP medication when they enter the trial, therefore the overall GPP flare rate is expected to be higher for these patients within the first three months of the maintenance treatment period (due to withdrawal of previous medication being a potential trigger for onset of a GPP flare event).

Under the base scenario, the overall hazard ratio between BI 300 mg q4w and placebo is assumed to be 0.1, between BI 300 mg q12w and placebo is assumed to be 0.15 and between BI 150 mg q12w and placebo is assumed to be 0.3. It assumes a piecewise exponential distribution (i.e., first 3 month vs post 3 months) for the time to first GPP flare of each arm in this trial. It is anticipated that within the first 3 months of treatment, with dose of BI 300 mg q4w, BI 300 mg q12w and BI 150 mg q12w, that approximately 1.7%, 2.6% and 5.1% of patients will experience a first GPP flare per month respectively under the base scenario. In

contrast, the first flare rate on placebo within the first 3 months is expected to be much higher, i.e. approx. 17.1% per month under the base scenario. After 3 months, the overall first flare rate is expected to decline and, thereafter, to be stable for the remainder of the trial. The expected first flare rate after 3 months is 0.3%/month for patients on BI 300 mg q4w, 0.4%/month for patients on BI 300 mg q12w, 0.9%/month for patients on BI 150 mg q12w and 3%/month for patients on the placebo arm under the base scenario.

It is expected to take about 13 months to recruit 120 randomized patients in this trial. The primary analysis will be performed when last patient completes or early discontinue the 48-week treatment. At that time, the target number of events will be 27. The powers of this trial are not driven by the target number of events but based on the number of events truly observed at the time of primary analysis.

Table 7.5: 1 shows the success probability estimates for the dose finding analysis based on the primary endpoint when the primary analysis is performed at the time that the last patient has completed or early discontinued 48-week treatment. All calculations are performed using R version 3.5.1, for a sample size of 120 patients (1:1:1:1 ratio), and a 1-sided type I error of 0.05.

The probability of success of this trial is defined as the probability to obtain a significant test for non-flat dose-response curve.

Based on these assumptions, the success probability is approximately 99.5% for the base scenario described above.

In the case that there is no treatment benefit, the false positive probability is limited by the α-level for the significance testing of the non-flat dose-response curve of 5% (one-sided).

Table 7.5: 1 Dose-Finding analysis - Multiplicity-adjusted success probability given a total sample size of 120 patients based on MCPMod alpha-level of 5% (one-sided).

Scenario	**First flare rates assumption: BI 655130 300 mg q4w vs. BI 655130 300 mg q12w vs. BI 655130 150 mg q12w vs. Placebo****		**Hazard Ratio: BI 655130 300 mg q4w vs. placebo; BI 655130 300 mg q12w vs. placebo; BI 655130 150 mg q12w vs. placebo**	***Success probability to demonstrate non-flat dose-response curve**
	First flare rates per month within first 3 months	**First flare rates per month (post 3 month)**		
Base	1.7% vs. 2.6% vs. 5.1% vs. 17.1%	0.3% vs. 0.4% vs. 0.9% vs.; 3.0%	0.1 0.15 0.3	99.5%
BaseMinus	1.7% vs. 2.6% vs. 5.1% vs. 11.4%	0.3% vs. 0.4% vs. 0.9% vs.; 2.0%	0.15 0.225 0.45	90.7%
Low effect	10.3% vs. 10.3% vs. 10.3% vs. 15.5 % vs.	1.6% vs. 1.6% vs. 1.6% vs. 2.4%	0.67; 0.67; 0.67	28.8%
No effect	13.5 % vs. 13.5 % vs. 13.5 % vs. 13.5 %	2.5% vs. 2.5% vs. 2.5% vs. 2.5%	1; 1; 1	5.0%

* Success probabilities have been calculated using R Version 3.5.1 based on simulations (10000 simulations per scenario), using DoseFinding R-package 0.9-16 [R15-2001].

** The primary trial analysis will be performed once the last randomized patient has completed 48 weeks on treatment. Each patient will participate in the trial for a maximum of 48 week

Table 7.5: 2 shows the power estimates for the formal analysis based on the primary endpoint and key secondary endpoint when the primary analysis is performed at the time that the last patient has completed or early discontinued 48-weeek treatment and non-flat dose-response curve in the dose finding analysis has been demonstrated. All calculations are performed using R version 3.5.1, for a sample size of 120 patients (1:1:1:1 ratio) and a 1-sided type I error of 0.025.

The 120 patients are planned to be recruited in order that a power of at least 90% for at least one successful dose of BI 655130 (High or Medium doses) versus placebo on the primary and key secondary endpoints can be achieved under the base scenario as defined above.

Table 7.5: 2 Power to achieve statistical significance with BI 655130 High and Medium doses versus Placebo on primary endpoint and key secondary endpoint conditional on the successful dose-finding analysis

Scenario	First flare rates assumption: BI 655130 300 mg q4w vs. BI 655130 300 mg q12w vs. (BI 655130 150 mg q12w) ** Placebo		Hazard Ratio: BI 655130 300 mg q4w vs. placebo; BI 655130 300 mg q12w vs. (BI 655130 150 mg q12w vs.)** placebo	Median event (first flare) free time by month	Approximately total number of events (first flare) observed during 48-week treatment	Formal testing part: Power at least one BI dose is stat. sig. vs Placebo*	
	First flare rates per month within first 3 months	First flare rates per month post-first 3 months				Success on primary endpoint	Success on primary and key secondary endpoints
BasePlus	1.7% vs. 2.6% vs. (5.1% vs.) 24.4%	0.3% vs. 0.4% vs. (0.9% vs.); 4.2%	0.07 0.105 (0.21)	225.4; 146.3; (65.6); 4.2	2; 3; 6; 20	99.9%	99.9%

Table 7.5: 2 Power to achieve statistical significance with BI 655130 High and Medium doses versus Placebo on primary endpoint and key secondary endpoint conditional on the successful dose-finding analysis (cont.).

Scenario	First flare rates assumption: BI 655130 300 mg q4w vs. BI 655130 300 mg q12w vs. (BI 655130 150 mg q12w) ** Placebo		Hazard Ratio: BI 655130 300 mg q4w vs. placebo; BI 655130 300 mg q12w vs. (BI 655130 150 mg q12w vs.)** placebo	Median event (first flare) free time by month	Approximately total number of events (first flare) observed during 48-week treatment	Formal testing part: Power at least one BI dose is stat. sig. vs Placebo*	
	First flare rates per month within first 3 months	First flare rates per month post-first 3 months				Success on primary endpoint	Success on primary and key secondary endpoints
Base	1.7% vs. 2.6% vs. (5.1% vs.) 17.1%	0.3% vs. 0.4% vs. (0.9% vs.); 3.0%	0.1 0.15 (0.3)	225.4; 146.3; (65.6); 9.9	2; 3; 6; 16;	98.6%	96.0%
BaseMinus	1.7% vs. 2.6% vs. (5.1% vs.) 11.4%	0.3% vs. 0.4% vs. (0.9% vs.); 2.0%	0.15 0.225 (0.45)	225.4; 146.3; (65.6); 21.6	2; 3; 6; 12	83.4%	69.5%

* Success probabilities have been calculated using R Version 3.5.1 based on simulations (10000 simulations per scenario).
** Low dose (in brackets) is only used for dose finding analysis but not included in the power calculation for the formal analysis

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

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as “protocol deviation”.

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

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to patient participation in the trial, written informed 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/assent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent/assent form (as applicable) and any additional patient information must be given to each patient or the patient’s legally accepted representative.”

For adolescents, the patient will be provided with an age-adapted information sheet where his/her assent will be collected according to the regulatory and legal requirements of the

participating country. The refusal of an adolescent to participate must be accepted independently of the consent of his/her parent(s)/legal guardian.

For patients who may legally consent during the trial participation (turning to the age of legal consent in the participating country), written informed consent must be obtained to confirm the patient's willingness to pursue trial participation.

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 (or patient's parent(s)/legal guardian) must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent/assent of the patient's (or patient's parent(s)/legal guardian) own free will with the informed consent/assent form after confirming that the patient understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent/assent 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/assent.

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent/assent and re-consenting/re-assenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

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

8.3 RECORDS

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

8.3.1 Source documents

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

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

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

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

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector

(e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

Remote source data verification is acceptable in exceptional cases where onsite monitoring visits cannot take place due to circumstances like the COVID-19 pandemic or other relevant reasons. This must first be approved by the sponsor's trial team.

8.3.3 Storage period of records

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

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

Personalised treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

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

- 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, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data
- 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 Completed").

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

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

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

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

The IEC / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report. The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

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

A project-independent 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 time-point (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.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF. The investigators will have access to the BI clinical trial portal (Clinergize) to facilitate document exchange and maintain electronic ISF.

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

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

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

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

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

A central laboratory service, vendor for photo documentation and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual, Central Laboratory Manual, and other vendor specific manuals (as applicable) available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P09-07583 Aksentijevich I, Masters SL, Ferguson PJ, Dancey P, Frenkel J, van Royen-Kerkhoff A, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med. 2009;360(23):2426-37.

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

R05-2548 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.

R07-4311 Yellen SB, Cella DF, Webster K, Blendowski C, Kaplan E. Measuring fatigue and other anemia-related symptoms with the Functional Assessment of Cancer Therapy (FACT) measurement system. J Pain Symptom Manage. 1997;13(2):63-74.

R09-1299 Greenland S, Robins JM. Estimation of a common effect parameter from sparse follow-up data. Biometrics 41, 55 - 68 (1985)

R10-0936 Walters SJ, Brazier JE. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. Qual Life Res. 2005;14(6):1523-32.

R10-1424 Pinheiro J, Bornkamp B, Bretz F. Design and analysis of dose-finding studies combining multiple comparisons and modeling procedures. J Biopharm Stat 16 (5), 639 - 656 (2006)

R10-6267 Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012-24.

R11-4890 Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117(2):391-7.

R12-1920 Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20(10):1727-36.

R12-2378 Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons (1987)

R13-3515 Woodworth T, Furst DE, Alten R, Bingham CO, 3rd, Yocum D, Sloan V, et al. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. J Rheumatol. 2007;34(6):1401-14.

R14-5158 Marrakchi S, Guigue P, Renshaw BR, Puel A, Pei XY, Fraitag S, et al. Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis. N Engl J Med. 2011;365(7):620-8.

R15-1421 Onoufriadis A, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, et al. Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis. Am J Hum Genet. 2011;89(3):432-7.

R15-2001 Bornkamp B, Pinheiro J, Bretz F. Package 'DoseFinding' (February 19, 2015). http: // cran. rproject. org/ web/ packages/ Dose Finding/ DoseFinding.pdf (access date: 28 April 2015); Comprehensive R Archive Network (2015)

R15-4293 Model-based dose finding under modeluncertainty using eneralparametric models". Pinheiro et al. 2014

R15-5200 Langley RG, Feldman SR, Nyirady J, van de Kerkhof P, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) Scale: A modified tool for evaluating plaque psoriasis severity in clinical trials. J Dermatolog Treat. 2015;26(1):23-31.

R16-0030 Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70.

R16-0032 Ware JE. SF-36 health survey update. Spine 2000;25(24):3130-3139.

R16-0033 Frendl DM, Ware JE. Patient-reported functional health and well-being outcomes with drug therapy: a systematic review of randomized trials using the SF-36 health survey. Med Care 2014;52(5):439-445.

R16-0581 Mehta NN, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. Eur Heart J 31 (8), 1000 - 1006 (2010)

R16-0929 Berki DM, Liu L, Choon SE, David Burden A, Griffiths CEM, Navarini AA, et al. Activating CARD14 Mutations Are Associated with Generalized Pustular Psoriasis but Rarely Account for Familial Recurrence in Psoriasis Vulgaris. J Invest Dermatol. 2015;135(12):2964-70.

R16-0930 Hussain S, Berki DM, Choon SE, Burden AD, Allen MH, Arostegui JI, et al. IL36RN mutations define a severe autoinflammatory phenotype of generalized pustular psoriasis. J Allergy Clin Immunol. 2015;135(4):1067-70 e9.

R16-0932 von Zumbusch L. Psoriasis und pustuloses Exanthem. Archives of Dermatology and Syphilology. 1910;99:335-46.

R16-0933 Choon SE, Lai NM, Mohammad NA, Nanu NM, Tey KE, Chew SF. Clinical profile, morbidity, and outcome of adult-onset generalized pustular psoriasis: analysis of 102 cases seen in a tertiary hospital in Johor, Malaysia. Int J Dermatol. 2014;53(6):676-84.

R16-1462 Imafuku S, Honma M, Okubo Y, Komine M, Ohtsuki M, Morita A, et al. Efficacy and safety of secukinumab in patients with generalized pustular psoriasis: A 52-week analysis from phase III open-label multicenter Japanese study. J Dermatol. 2016;43(9):1011-7.

R16-1463 Borges-Costa J, Silva R, Goncalves L, Filipe P, Soares de Almeida L, Marques Gomes M Clinical and laboratory features in acute generalized pustular psoriasis: a retrospective study of 34 patients. Am J Clin Dermatol 12 (4), 271 - 276 (2011)

R16-2698 Augey F, Renaudier P, Nicolas JF Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. Eur J Dermatol 16 (6), 669 - 673 (2006)

R16-3360 Brunasso AM, Salvini C, Massone C. Efalizumab for severe palmo-plantar psoriasis: an open-label pilot trial in five patients. J Eur Acad Dermatol Venereol. 2009;23(4):415-9.

R16-3932 Horreau C, Pouplard C, Brenaut E, Barnetche T, Misery L, Cribier B, et al Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. J Eur Acad Dermatol Venereol 27 (Suppl 3), 12 - 29 (2013)

R17-2617 Winthrop KL, Novosad SA, Baddley JW, Calabrese L, Chiller T, Polgreen P, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis. 2015;74(12):2107-16.

R17-3403 Navarini AA, Burden AD, Capon F, Mrowietz U, Puig L, Koks S, et al. European consensus statement on phenotypes of pustular psoriasis. J Eur Acad Dermatol Venereol. 2017;31(11):1792-9.

R17-3456 Tay YK, Tham SN. The profile and outcome of pustular psoriasis in Singapore: a report of 28 cases. Int J Dermatol 36 (4), 266 - 271 (1997)

R17-3600 Robinson A, Van Voorhees AS, Hsu S, Korman NJ, Lebwohl MG, Bebo BF, Jr., et al. Treatment of pustular psoriasis: from the Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol. 2012;67(2):279-88.

R17-3602 Johnston A, Xing X, Wolterink L, Barnes DH, Yin Z, Reingold L, et al. IL-1 and IL-36 are dominant cytokines in generalized pustular psoriasis. J Allergy Clin Immunol. 2017;140(1):109-20.

R17-3603 Levin EC, Debbaneh M, Koo J, Liao W. Biologic therapy in erythrodermic and pustular psoriasis. J Drugs Dermatol. 2014;13(3):342-54.

R17-3605 Zelickson BD, Muller SA Generalized pustular psoriasis: a review of 63 cases. Arch Dermatol 127 (9), 1339 - 1345 (1991)

R17-3626 Japanese Journal of Dermatology. 2010;120(4):815-39.

R17-3632 Mahil SK, Catapano M, Di Meglio P, Dand N, Ahlfors H, Carr IM, et al. An analysis of IL-36 signature genes and individuals with IL1RL2 knockout mutations validates IL-36 as a psoriasis therapeutic target. Sci Transl Med. 2017;9(411).

R17-3898 Jin H, Cho HH, Kim WJ, Mun JH, Song M, Kim HS, et al
Clinical features and course of generalized pustular psoriasis in Korea.
J Dermatol 42, 674 - 678 (2015)

R18-1702 Review Report - Cosentyx. Pharmaceutical and Medical Devices Agency (PMDA) Nov. 12, 2015.

R18-1705 Diagnostic Criteria: European Rare and Severe Psoriasis Expert Network (ERASPEN); 2018

R18-1988 Finlay AY. Cardiff University, Department of Dermatology; [Available from: http: // sites. cardiff.ac. uk/ dermatology/ quality-of-life/ dermatology-quality-of-life-index-dlqi/ dlqi-instructions-for-use-and-scoring/.

R18-1989 Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res (Hoboken). 2011;63 Suppl 11:S240-52.

R18-1990 Rentz AM, Skalicky AM, Burslem K, Becker K, Kaschinski D, Esser D, et al. The content validity of the PSS in patients with plaque psoriasis. J Patient Rep Outcomes. 2017;1(1):4.

R20-2256 National Psoriasis Foundation (NPF) Task Force. Updated: COVID-19 Recommendations

R20-2257 National Institute for Health and Care Excellence (NICE). COVID-19 rapid guideline: severe asthma NICE guideline

R20-2258 American Academy of Allergy Asthma & Immunology. An Update on COVID-19 for the Practicing Allergist/immunologist

R96-0739 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). Med Care 30, 473 - 383 (1992)

R96-2382 EuroQol G. EuroQol--a new facility for the measurement of health-related quality of life. Health Policy. 1990;16(3):199-208.

R96-3541 Fredriksson T, Pettersson U. Severe psoriasis--oral therapy with a new retinoid. Dermatologica. 1978;157(4):238-44.

R97-1093 Ware JE, editor. SF-36 Health Survey: Manual and Interpretation Guide.Boston: The Health Institute, New England Medical Center; 1993.

R97-1149 Guy W, 048 HAMA Hamilton anxiety scale. In: ECDEU Assessment Manual for Psychopharmacol ogy.Rockville: U.S. Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration , 194 - 198 (1976)

9.2 UNPUBLISHED REFERENCES

c03320877 Investigator's Brochure. Current Version.

c09985235-01 [redacted] Single-blind, partially randomised, placebo-controlled Phase I study to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of single rising intravenous doses of BI 655130 in healthy male volunteers, April 7, 2017.

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

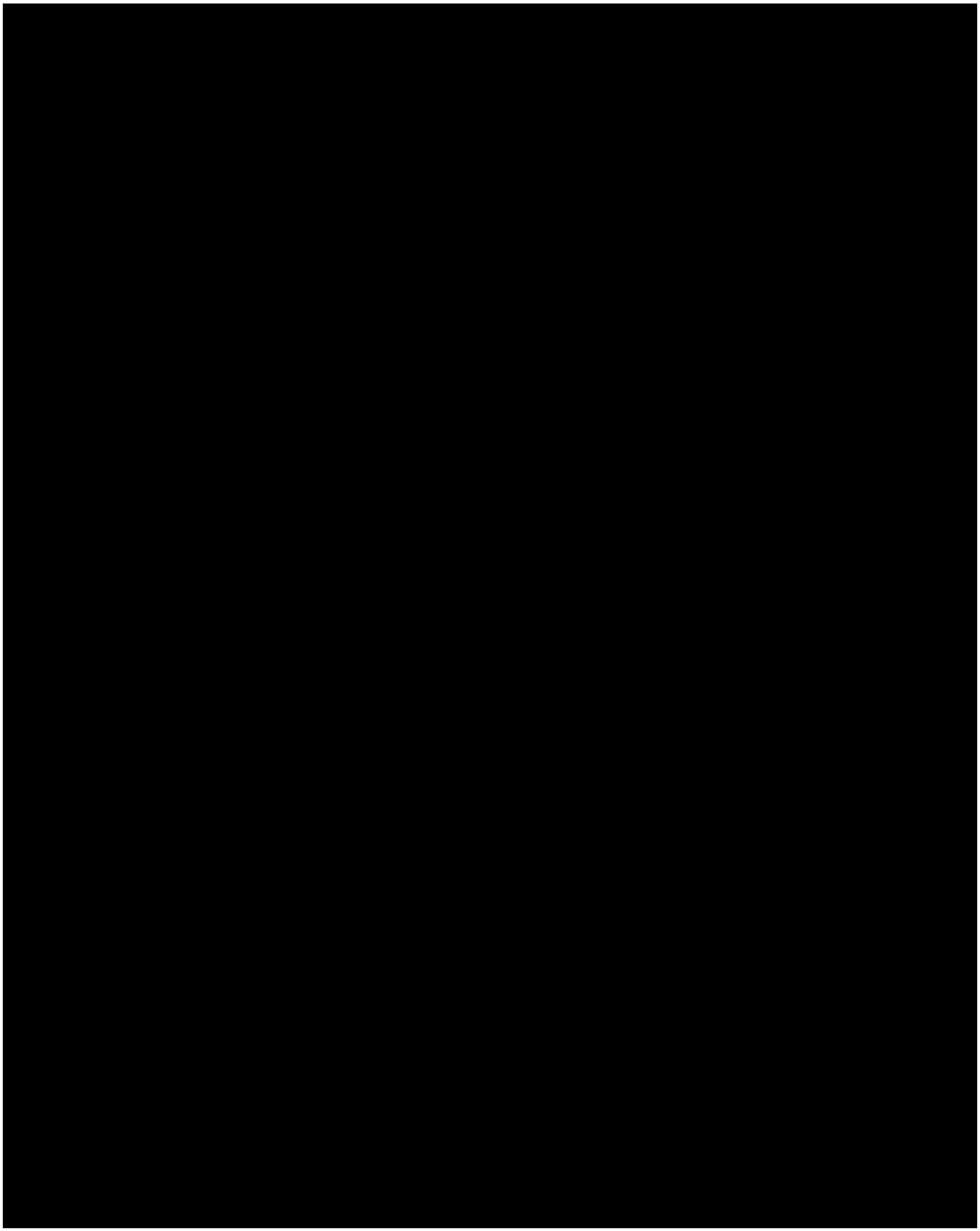
Scaling/crusting

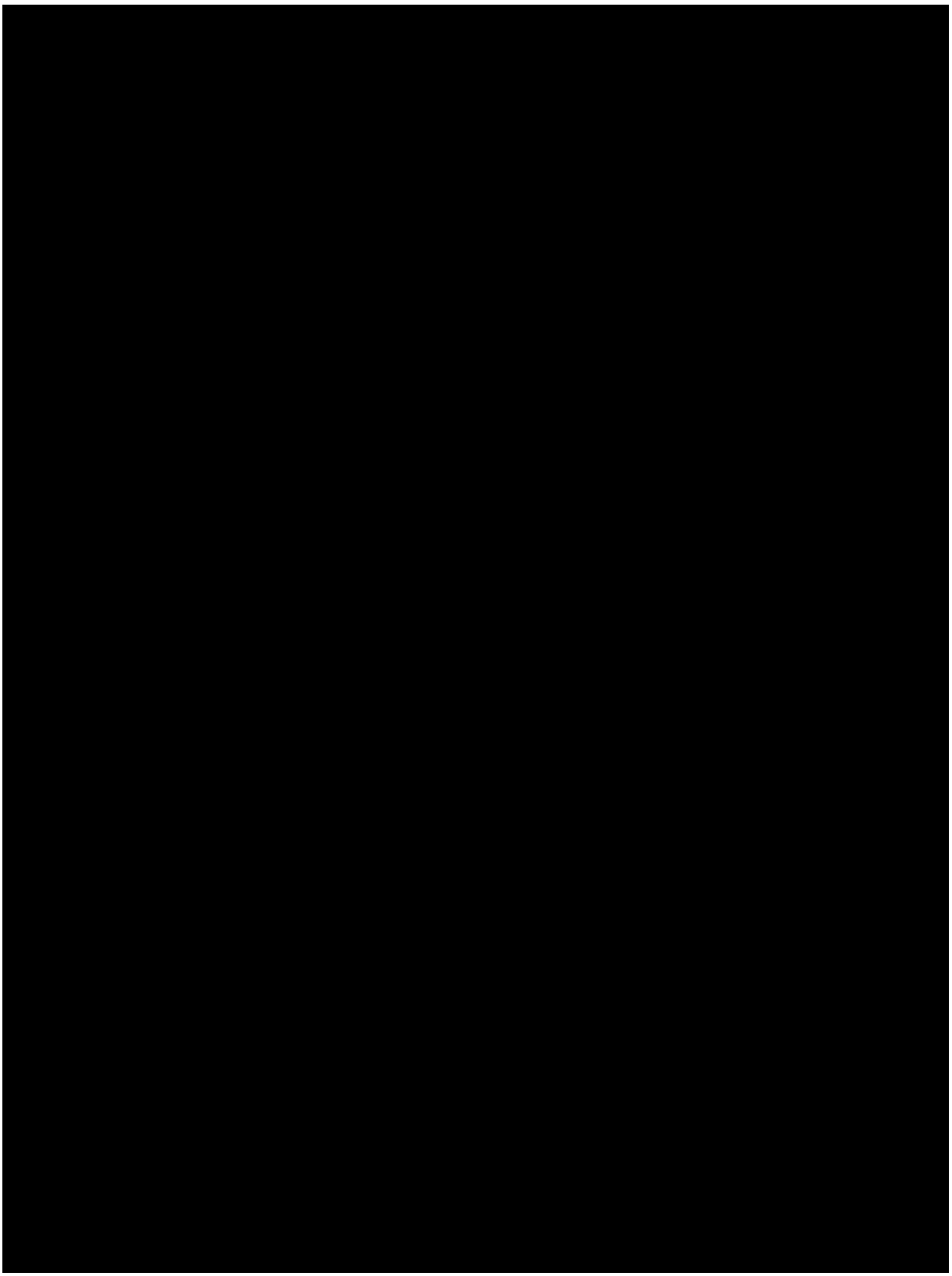
☐ 0 = Clear:	No scaling and no crusting
☐ 1 = Almost Clear:	Superficial focal scaling or crusting restricted to periphery of lesions
☐ 2 = Mild:	Predominantly fine scaling or crusting
☐ 3 = Moderate:	Moderate scaling or crusting covering most or all of lesions
☐ 4 = Severe:	Severe scaling or crusting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

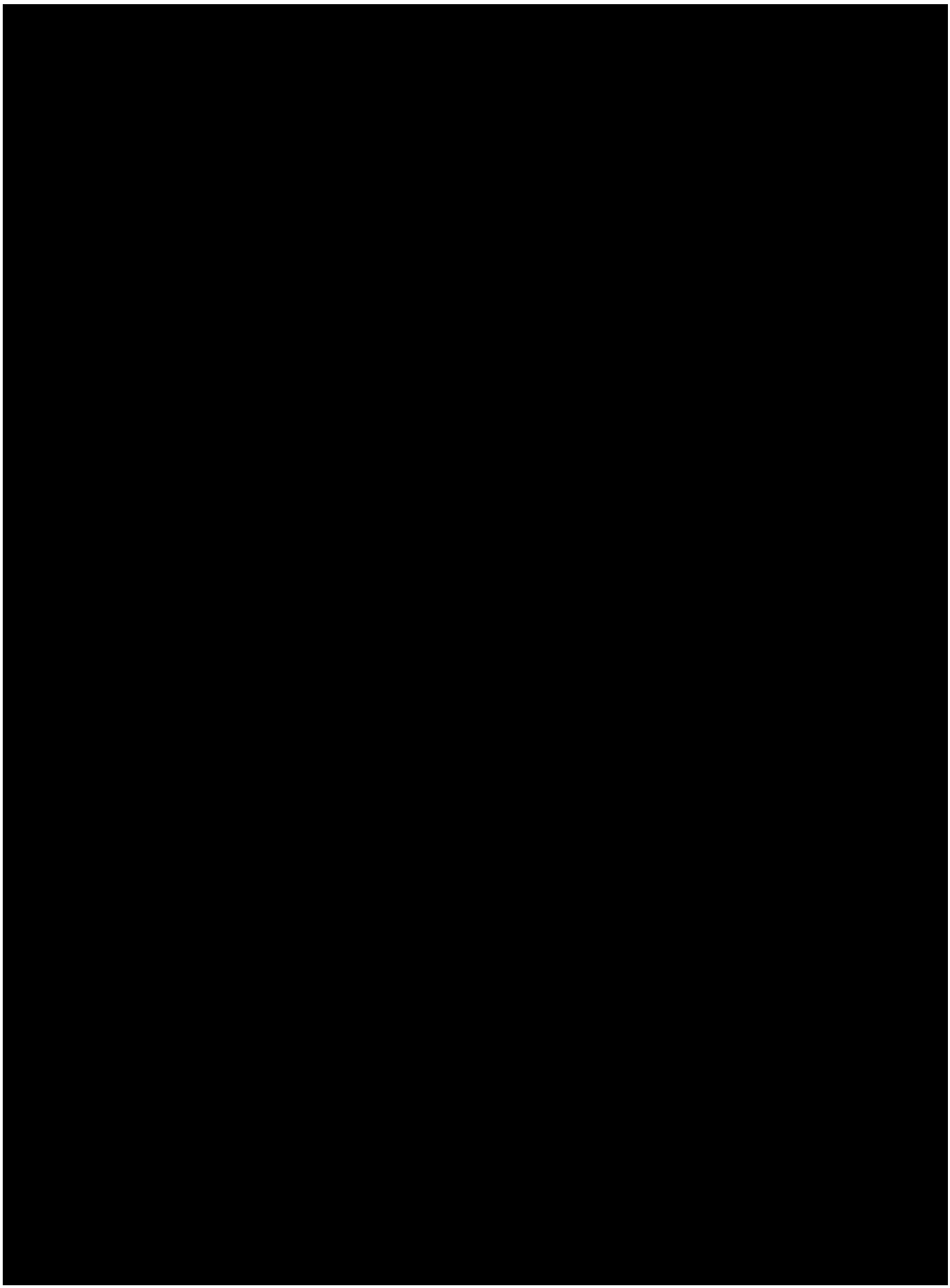
PGA Score for GPP

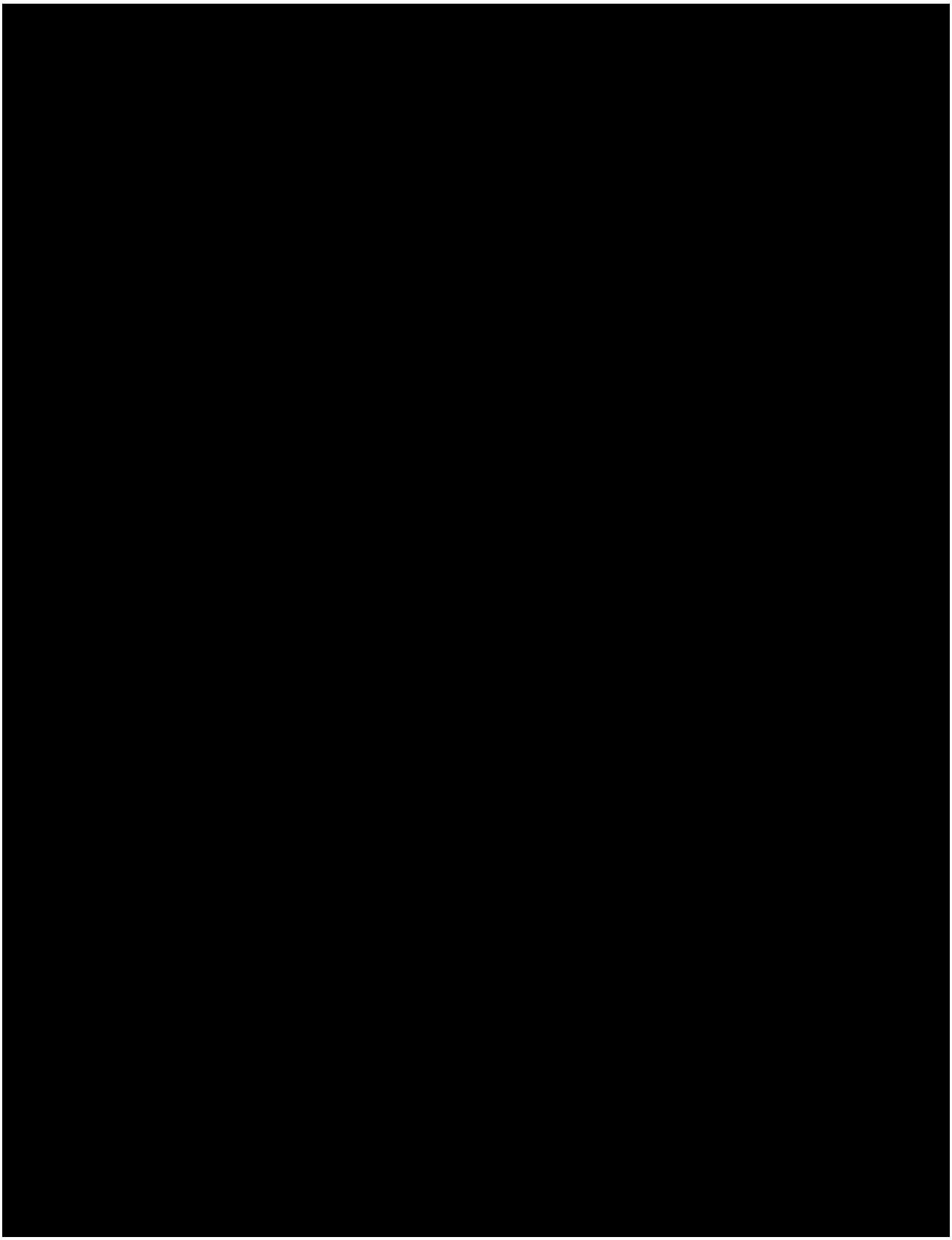
0 = If mean=0 for all three components
1 = If 0 < mean <1.5
2 = If (1.5 <= mean <2.5)
3 = If 2.5 <= mean <3.5
4 = If mean >=3.5

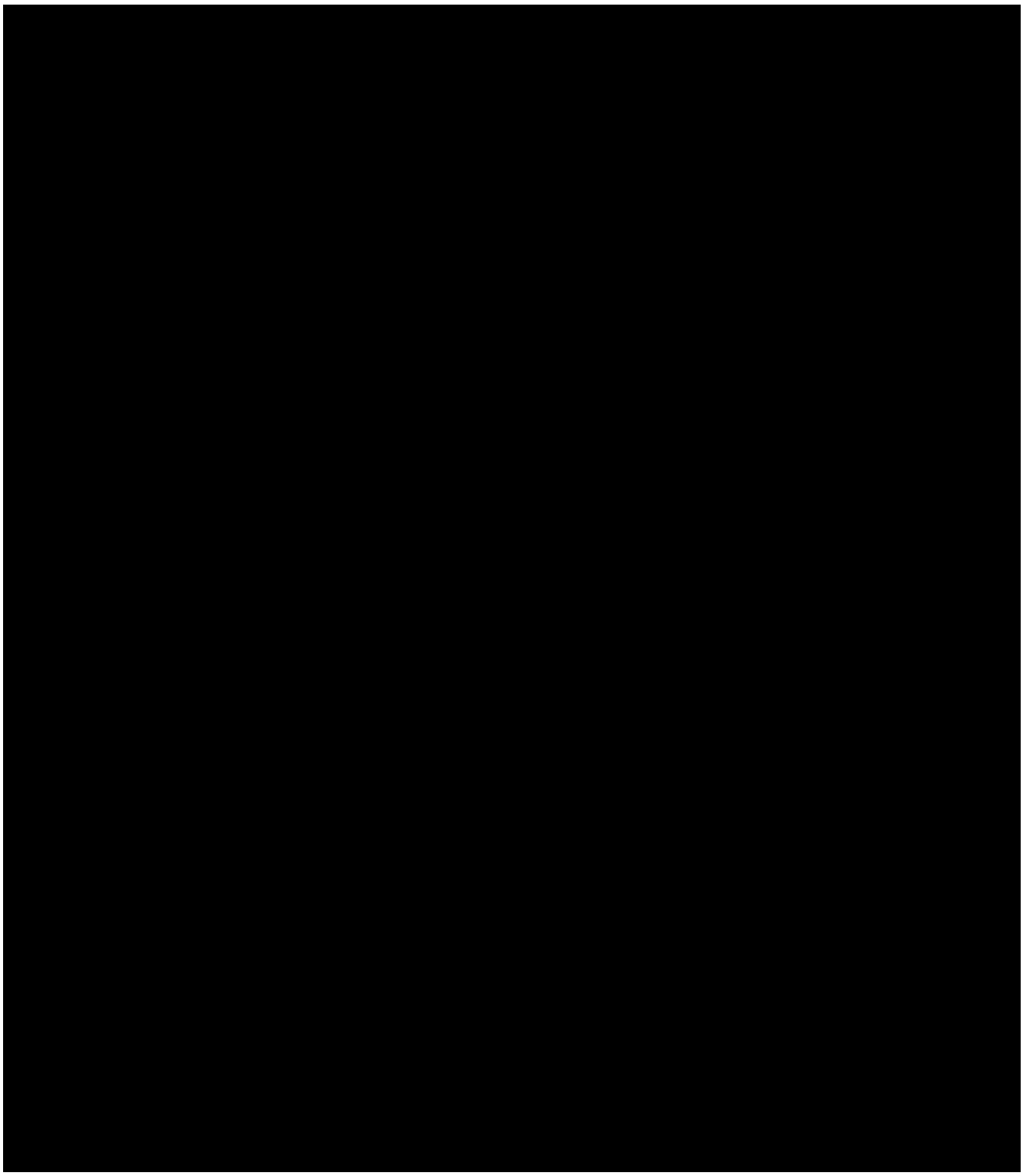
Source: (R15-5200)

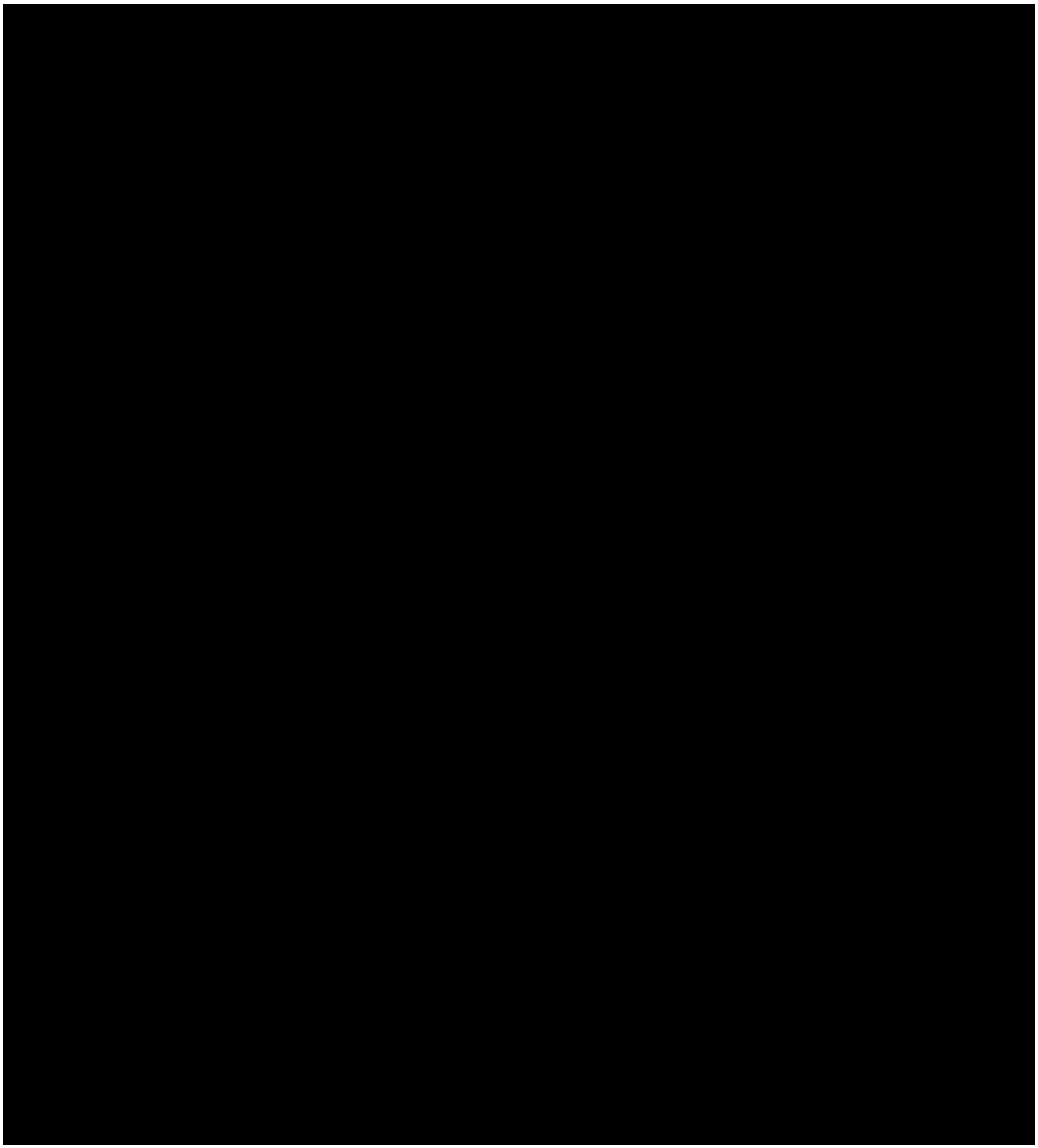


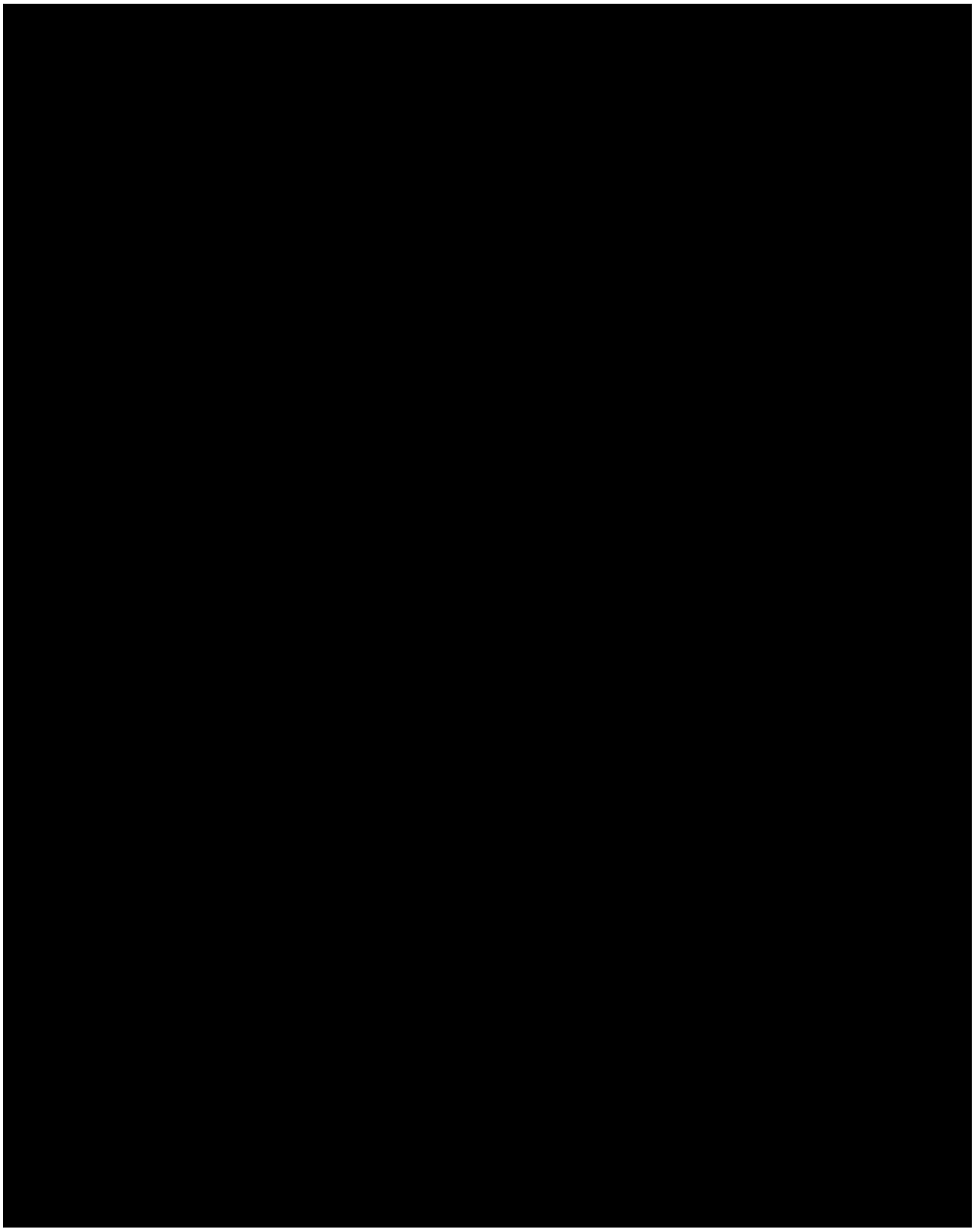












10.1.5 Psoriasis Symptom Scale

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)

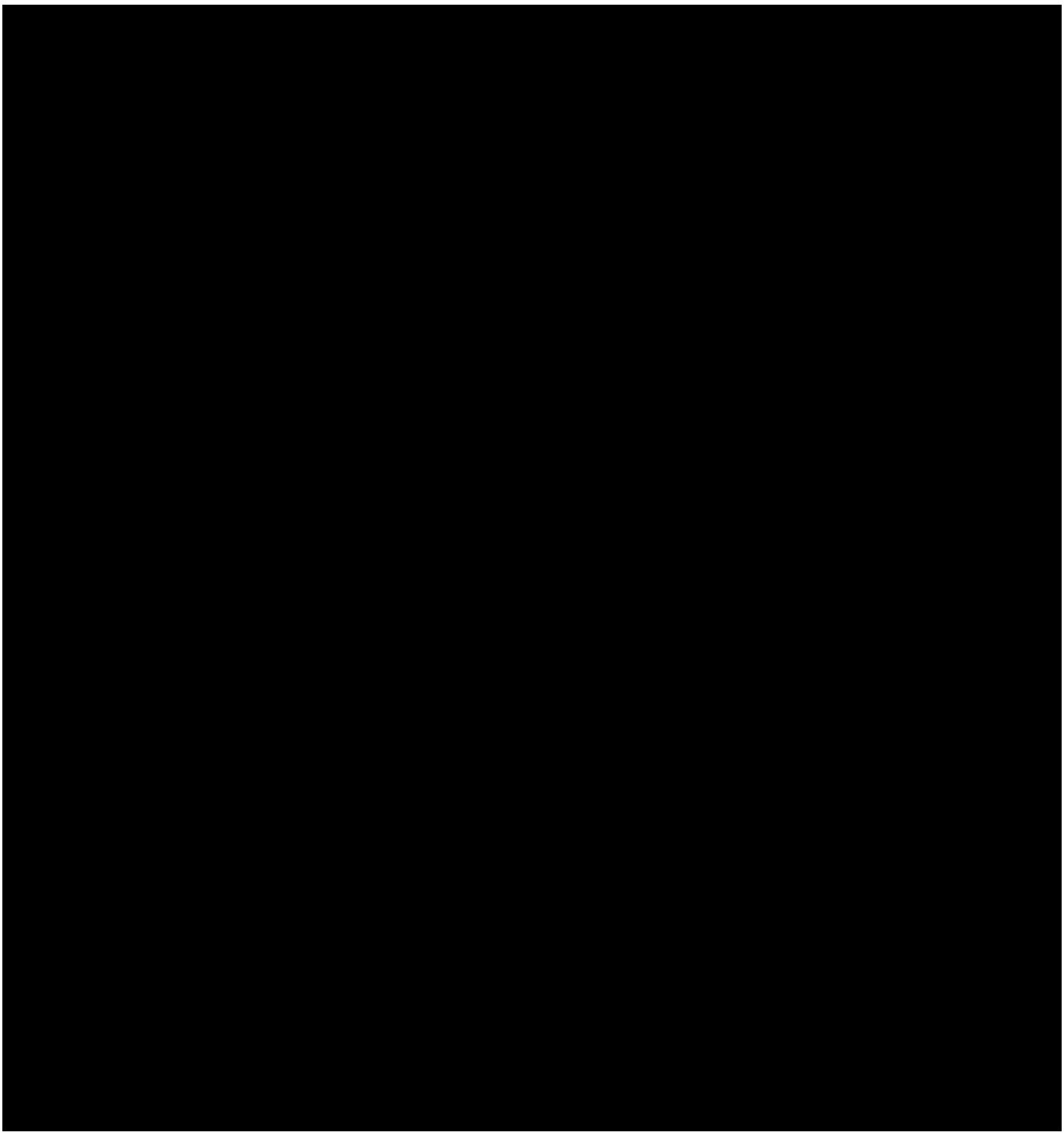
10.1.6 Diagnosis of Anaphylaxis

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

PEF, Peak expiratory flow; BP, blood pressure.

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



10.1.10 Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date: Score: ☐

Name: Diagnosis:

Address:

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please check one box for each question.

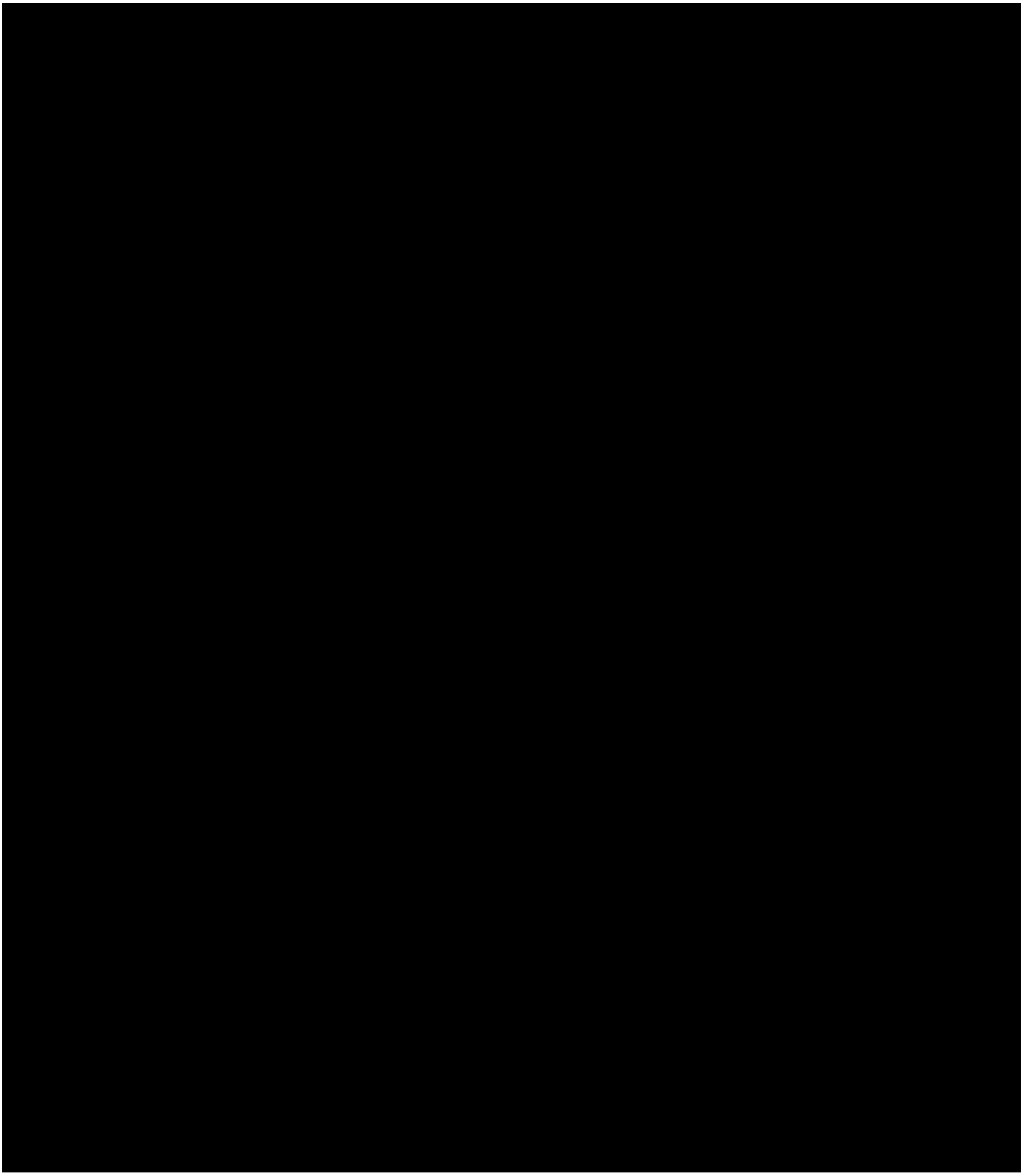
1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **yard?**	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
7.	Over the last week, has your skin prevented you from **working** or **studying**?	yes no	☐ ☐	Not relevant ☐
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	☐ ☐ ☐	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

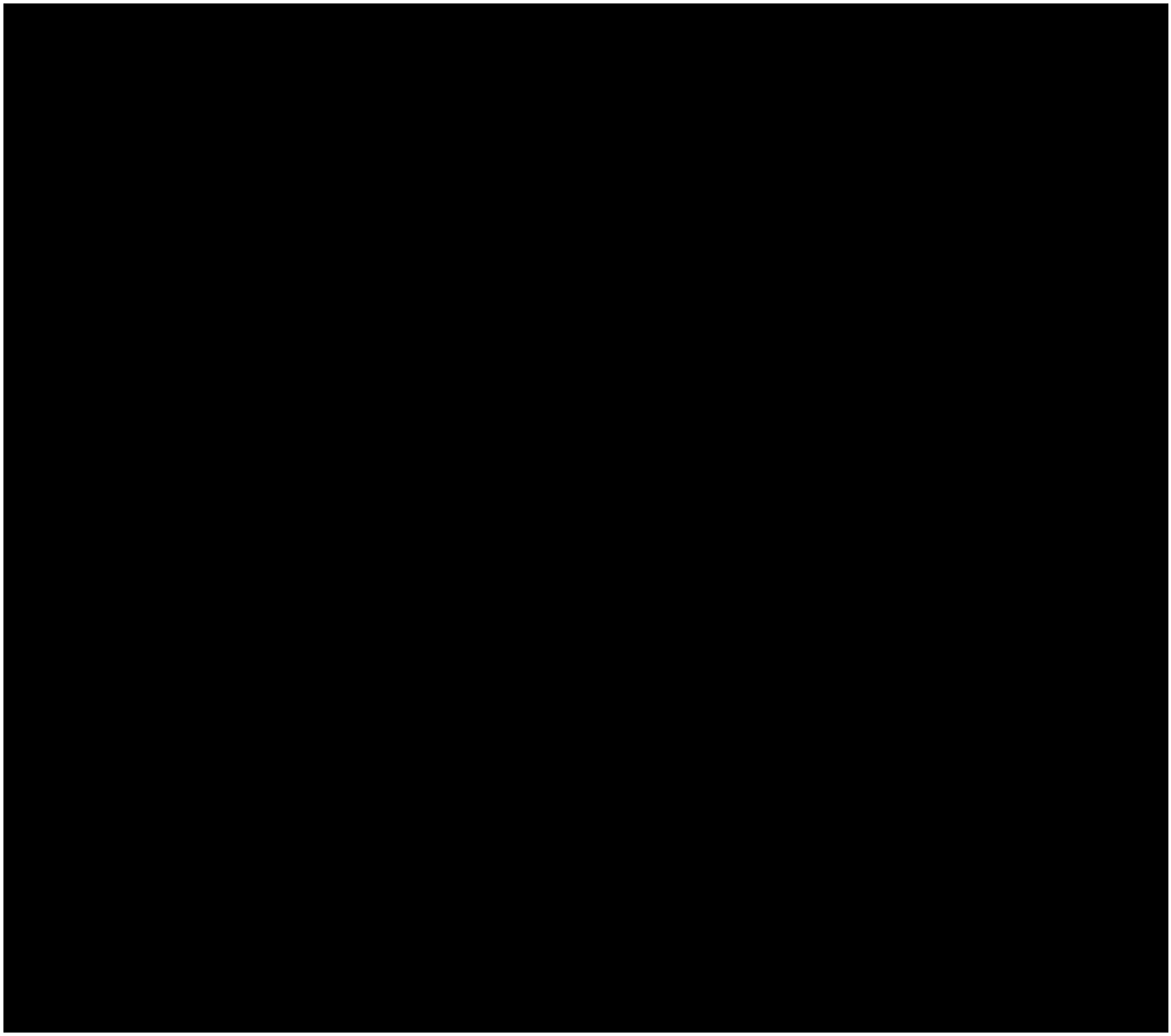
Dermatology Life Quality Index (DLQI) (cont'd.)

9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	☐ ☐ ☐ ☐	Not relevant ☐

Please check you have answered EVERY question. Thank you

Source: (R05-2548)





11 DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		29 July 2020
EudraCT number **EU number**		2018-003081-14
BI Trial number		1368-0027
BI Investigational Medicinal Product(s)		BI 655130 (Spesolimab)
Title of protocol		Effisayil™ 2: Multi-center, randomized, parallel group, double blind, placebo controlled, Phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (Spesolimab) compared to placebo in preventing generalized pustular psoriasis (GPP) flares in patients with history of GPP
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Clinical Trial Protocol Synopsis Table: Trial Objective(s), Trial Design and Rescue Medication
Description of change		The use of ~~a single~~ i.v. dose of BI 655130 for treating patients with onset of acute GPP flares will be evaluated for safety and efficacy as an additional objective.
Rationale for change		Added the option for a 2nd i.v. rescue dose for patients who meet criteria, therefore removed the word "single" to avoid confusion as the patient could receive 2 rescue doses with i.v. BI 655130 (at R1/D1 and R3/D8) if protocol specified criteria is met.
Section to be changed		Clinical Trial Protocol Synopsis Table: Trial Design and Section 3.1 Overall Trial Design
Description of change		Updated the text as following in synopsis (See text in bold): This is a multicenter, randomized, **parallel group**, double-blind, placebo-controlled Phase IIb **dose finding** study **to evaluate efficacy and safety compared to placebo** with multiple subcutaneous (s.c.) doses of BI 655130/placebo **in adolescents from 12 years to less than 18 years of age and adult** patients with history of GPP and currently presenting (at screening and at randomization) with a GPPGA score of 0 or 1 (clear or almost clear).

		Updated the text as following in Section 3.1 (See text in bold): This is a multicenter, randomized, **parallel group**, double-blind, placebo-controlled Phase IIb study comprising of 3 active doses compared to placebo in **adolescents from 12 years to less than 18 years of age and adult** patients ~~(adult and adolescent)~~ with history of GPP and currently presenting (at screening and at randomization) with a GPPGA score of 0 or 1 (clear or almost clear).
Rationale for change		Adapted the trial design text to match the wording from the PIP Decision.
Section to be changed		Clinical Trial Protocol Synopsis Table: Total Number of patients randomized
Description of change		Changed from "12-17 years" to **"12 years to less than 18 years of age"**. For the adolescent patients, it was also clarified that 2 adolescents per treatment group will be included.
Rationale for change		Adapted to match the wording from the PIP Decision.
Section to be changed		Clinical Trial Protocol Synopsis Table: Main In- and exclusion criteria & Section 3.3.2 Inclusion Criteria.
Description of change		Inclusion Criteria #3, 4 and 5 were updated as following (see text in bold): Inc#3 Patients who are not on concomitant GPP treatment at time of randomization (V2) must have had at least two presentations of moderate to severe GPP flare in the past year, at least one of which had evidence of either fever and/or elevated CRP and/or elevated WBC **and/or asthenia and/or myalgia.** Inc#4 Patients who are not on concomitant GPP treatment at time of randomization (V2) but who were on concomitant GPP treatment until shortly before randomization (V2) (≤ 12 weeks before randomization), these patients must have a history of flaring **while on concomitant treatment for GPP or** in case of dose reduction or discontinuation of their concomitant medication. Inc#5 Patients who are on concomitant treatment regimen with retinoids and/or methotrexate and/or cyclosporine must stop at the day of randomization

		(V2). These patients must have a history of flaring **while on concomitant treatment for GPP or** in case of dose reduction or discontinuation of these concomitant medications.
Rationale for change		Clarification/Update
Section to be changed		Clinical Trial Protocol Synopsis Table: Main In- and exclusion criteria & Sections 3.3.3 Exclusion Criteria.
Description of change		Removed Exclusion Criteria #9. ~~Adolescent patients (12-17 years) with hereditary fructose intolerance (HFI).~~
Rationale for change		It is the Sponsor's position that patients with HFI do not need to be excluded from the trial as the BI 655130 formulations do not include fructose. Regarding the sucrose content of the formulation, in humans, sucrose is catabolized to monosaccharides, glucose and fructose by sucrase or isomaltase glycoside hydrolases in the intestines after oral ingestion. However, as these enzymes are limited to the microvilli of the duodenum, sucrose is eliminated unchanged through urinary excretion after intravenous administration. Therefore, patients with HFI should not have adverse effects related to the exposure to sucrose.
Section to be changed		Flow Chart 1 and 2, Footnote 9 in Flow Chart 1 and Footnote 7 in Flowchart 2, Section 5.6 Other Assessments and Section 6.2.2 Treatment Periods
Description of change		Revised from Photographs of skin lesions" to "Photographs of **skin**/skin lesions"
Rationale for change		Clarification. Since the patients are coming in with clear/almost clear skin condition, there may not be any lesions on the body. However, the expectation is that photographs are taken in all regions specified in Section 5.6 irrespective of presence of lesions or not.
Section to be changed		Flow Chart 1&2, Footnotes 19& 20 of Flow chart 1&2 and Section 5.2.6.2.1 AE collection
Description of change		Vital status collection time points included and clarified.
Rationale for change		Clarification
Section to be changed		Flowchart 1 – screening visit window, Flow Chart 1- Footnote 1, Section 6.2.1 Screening and Run-In

		Periods and Figure 3.1:1.
Description of change		Updated screening visit window (day) in Flow chart 1 from "-28 days to -1 day" to "-84 days to -1 day". Updated screening visit window (week) in Flow chart 1 from "-4 wks to 0" to "-12 wks to 0" day". Also updated screening period as following is section 6.2.1 Screening (Visit 1) should normally take place no more than ~~28~~ **84** days before Visit 2. Visit 1 procedures may be completed over multiple physical visits, if needed. Updated Flow chart 1- Footnote 1 as footnote 1a) &1b) as following: 1**a)** Infection testing includes tuberculosis, hepatitis, hepatitis C, and HIV assessments. **b) For patients who sign the informed consent ≥ 4 weeks prior to V2, infection testing must be repeated 2 to 4 weeks prior to V2.** Updated the screening window to -84 to -1 day in figure 3.1:1.
Rationale for change		Updated the screening visit window to -84 days to – 1 day to account for washout period for biologics. Also clarified that for patients who sign the informed consent ≥ 4 weeks prior to V2, infection testing must be repeated 2 to 4 weeks prior to V2 to rule out active infection prior to study drug administration.
Section to be changed		Flow Chart 1- Footnote 4, Section 5.2.2 Vital Signs and Section 6.2.2 Treatment Periods
Description of change		It was clarified that on s.c. study drug administration days, vital signs will be assessed at predose (prior to blood sampling) and 10 mins after the end of drug administration **and at Visit 2 and Visit 3 additional measurements will be performed approximately 60 minutes after the end of drug administration (i.e. 60 minutes after last injection).**
Rationale for change		Update. Visits 2 and 3 represent the first visits, where trial medication will be administered – which is why the time window for the monitoring of vital signs has been extended during these visits.

Section to be changed		Flow Chart 1- Footnote 5 and Flow Chart 2- Footnote 4
Description of change		Added clarification that if urine pregnancy test is positive, study drug administration will be postponed until negative result of serum pregnancy test is available.
Rationale for change		Clarification
Section to be changed		Flow Chart 1- Footnote 16, Flow Chart 2- Footnote 8 and Section 5.5.1 Methods and timing of sample collection
Description of change		Clarified that optional lesional **or non-lesional (if no lesions are present)** skin biopsies are to be collected. In Section 5.5.1, it was further clarified that **in an event of a GPP flare, a lesional biopsy** will be collected at the site of most inflammatory (deepest red erythema) lesion. **For consistency, all future biopsies should be taken from this lesion or closest proximity (absolutely same anatomical area).**
Rationale for change		Clarification
Section to be changed		Flow Chart 1- Footnote 13, Flow Chart 2- Footnote 12, Section 5.2.5 and Section 6.2.2
Description of change		Updated From: ~~At the visit with i.v. administration, the local tolerability will be assessed approximately 1 hour after the end of infusion and at visits with s.c. administration, local tolerability will be assessed approximately 10 mins after the end of s.c. injection(s).~~ To: **Local tolerability at the administration site of BI 655130/placebo will be assessed during the study drug administration (i.v. or s.c.) and at the time of AE assessment by questioning retrospectively since the last visit. Any observed local tolerability reaction, e.g. swelling, induration, heat, redness, pain, and other findings should be reported as an adverse event.**
Rationale for change		Clarified that the local tolerability reactions should be captured as AEs reporting and added the retrospective questioning for local tolerability

		reactions to the next visit in order to capture any potential adverse event consistent with a local tolerability reaction.
Section to be changed		Flow Chart 1 and 2 -Footnotes 14 &15, Section 3.1 Overall Trial Design, Footnotes 2& 3 of Figure 3.1:1, Footnotes 5&6 of Figure 3.1:1 overall trial design, Section 3.3.4.1 Discontinuation of trial treatment and Section 6.2.3 follow-up period and trial completion
Description of change		Clarified that V14 will be recorded as the End of Study visit (i.e., EoS1) for patients who qualify and agree to enter the OLE trial (1368-0025). V14 will also be recorded as End of Study Visit for patients who prematurely discontinue with the last dose of treatment up to and including Day 232 and who agree to complete all remaining study visits up to Wk 48 from randomization. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. It was also clarified that EoS2 visit is applicable for patients who do not qualify or who do not agree to enter into the OLE trial at Week 48. EoS2 is also applicable for patients who prematurely discontinue with the last dose of treatment after Day 232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. In Section 3.3.4.1, it was further clarified that even if the trial treatment is discontinued, the patient remains in the trial and, given his/her agreement considering the GCP-guidelines, ideally should follow all of the remaining scheduled study visits and procedures as outlined in the Flow Chart 1 or Flow Chart 2 (as applicable) and Section 6.2.3 up to Wk 48 from randomization; If a patient is not willing to follow the whole visit schedule, the patient should at a minimum be followed for 16 weeks after last study drug administration (REP) and at least the scheduled visit at Week 48 (i.e. at the end of treatment period) should be conducted. Patients refusing to return to the study site should at least provide safety information by phone at the respective visits. Definition of Trial Completion was also updated as following: Trial completion for an individual patient who

		~~qualifies and agrees to enter OLE trial~~ has completed **end of study visit per protocol**. **It could b**e EoS1 **visit or EoS2 visit as defined above.** ~~at week 48 **or** a patient who doesn't qualify to enter OLE trial or who may have qualified, but do not agree to participate on the OLE trial and has completed EoS2 visit per protocol.~~
Rationale for change		Provided clarification on the expectation of visits to be completed including end of study visit for all patients irrespective of premature discontinuation or not.
Section to be changed		Flow Chart 2 - Footnote 21
Description of change		"For Visit R3, added an "X" with a new coordinating footnote #21 for "pregnancy test", '12 Lead ECG", "IRT call", "dispense/administration study drug" and "local tolerability"
Rationale for change		Update. If a patient meets a protocol specified criteria for receiving R3/D8 dosing, then these procedures are to be completed.
Section to be changed		Abbreviations
Description of change		Included abbreviations for Alkaline Phosphatase and Tuberculin Skin Test
Rationale for change		Update
Section to be changed		Section 1.1 Medical Background and Section 3.2 Discussion of trial design, including choice of control groups
Description of change		Added certolizumab (Cimzia®) to the list of medications that have been approved in Japan for treatment of GPP.
Rationale for change		Certolizumab has been approved in Japan for treatment of GPP.
Section to be changed		Section 1.2 Drug Profile (Data from clinical studies)
Description of change		Added Hidradenitis Suppurativa (HS)
Rationale for change		Included Hidradenitis Suppurativa (HS) as this is also considered to be an inflammatory disease similar to GPP, PPP, AD and IBD.
Section to be changed		Section 1.2 Drug Profile (Data from clinical studies)
Description of change		Included additional details on the 1368.3 trial

		results.
Rationale for change		Updated information as this 1368.3 is completed with CTR archived in 2018.
Section to be changed		Section 1.2 Drug Profile
Description of change		Included additional results/data for 1368.15 trial
Rationale for change		Update based on IB version 7
Section to be changed		Section 1.4 Benefit-Risk Assessment
Description of change		A total of ~~more than 212~~ **an estimated 378** subjects have been exposed to single or multiple i.v. doses of BI 655130 as of September ~~2018~~**2019**. Also included the summary of Benefit-Risk Assessment in context of COVID-19 pandemic for patients participating in clinical trials investigating Spesolimab.
Rationale for change		Exposure data has been updated based on SEP 2019 DSUR which was included in IB version 7. Summary of Spesolimab Benefit-Risk Assessment in context of COVID-19 infection has been included.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		Section 3.1 Overall Trial Design and Table 3.1:3 Study Definitions
Description of change		Included the following criteria for receiving i.v. infusion with 900 mg of BI 655130 on R3/D8. • **For patients with GPPGA score of ≥ 3 and a pustular component of GPPGA of ≥2 at R1: the pustular component of GPPGA is ≥2 and total GPPGA is ≥2 at R3/D8.** • **For patients with GPPGA score of 2 and a pustular component of GPPGA of ≥2 at R1: the pustular component of GPPGA is ≥2 at R3/D8.**

Rationale for change		Update. In an event of a GPP flare, in addition to receiving i.v. rescue treatment with OL BI 655130 on R1/D1, another dose of i.v. BI 655130 is being allowed on R3/D8 if the patient meets protocol specified criteria.
Section to be changed		Section 3.1 Overall Trial Design and Flow Chart 2 – footnote 13
Description of change		It was clarified that once the OL s.c. visit assignment is calculated by referring to Flow Chart 1, all study procedures scheduled for this first dose of OL s.c. maintenance treatment visit and subsequent OL maintenance treatment visits should be completed per Flow Chart 2.
Rationale for change		Clarification
Section to be changed		Section 3.1 Overall Trial Design and Table 3.1:3 Study Definitions
Description of change		Included the following threshold for switching from OL s.c. dose of 300 mg BI 655130 q12 weeks to intensified maintenance therapy with open label s.c. dose of 300 mg BI 655130 q4 weeks. **If the patient's GPPGA total score increases by ≥ 1 (with or without the presence or new appearance of pustules), or if there is an increase in the pustular component of GPPGA ≥ 1 from any of the previous OL maintenance visit(s)**, then the investigator ~~should~~ **may** treat the patient with intensified maintenance therapy with open label s.c. dose of 300 mg BI 655130 q4 weeks.
Rationale for change		Updated Information. Included criteria to switch the patient from OL s.c. dose of 300 mg BI 655130 q12 weeks to intensified maintenance therapy with open label s.c. dose of 300 mg BI 655130 q4 weeks.
Section to be changed		Section 3.1 Overall Trial Design, Table 3.1:3 Study Definitions and Section 4.2.2 Restrictions
Description of change		Included allowance of use of topical treatments and topical corticosteroids after four weeks following i.v. dose rescue treatment with open label BI 655130 at R1/D1and during OL maintenance treatment period. Use of these treatments does not lead to IMP discontinuation.

Rationale for change		Clarification/Update.
Section to be changed		Section 3.1 Overall Trial Design
Description of change		Added the following text: **The primary analysis of this trial is planned to be performed once all randomized patients have completed or early discontinued from the 48 week treatment period; 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.**
Rationale for change		Updated and provided brief summary on timing of primary and final analysis. Further details are also described in Section 7 of the CTP.
Section to be changed		Figure 3.1:1 Overall Study Design
Description of change		Updated figure and footnotes as following: ** Please refer to Figure 3.1:2 for study design in the event experiences 1st GPP flare and Section 3.1 for further details. [1] Investigator should treat the patient with intensified maintenance therapy of OL BI 655130 s.c. 300 mg q4weeks if the patient experiences any further disease worsening. **If the patient's GPPGA total score increases by ≥ 1 (with or without the presence or new appearance of pustules), or if there is an increase in the pustular component of GPPGA ≥ 1, the Investigator may treat the patient with intensified maintenance therapy of OL BI 655130 s.c. 300 mg q4weeks.** **[2] V14 will be recorded as the End of Study visit (i.e., EoS1) for patients who qualify and agree to enter the OLE trial (1368-0025). V14 will also be recorded as End of Study Visit (EoS 1) for patients who prematurely discontinue with the last dose of treatment up to and including Day 232 and who agree to complete all remaining**

		study visits up to Wk 48 from randomization. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. ~~EOS1: Visit will be conducted at week 48 from randomization visit. This is the last visit for patients who qualify and agree to enter into the OLE trial.~~ This visit will be their End of Study visit for this trial. [3]EoS 2 visit is applicable to patients who do not qualify or who do not agree to enter into the OLE Trial (1368-0025) at Wk 48. EoS2 visit is also applicable for patients who prematurely discontinue with the last dose of treatment after D232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. ~~These patients need to be followed for 16 weeks after the last dose of the study drug administration. EoS2 will be their End of Study visit for the trial~~.
Rationale for change		Update/Clarification
Section to be changed		Table 3.1:2
Description of change		Footnotes updated as following [1]EoS1should be performed at least 7 days after ~~R1~~**the last rescue treatment with i.v. OL BI 655130 is given.** ~~[2]If patients on randomized treatment and flare at the visit of V14 (Week 48), the investigator could still treat the patient with the rescue treatment with BI 655130 and determine whether to roll over the patient by planning another visit 7 days after R1.~~ [~~3~~**2**]If it was determined that a patient does not qualify or not agree to roll over to OLE, the ~~then at the time of the decision, no further~~**patient still needs to attend the** visits ~~listed in this table beyond will be required, patient will go directly to EoS2~~**planned in the table if possible.**
Rationale for change		Update/Clarification
Section to be changed		Figure 3.1:2 Study Design in the event a patient experiences 1st GPP Flare
Description of change		Updated figure and footnotes as following: [3]Investigator may treat the patient with intensified maintenance therapy of OL BI 655130 s.c. 300 mg q4 weeks if the patient ~~experiences any further disease worsening~~ meets protocol specified criteria. Please refer to Section 3.1. ***Dosing days. Please refer to Section 3.1 for further details.** **[5] V14 will be recorded as the End of Study visit**

		(i.e., EoS1) for patients who qualify and agree to enter the OLE trial (1368-0025). V14 will also be recorded as End of Study Visit (EoS 1) for patients who prematurely discontinue with the last dose of treatment up to and including Day 232 and who agree to complete all remaining study visits up to Wk 48 from randomization. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. ~~EoS1, Visit will be conducted at week 48 from randomization visit. This is the last visit for patients who qualify and agree to entre into the OLE trial.~~ [6]EoS2 is applicable for patients who do not qualify **or who do not agree to** enter OLE trial (1368-0025) **at Week 48. EoS2 is also applicable for patients who prematurely discontinue with the last dose of treatment after D232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial.**
Rationale for change		Update/Clarification
Section to be changed		Section 3.3.4 Withdrawal of patients from treatment or assessments
Description of change		Removed the following statement: ~~Every effort should be made to keep the patients in the trial: if possible on treatment, or at least to collect necessary data until 16 weeks following the last study drug administration.~~
Rationale for change		Removed duplicate information as sections 3.3.4.1 & 3.3.4.2 includes details on handling of patients with premature treatment or trial discontinuation.
Section to be changed		Table 4.1.1:1 BI 655130 for Rescue Treatment, Section 4.1.2 Selection of doses in the trial and dose modifications , and Table 4.1.4:1Treatments used in the trial
Description of change		BI 655130 for Rescue Treatment **(at RI/D1 Or at R1/D1& R3/D8)**
Rationale for change		Updated and Clarified the visits where rescue dose with i.v. OL BI 655130 could be given to the patient.

[redacted]

[redacted]

Section to be changed		Section 4.1.5.1 Blinding
Description of change		Added a statement in section 4.1.5.1 that if interim analysis is performed, only data with rescue treatment periods will be used and therefore no unblinding of randomized treatments will be required.
Rationale for change		Clarification/Update. The interim analysis may be performed to support potential submission for acute flare treatment with i.v. regimen. Keeping blinding of the randomized s.c. treatment ensures the integrity of the trial.

[redacted]

Section to be changed		Section 5.2 Assessment of Safety
Description of change		Removed “Injection site reactions” and added with “Immunogenicity (ADA)”
Rationale for change		Injection site reactions was removed as Local tolerability assessments will be performed throughout the trial. The assessment of local tolerability will be based on reported adverse events. Immunogenicity (ADA) was added for consistency with Section 7.2.5 of the CTP.
Section to be changed		Section 5.2.3 Safety Lab Parameters
Description of change		Updated text to clarify that local labs are to be used at visits involving i.v. administration of OL BI 655130. The following statement has been included as well. It is highly encouraged to collect and assess the labs the day of i.v. administration; however in exceptional cases, labs may be collected one day prior to ensure lab results are available prior to dosing.
Rationale for change		Clarification
Section to be changed		Table 5.2.3:1 Safety Lab Tests & Section 3.3.3

		Exclusion criteria
Description of change		Footnote 1 in table 5.2.3:1 updated to clarify that for patients who sign the informed consent ≥ 4 weeks prior to V2, infection testing must be repeated 2 to 4 weeks prior to V2. Footnote 1 added to the infection tests which are to be collected only at screening. Footnote 3 was clarified that TST can be done at site if retest QuantiFERON test result is indeterminate. Exclusion 7 and footnotes 3, 4 and 5 in table 5.2.3:1 were also updated to include option for using alternative test/procedure (as per local standards) to rule out TB if tuberculin skin test is not used within some countries.
Rationale for change		Clarification/Updated Information
Section to be changed		Section 6.2.1 Rescreening
Description of change		Added the following clarification. Rescreening transaction must be registered in the IRT system. A new patient number will be provided which will be linked to the previous patient number in the IRT system.
Rationale for change		Clarification
Section to be changed		Section 6.2.3 Follow-up period and trial completion
Description of change		Added clarification that End of Study visit must be registered in IRT system for all randomized patients.
Rationale for change		Clarification
Section to be changed		Section 7 Stats Methods and Determination of Sample Size
Description of change		Removed “During the conduct of the trial, the event rate will be closely monitored in a blinded way. If the event rate is lower than expected, the sample size may be expanded to ensure that at the time when the last randomized patient has completed (or discontinued from) 48 weeks of treatment, that at least the target number of events has been observed.”
Rationale for change		It is expected that sufficient events could be observed in current target population. So the monitoring is not needed.

Section to be changed		Section 7 Stats Methods and Determination of Sample Size Section 7.2.7 Interim Analysis
Description of change		Added the following statement is Section 7: To support a potential BI 655130 acute GPP flare treatment submission, an interim analysis of the clinical efficacy and safety data collected during the BI 655130 OL i.v rescue and s.c. maintenance treatment periods may be performed. For further details refer to Section 7.2.7. Added further description is section 7.2.7 on the interim analysis for i.v. rescue treatment period and OL maintenance treatment period.
Rationale for change		This interim analysis is needed to support potential submission for acute flare treatment.
Section to be changed		Section 7.4 Randomization
Description of change		The first twelve adolescent patients will be randomized in a 1:1:1:1 ratio to the four arms regardless of concomitant use of systemic GPP medications at randomization (yes vs. no) and blocking factor region (Japan vs. Rest of world).
Rationale for change		To ensure at least 2 adolescent patients in each randomized treatment arm
Section to be changed		Section 7 Stats Methods and Determination of Sample Size, Section 7.5 Determination of Sample Size and Table 7.5:1
Description of change		Changed “final analysis” to “primary analysis”
Rationale for change		Correction
Section to be changed		Section 8.3.1 Source Documents
Description of change		Removed the following text as this is not applicable. ~~Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient’s name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients’ source documents~~
Rationale for change		The text was removed as it is not applicable for the trial. There is no source documents that are being sent to external committees such as adjudication committee etc.

11.2 GLOBAL AMENDMENT 2

Date of amendment		19 April 2021
EudraCT number **EU number**		2018-003081-14
BI Trial number		1368-0027
BI Investigational Medicinal Product(s)		BI 655130 (Spesolimab)
Title of protocol		Effisayil™ 2: Multi-center, randomized, parallel group, double blind, placebo controlled, Phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (Spesolimab) compared to placebo in preventing generalized pustular psoriasis (GPP) flares in patients with history of GPP
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Clinical Trial Synopsis Table: Statistical Methods
Description of change		Included the following text in synopsis: **Descriptive comparison of adult versus paediatric data will be performed.**
Rationale for change		Added the clarification to align with the Pediatric Investigational Plan.
Section to be changed		Flow chart 1
Description of change		Added a footnote 21 to clarify that IRT registration is expected once at End of Study visit (as applicable) for a patient.
Rationale for change		Clarification

Section to be changed		Flow Chart 2
Description of change		• Add a footnote 22 that "IRT call" is applicable for dosing visits only (q 12wks or q 4 wks in case the patient has been switched to intensified maintenance treatment schedule) • Added a footnote 23 to clarify that IRT registration is expected once at End of Study visit (as applicable) for a patient.

		• Clarified foot note 4 as following: Only applicable for women of childbearing potential. S – serum pregnancy test. U – urine pregnancy tests will be performed at all other visits indicated. 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 (via central lab **with the exception of R1 and R3 [if patient qualifies to receive i.v. dosing**] visits where serum pregnancy test can be performed locally) and study drug administration will be postponed until negative result of serum pregnancy test is available.
Rationale for change		Clarification
Section to be changed		Section 1.4.2 Risks
Description of change		Added the following guidance related to COVID-19 vaccination: Patients may receive COVID-19 vaccination in line with local recommendations/guidance and approved labels. However, it is not known whether there is any negative impact of spesolimab on the protective effect of COVID-19 vaccines.
Rationale for change		Update
Section to be changed		Section 3.1: Handling of Investigator Prescribed Standard of Care (SoC) for GPP disease during Rescue Treatment Period of the 1st GPP Flare
Description of change		Clarified that use of Investigator prescribed SoC during the first 4 weeks of receiving i.v. rescue treatment with open label BI 655130 at R1/D1 is not allowed and if used, it will lead to patient discontinuation from trial treatment. Allowed treatment with topical treatments/topical corticosteroids, methotrexate, cyclosporine and retinoids after 4 weeks following i.v. rescue treatment with open label BI 655130 at R1/D1. These patients may continue on receiving open label s.c. BI 655130.
Rationale for change		Experience from other completed and ongoing GPP trials as well as feedback from investigators indicate that a most patients are benefitting from i.v. rescue treatment with Spesolimab, especially with regards to the cardinal symptom of pustulosis.

		However, a subset of these patients still suffer from residual symptoms and may require adjunctive treatment. Therefore the use of methotrexate, cyclosporine and retinoids is being allowed after 4 weeks following i.v. rescue treatment in order to bridge the period before open label s.c. treatment is started. As this will be allowed only 4 weeks after the first dose of i.v. rescue treatment no primary or secondary endpoints will be affected.
Section to be changed		Section 3.1: Handling of Investigator Prescribed Standard of Care (SoC) for GPP disease during Open Label Maintenance Treatment Period
Description of change		Allowed treatment with methotrexate, cyclosporine and retinoids during OL maintenance treatment period.
Rationale for change		Clarified/updated the time point after Completing the rescue treatment period when additional non-restricted GPP treatment may be initiated.
Section to be changed		Table 3.1:3 Study Definitions
Description of change		• Clarified what should be considered as baseline value for efficacy measurements. **Baseline value for efficacy measurements is the last value measured before 1st IMP dose at V2.** • Updated the below text for "Investigator Prescribed Standard of Care" as following: Note: Any use of Investigator Prescribed SoC for GPP disease during the trial will lead to the discontinuation of the trial treatment with the following exceptions. Use of topical treatment/topical corticosteroid, **methotrexate, cyclosporine and retinoids** is permitted after four weeks following i.v. dose rescue treatment with open label BI 655130 at R1/D1 and also during the OL maintenance treatment period. Refer to section 4.2.2.2 for further details.
Rationale for change		Clarification/Update
Section to be changed		Table 3.1:3 Study Definitions
Description of change		Added Definition for Partial Response to GPP flare treatment:

		a GPPGA score 0 or 1 was not achieved, but a reduction in GPPGA score (to <3) **or** GPPGA pustule sub-score (to <2) was observed after receiving the rescue treatment with OL i.v. dose of BI 655130.
Rationale for change		Update
Section to be changed		Figure 3.1:1 Study Design in the event a patient experiences 1st GPP Flare
Description of change		Removed "o" from footnote#3 as it was a typographical error. **[3]EoS 2:** It is applicable to patients who do not qualify or who do not agree to enter into the OLE Trial (1368-0025) at Wk 48. EoS2 is also applicable for ~~o~~ patients who prematurely discontinue with the last dose of treatment after Day 232. Since these patients prematurely discontinued, they would not qualify to enter OLE trial. EoS2 will be their End of Study visit for the trial.
Rationale for change		Corrected typographical error
Section to be changed		Figure 3.1:2 Study Design in the event a patient experiences 1st GPP Flare
Description of change		Updated figure to clarify that any use of Investigator Prescribed SoC for GPP disease during the trial will lead to the discontinuation of the trial treatment with the following exceptions. Use of topical treatment/topical corticosteroid, methotrexate, cyclosporine and retinoids is permitted after four weeks following i.v. dose rescue treatment with open label BI 655130 at R1/D1 and also during the OL maintenance treatment period.
Rationale for change		Clarification/Update
Section to be changed		Section 3.3 Selection of Trial Population
Description of change		A suitable number of countries/sites will participate globally in order to minimize the risk of under recruiting **and to meet the goal of 120 patients (including 8 adolescent patients) randomized**. Due to the rareness of the disease, a high number of sites will participate relative to the number of patients required.
Rationale for change		Clarification to align what is noted under synopsis, section 3.1 and section 7.5.

Section to be changed		Section 3.3.4.1: Discontinuation of Trial Treatment
Description of change		Included the following as one of the discontinuation of trial treatment reasons: **• Worsening of clinical status or GPP symptoms requiring treatment with restricted medication (Section 4.2.2.1) in the investigator's opinion.** **• The patient experiences an infection with SARS-CoV-2 (as confirmed by PCR test). The patient may resume trial treatment following recovery from SARS-CoV-2 infection if the patient is expected to derive clinical benefit, as agreed between the investigator and sponsor.**
Rationale for change		Update
Section to be changed		Section 4.1.4 Drug Assignment and Administration of doses for each patient
Description of change		Added the following statement: **During the COVID-19 pandemic, physical visits to the sites may need to be restricted to ensure patient's safety. Based on a thorough assessment of the benefits and risks, the investigator may still decide to continue the trial treatment and the administration of the study medication may be performed at patient's home under the supervision of the investigating physician or a designee. The trial medication may be shipped to the patient's home if acceptable according to local law and regulations. This must be approved by the sponsor's trial team.**
Rationale for change		Added pre-emptive mitigations to ensure patient safety and trial continuity during the COVID-19 pandemic.
Section to be changed		Section 4.2.1: Other treatments and emergency procedures
Description of change		The following update was made. The use of Investigator Prescribed SoC will lead to the discontinuation of the trial treatment except for the use of topical treatment/topical corticosteroids**, methotrexate, cyclosporine and retinoids** during OL rescue treatment period (4 weeks following i.v. dose rescue treatment with OL BI 655130 at R1/D1) and OL maintenance treatment period.

Rationale for change		Update
Section to be changed		Table 4.2.2.1:1: Restricted Medication Table
Description of change		Wash out requirement of the phototherapy and topical treatments was removed. Also, for topical corticosteroids, there is no wash out requirement prior to randomization, however these must be stopped at the day of randomization.
Rationale for change		Topical treatments/phototherapy: are not expected to have any substantial impact on the core symptoms of the GPP disease (erythema, scaling, pustulosis) and therefore wash out requirement was removed. Topical corticticosteroids: As there is no washout for systemic treatment such as cyclosporine, methotrexate and retinoids, no washout is considered to be needed for topical steroids which are not as effective. However, as their impact on "soft" disease symptoms like erythema and itching cannot be ruled out, and therefore they should be stopped at the time of randomization.
Section to be changed		Section 4.2.2.2 Restrictions regarding concomitant treatment during the trial (Post V2)
Description of change		**<u>Topical Treatments:</u>** Topical treatment and any other therapies (e.g. Phototherapy) for GPP are not allowed throughout the study with the following exceptions: • Topical treatment for other conditions (e.g. fungal infections, **plaque psoriasis etc.**) is allowed. • Topical treatment is permitted **for treatment of GPP** after 4 weeks following i.v. dose rescue treatment with OL BI 655130 at R1/D1. • Topical treatment is permitted **for treatment of GPP** during the OL maintenance treatment period. **<u>Topical corticosteroids:</u>** Topical corticosteroids for the treatment of GPP are not allowed throughout the study with the following exceptions: • **Topical corticosteroid for other conditions (e.g. fungal infections, plaque psoriasis etc.) may be initiated post visit 2 if needed.**

		• Topical corticosteroid is permitted **for treatment of GPP** after 4 weeks following i.v. dose rescue treatment with OL BI 655130 at R1/D1. • Topical corticosteroid is permitted **for treatment of GPP** during the OL maintenance treatment period. **<u>Methotrexate, Cyclosporine, Retinoids:</u>** **Randomized Treatment Period: Treatment with Methotrexate, Cyclosporine, Retinoids are not allowed.** **Rescue Treatment Period and Open Label Maintenance Treatment Period: Methotrexate, Cyclosporine, or Retinoids may be allowed for the treatment of GPP only for those who have received a flare rescue treatment with i.v. dose of BI 655130 and have a partial response to the rescue treatment as following.** **After at least 4 weeks from the rescue treatment at R1/D1, it is recommended to first initiate treatment with topical corticosteroids to manage skin symptoms, and then if further adjunctive treatment is required, then methotrexate, cyclosporine and/or retinoids may be initiated and continued with stable dosing until the patient achieves GPPGA score of 0 or 1. The treatment with methotrexate, cyclosporine and/or retinoids should be immediately discontinued after the patient achieves GPPGA score of 0 or 1.**
Rationale for change		Clarification
Section to be changed		Section 4.3 Treatment Compliance
Description of change		Updated the text as following: Administration of the study medication will be done in the study center **(or at home in exceptional cases such as COVID-19 pandemic where physical visits to the clinic may not be possible. See section 4.1.4 and section 6.1 for additional details)** under the supervision of the investigator or a designee.
Rationale for change		Update

Section to be changed		Table 5.2.3:1 Safety Laboratory Tests
Description of change		• Correction made to typographical error to footnote 3 and 4 – replaced "undetermined" to "indeterminate" • Clarified that for adolescent patients, Bedside Schwartz Equation will be used for eGRF calculation. • Made the following updates to the following lab parameters for Urinalysis (Stix): Urine erythrocytes replaced with **Urine blood** Urine Leukocytes replaced with **Urine leukocyte esterase**
Rationale for change		Correction to typographical errors. Clarification on the equation to be used for adolescent patients for eGFR calculation. Updated to match with what is being analyzed/reported by the central lab.

[redacted]

Section to be changed		Section 6.1: Visit Schedule
Description of change		Added the following statement: **In exceptional cases, if standard visits at the trial sites are impossible because of COVID-19 related safety risks or restrictions, the study visit may be performed at the patient's home or remotely (via telephone and/or internet based means of communication). The visit may also be performed as a combination of home and remote visit (via telephone and/or internet based means of communication). The study drug administration may be performed at patient's**

		home under the supervision of the investigating physician or a designee. The trial medication may be shipped to the patient's home if acceptable according to local law and regulations. **All home/remote visits need to be discussed with and approved by the sponsor's trial team. Local regulatory and legal requirements of the participating country still apply.** **All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.**
Rationale for change		Added pre-emptive mitigations to ensure patient safety and trial continuity during the COVID-19 pandemic.
Section to be changed		Section 6.2: Details of Trial Procedures at selected visits
Description of change		Added the following text: **Safety laboratory tests** **If blood sampling for central lab safety analyses at the trial site is not possible in exceptional cases (e.g., due to COVID-19 pandemic), these analyses can be performed at a local lab until central lab testing becomes available. The results of the local lab tests must be transferred to the investigator to ensure medical review and proper documentation of the lab results with clinical relevance for safety in the eCRF. For the minimum required safety lab parameters, follow Table 5.2.3: 2.**
Rationale for change		Added pre-emptive mitigations to ensure patient safety, trial continuity and validity of the data during the COVID-19 pandemic.
Section to be changed		Section 6.2.2: Treatment Period(s)
Description of change		Updated as following: ~~Study drug allocation via the IRT system and~~ **A~~d~~**ministration of the study drug should be the last activity at visits with study drug administration, with the exception of ~~local tolerability and~~ post dose vital signs assessments. Details relating to study drug administration are provided in Section 4.1.4.

Rationale for change		Update
Section to be changed		Section 7.2.2: Primary Endpoint Analysis
Description of change		Updated as following: **Descriptive comparisons between the levels of each stratification (concomitant use of systemic GPP medications at randomization (yes or no)) and blocking factors (region (Japan or Rest of world) and population (adults versus adolescents)) will be performed.** ~~A subgroup assessment according to the levels of each stratification and blocking factors will be assessed descriptively.~~
Rationale for change		Added the clarification to align with the Pediatric Investigational Plan.
Section to be changed		Section 7.2.3: Secondary Endpoint Analysis
Description of change		All secondary endpoints will be descriptively displayed. **Descriptive comparison for adults versus adolescents will be performed for secondary endpoints in the hierarchical testing.** Statistical tests on the remaining secondary binary endpoints will be performed as described for the key secondary endpoint.
Rationale for change		Added the clarification to align with the Pediatric Investigational Plan.
Section to be changed		Section 8: Informed Consent, Trial Records, Data Protection, Publication Policy, And Administrative Structure
Description of change		Added the below bolded text to the paragraph: The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), **the EU directive 2001/20/EC**, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Rationale for change		Clarification. Since EU countries are also participating on the trial, the EU clinical trial

		directive/EU regulation has been included in this section.
Section to be changed		Section 8.3.2: Direct Access to source data and documents
Description of change		Included the following text as contingency measure due to COVID-19: **Remote source data verification is acceptable in exceptional cases where onsite monitoring visits cannot take place due to circumstances like the COVID-19 pandemic or other relevant reasons. This must first be approved by the sponsor's trial team.**
Rationale for change		Update
Section to be changed		Section 9.1 Published References
Description of change		The following reference #s were deleted as these were not referenced in the body of the protocol. R13-4749, R13-4750, R12-4753, R13-4754, R16-0020, R16-2960
Rationale for change		Correction

11.3 GLOBAL AMENDMENT 3

Date of amendment		28 Jul 2022
EudraCT number **EU number**		2018-003081-14
BI Trial number		1368-0027
BI Investigational Medicinal Product(s)		BI 655130 (Spesolimab)
Title of protocol		Effisayil™ 2: Multi-center, randomized, parallel group, double blind, placebo controlled, Phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (Spesolimab) compared to placebo in preventing generalized pustular psoriasis (GPP) flares in patients with history of GPP
Global Amendment due to urgent safety reasons		
Global Amendment		X
Section to be changed		Synopsis
Description of change		Update to contact information.
Rationale for change		Change in Clinical Trial Leader for the trial.
Section to be changed		Table 1.4.2: 1 Risks
Description of change		The risk “Peripheral Neuropathy” was added to the table including a summary of data and mitigation strategy.
Rationale for change		Added to inform about the newly added potential risk “peripheral neuropathy” deriving from the three cases reported as Guillain-Barré syndrome by the investigator in Spesolimab trials (details in the CTP). The cases were considered as peripheral neuropathy by the external neurologist expert panel’s assessment.
Section to be changed		Section 3.3.4.1
Description of change		Following information was added: “Peripheral Neuropathy If peripheral neuropathy is suspected, treatment with Spesolimab should be temporarily discontinued until a full neurological investigation has been conducted. After completion of the neurological investigation, treatment can be restarted based on medical judgement of the investigator.”

Rationale for change		Added as mitigation strategy to account for the three cases reported as Guillain-Barré syndrome in Spesolimab trials. The cases were considered as peripheral neuropathy by the external neurologist expert panel's assessment (details in the CTP).
Section to be changed		4.2.2.2 Restrictions regarding concomitant treatment during the trial (Post V2)
Description of change		The following text: "The treatment with methotrexate, cyclosporine, and /or retinoids should be immediately discontinued after the patient achieves GPPGA score or 0 or 1." was replaced with "or as per the investigator's judgement."
Rationale for change		To place decisions regarding the continuation of rescue treatment under the judgement of the investigator.
Section to be changed		5.2.6.1.4 Adverse events of special interest
Description of change		Added Peripheral Neuropathy as an Adverse events of special interest.
Rationale for change		To update reporting requirements to ensure all cases of suspected peripheral neuropathy including the non-serious ones are analysed quickly.

APPROVAL / SIGNATURE PAGE

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Title: Effisayil 2: Multi-center, randomized, parallel group, double blind, placebo controlled, Phase IIb dose-finding study to evaluate efficacy and safety of BI 655130 (Spesolimab) compared to placebo in preventing generalized pustular psoriasis (GPP) flares in patients with history of GPP

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	08 Aug 2022 16:15 CEST
Approval-Clinical Pharmacokinetics		09 Aug 2022 15:47 CEST
Approval-Therapeutic Area [redacted]		15 Aug 2022 08:29 CEST
Approval-Biostatistics		15 Aug 2022 14:52 CEST
Approval-Team Member Medicine		15 Aug 2022 18:03 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**