Clinical Trial Protocol

	Document Number: c08910926-02
EudraCT No.:	2016-001236-35
BI Trial No.:	1368.11
BI Investigational Product:	BI 655130
Title:	Multi-centre, open-label, single arm, phase I study to investigate safety, tolerability, pharmacokinetics, pharmacogenomics and efficacy of a single intravenous dose of BI 655130 in patients with active generalized pustular psoriasis.
Clinical Phase:	I
Trial Clinical Monitor:	Phone: Fax:
Co-ordinating Investigator:	Phone: Fax:
Status:	Final Protocol (Revised Protocol (based on global amendment 1))
Version and Date:	Version: 2.0 Date: 09 Nov 2016

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: Not applicable			
Name of active ingredient: BI 655130			
Protocol date: 22 July 2016	**Trial number:** 1368.11		**Revision date:** 09 Nov 2016
Title of trial:	Multi-centre, open-label, single arm, phase I study to investigate safety, tolerability, pharmacokinetics, pharmacogenomics and efficacy of a single intravenous dose of BI 655130 in patients with active generalized pustular psoriasis.		
Co-ordinating Investigator:	Phone: Fax:		
Trial site(s):	Multi-centre trial conducted in 7 countries		
Clinical phase:	I		
Objectives:	To investigate safety, tolerability, pharmacokinetics, pharmacogenomics and efficacy of a single intravenous dose of BI 655130 in patients with active generalized pustular psoriasis.		
Methodology:	Multi-centre, open-label, single arm, single dose		
No. of subjects: **total entered:** **each treatment:**	 Up to 10 Up to 10 (single arm study)		
Diagnosis:	Active Generalized Pustular Psoriasis (active GPP)		
Main criteria for inclusion:	Main criteria for inclusion: • Male or female patients, aged 18 to 75 years at screening (V2) • A known and documented history of Generalized Pustular Psoriasis regardless of the IL36RN mutation status, with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN) • Presenting with a flare of GPP with at least 10% BSA with		

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erythema and pustules

- A GPPGA score of at least moderate severity
- GPP patients receiving maintenance treatment with retinoids and/or methotrexate for at least 4 weeks or GPP patients not receiving any maintenance therapy at screening visit 2 (V2)
- Male and female patients must agree to use an effective birth control method

Main exclusion criteria:

- Immediate life-threatening GPP flare or requiring intensive care treatment, according to the investigator's judgement. Life-threatening complications mainly include, but are not limited to, cardiovascular/cytokine driven shock, pulmonary distress.
- Identified, ongoing serious/severe infection
- Acute generalized exanthematous pustulosis (AGEP)
- Patient's clinical presentation being considered due to the differential diagnosis of toxic epidermal necrosis or Stevens-Johnson syndrome
- Use of restricted medication (see Table 4.2.2.1:1)
- Patients with dose escalation of their maintenance therapy with methotrexate and/or retinoids within the 4 weeks preceding V2 (second screening visit)
- Background therapy with ciclosporin within the last 30 days preceding the second screening visit (V2)
- Severe, progressive, or uncontrolled renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof, as judged by the

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	investigator. Patients with less than 3-fold ULN increase in AST and/or ALT and/or alkaline phosphatase and/or with less than 2-fold ULN increase in total bilirubin on infusion day (V3) may be included, provided that no other cause of liver damage than GPP has been identified
Test product: **dose:** **mode of admin.:**	BI 655130 solution for infusion 10 mg/kg Intravenous
Comparator product:	Not applicable
Duration of treatment:	Single dose
Primary endpoint:	The primary endpoint to assess safety and tolerability of BI 655130 administered intravenously, is the number [(N (%)] of patients with adverse reactions, defined as drug-related AEs.
Secondary endpoints:	• Percent change from baseline in GPPASI total score at Week 2 • Proportion of patients with GPPGA total score of 0 (clear) or 1 (almost clear) at Week 2 • Change from baseline in FACIT-Fatigue scale score at Week 2 • Change from baseline in Pain VAS score at Week 2 The following pharmacokinetic parameters will be determined as secondary endpoints: C_{max}, $AUC_{0-\infty}$

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Further endpoints and parameters of interest:			
Criteria for safety:	AEs and SAEs, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs (blood pressure [BP], pulse rate [PR], body temperature, body weight), injection site reactions, immunogenicity (ADA)		
Statistical methods:	Descriptive statistics for safety, PK, and efficacy endpoints		

FLOW CHART

Trial periods	Screening		Treatment	Observation												End of Trial (EOT)
Week			1	1						2	3	4	8	12	16	20
Visit	1[1]	2	3[2,11]	4	5	6	7	8	9	10	11	12	12pc[3]	13	13pc[3]	14
Days from the day of treatment		Day-1	Day 1	D2	D3	D4	D5	D6	D7	D14	D21	D28	D56	D84	D112	D140
Time window for visits										±1d	±2d	±2d	±2d	±7d	±7d	+7d
Informed consent	X															
Patient's confirmation of participation[4]		X[4]														
Infection screening[5]	X															
IL36RN mutation status[6]	X															
Demographics	X															
Medical history	X	X														
Alcohol and smoking history	X	X														
Physical examination[7]	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Urine pregnancy test[8]		X										X	X	X	X	X
12 lead-ECG[9]		X		X	X	X			X			X				X
Safety laboratory tests[10]		X	X	X		X			X	X	X	X				
Review of in-/exclusion criteria	X	X	X													
PK Sampling[12]			X	X	X	X	X	X	X	X	X	X		X		X
			X													
Photographs of skin lesions[13]			X	X	X	X			X	X	X	X		X		X
Skin biopsies[14]			X						X	X[14]						
			X						X			X				
GPPGA and GPPASI			X	X	X	X	X	X	X	X		X		X		X

Trial periods	Screening		Treatment	Observation												End of Trial (EOT)
Week			1	1						2	3	4	8	12	16	20
Visit	1[1]	2	3[2,11]	4	5	6	7	8	9	10	11	12	12pc[3]	13	13pc[3]	14
Days from the day of treatment		Day-1	Day 1	D2	D3	D4	D5	D6	D7	D14	D21	D28	D56	D84	D112	D140
FACIT-fatigue, pain VAS, and PSS			X						X	X		X				
CGI-I									X	X		X				
Presence of edema (yes/no)			X						X	X		X		X		X
Pustular BSA			X						X	X		X		X		X
IRT call	X	X	X													X[16]
Dispense/administration study drug[17]			X													
Compliance check			X													
Local tolerability			X	X												
Adverse events[18]	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Concomitant therapy[18]	X	X	X	X	X	X	X	X	X	X	X	X		X		X
Completion of patient participation[19]																X
Vital status collection														X		X[20]

1 The first screening visit can be performed on any day following the study and trial site initiation

2 Visit 3 (infusion day) should be performed the day after Visit 2 (day of admission for the flare)

3 Visits 12pc and 13pc are phone calls and will only be performed by women of childbearing potential: the patient will inform the site team of the result of the urinary pregnancy test. The result will not be recorded in the eCRF but only in the patient's file

4 Informed consent will be signed at the first screening visit. As several weeks may elapse until the occurrence of a flare (qualifying event), the patient will be asked to confirm his/her consent to participate in the trial at the second screening visit when he/she is admitted for a GPP flare

5 Infection screening will include tuberculosis, hepatitis B, hepatitis C and HIV testing

6 IL36RN mutation status from historical patient's data

7 Physical examination will include vital signs assessment (BP, PR, body weight and temperature) and general appearance as well as evaluation of all relevant organ systems

8 For all female patients of childbearing potential. In case the urine pregnancy test at Visit 2 (Day -1) is positive, it should be repeated for confirmation.

9 ECG measurements should always precede blood sampling. Triple ECG will be performed at second Screening Visit (V2) and will be considered as baseline. Single ECG will be recorded at other time points.

10 Safety laboratory tests include clinical chemistry, haematology, coagulation, and urinalysis, and will be performed locally. On Day 1, the results of the laboratory tests, except tryptase, must be available before the study drug administration.

[11] On Day 1, all baseline blood (plasma, serum, whole blood) and skin biopsy samplings must be performed before trial drug administration. As well, photographs of skin lesions and measurements of GPPGA, GPPASI, FACIT-Fatigue scale, pain VAS, PSS, pustular BSA scores and presence of edema must also be performed before trial drug administration.

[12] Please refer to PK Flow Chart on next page for details.

[13] Photographs of skin lesions should always precede skin biopsies and study drug administration

[14] Baseline skin biopsies on Day 1: two lesional and two non-lesional skin biopsies of 3 mm punch each, for IHC and RNASeq, should be collected prior to receiving treatment; On Day 7: two lesional skin biopsies of 3 mm punch each should be collected; On Day 14 (optional): two lesional skin biopsies of 3 mm punch each would be collected. See sections 5.6.1 and 5.6.3

[15] DNA banking is optional and will only be performed in patients who give their consent

[16] EOT IRT call must also be performed in case of premature withdrawal

[17] Start- and end-time of infusion will be recorded in the CRF.

[18] AEs and concomitant therapies will be recorded throughout the trial, but will be specifically asked for at the time points indicated in the Flow Chart above.

[19] Completion of patient participation also needs to be completed if the patient withdraws prematurely following inclusion (see Section 3.3.4).

[20] For treated patients leaving the study before the planned EOT, then vital status should be collected at the planned day 140

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ABBREVIATIONS

ACD	Acid Citrate Dextrose
ADA	Anti-Drug Antibodies
AE	Adverse event
AESI	Adverse events of special interest
ALT/GPT	Alanine transaminase
AP	Alkaline phosphatase
AST/GOT	Aspartate transaminase
AUC_{0-168h}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to 168 hours
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in plasma over the time interval t1 to t2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last quantifiable data point
BI	Boehringer Ingelheim
BLQ	Below limit of quantification
BMS	BioMarker Set
BP	Blood pressure
BSA	Body Surface Area
b.w.	Body weight
CA	Competent authority
CK	Creatine kinase
CL	Total clearance of the analyte in plasma after intravascular administration
C_{max}	Maximum measured concentration of the analyte in plasma
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case report form
CGI-I	Clinical Global Impression – Improvement
CRP	C-reactive protein
CTP	Clinical trial protocol
CTR	Clinical trial report
CTSU	Clinical Trial Supply Unit
DILI	Drug induced liver injury
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
EOT	End of trial
FACIT-F	Functional Assessment of Chronic Illness Therapy Fatigue
FAS	Full analysis set
FIH	First-In-Human
GGT	Gamma-glutamyl transferase
GPP	Generalized Pustular Psoriasis

GPPASI	Generalized Pustular Psoriasis Area and Severity Index
GPPGA	Generalized Pustular Psoriasis Physician Global Assessment
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPLC-MS/MS	High performance liquid chromatography with tandem mass spectrometry
IB	Investigator's brochure
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL	Interleukin
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator site file
ITE	Indirect target engagement
IV	Intravenous
λ_z	Terminal rate constant of the analyte in plasma
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time of the analyte in the body after intravenous bolus administration
NOA	Not analysed
NOP	No peak detectable
NOR	No valid result
NOS	No sample available
PD	Pharmacodynamic(s)
PGx	Pharmacogenomics
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PoCC	Proof-of-Clinical-Concept
PR	Pulse rate
PSS	Psoriasis Symptom Scale
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTcF	QT interval corrected for heart rate using the method of Fridericia
RDC	Remote data capture
REP	Residual effect period
SAE	Serious adverse event
SOC	System Organ Class
SRD	Single-rising dose
ss	(at) steady state
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal half-life of the analyte in plasma
t_{max}	Time from (last) dosing to the maximum measured concentration of the

	analyte in plasma
TB	Tuberculosis
TDMAP	Trial Data Management and Analysis Plan
TEAE	Treatment-emergent adverse event
TMF	Trial master file
TMM	Team Member Medicine
TNFi	Tumor necrosis factor inhibitor
TSAP	Trial statistical analysis plan
ULN	Upper limit of normal
VAS	Visual Analog Scale
V_{ss}	Apparent volume of distribution at steady state after intravascular administration
V_z	Apparent volume of distribution during the terminal phase after intravascular administration
WOCBP	Woman Of Childbearing Potential

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Generalized Pustular Psoriasis (GPP) is a life-threatening orphan disease characterized by systemic inflammation affecting the skin and internal organs. It manifests as repeated flares of widespread sterile pustules and diffuse erythema causing significant morbidity and even mortality to GPP patients [R16-0933]. Systemic symptoms include fever, marked leucocytosis with neutrophilia and elevated serum levels of C-reactive protein. Skin is often painful and tender. Patients are usually uncomfortable, and often febrile.

While GPP flares may be self-limiting (without treatment), the flare duration usually lasts for weeks to months. Over a 2-week period, self-resolution of the flare would not be typically expected (Reference: Expert feedback). In contrast, GPP patients presenting with flares may rather progress to a life-threatening status without treatment. The mean duration of a treated flare is 16 days (range 7-60 days) and mean duration of hospital stay in the acute phase of disease is 10 days (range 3-44 days) [R16-0933] [R16-2960]. Complications include sepsis and renal, hepatic, respiratory, and cardiac failure [R16-0933]. Triggers for GPP flares include infection, corticosteroid use, steroid withdrawal, stress and pregnancy [R16-0933]. Experts report that the frequency of flares (e.g., annual rate of flares) for an individual patient is unpredictable as well as the pattern i.e., clinical manifestations and rapidity of onset for an individual patient.

Mortality rates up to 7% have been reported but is likely an underestimate [R16-0933] [R16-2698] [R16-1463] due to lack of reported data.

Limited data exist in the literature about treatment of GPP and up to date no gold standard or standard of care is recognized for it. GPP flares are notoriously difficult to treat, and current treatment options for controlling the acute phase of disease are limited and include ciclosporin, retinoids and methotrexate [R16-0933]. The current treatment options did not show clear efficacy in reducing duration and severity of flares in all patients. Flare recurrences appear to be the norm and occur promptly on withdrawing systemic therapy. Biologics (i.e. TNFi such as Infliximab) have been used and positive case reports have been reported but more robust data on their efficacy is lacking and more information is necessary for conclusions in a non-biased manner and to guide clinical use. Secukinumab (Cosentyx®) and infliximab (Remicade®) have been studied in low patient numbers in Japan and are registered for the treatment of GPP in Japan, but not specifically for the treatment of flares (primary endpoint of the open label studies were at week 16 assessing CGI-Improvement).

The partial response of GPP to currently available agents and their limitations (i.e. safety of ciclosporin and its limitation for long term maintenance treatment) indicate that there is high unmet clinical need for a more effective and tolerated targeted therapy that might overcome current treatment limitations.

IL36R signaling drives skin inflammation in several animal models providing support for the strong link between IL36R biology and skin disorders based on human genetics [R14-5158].

Genetic human studies established a strong link between IL36R signaling and skin inflammation, as demonstrated by occurrence of familial generalized pustular psoriasis (GPP) in patients with a loss of function mutation in IL36RN (the naturally occurring receptor antagonist to IL36R) which results in uncontrolled IL36R signaling [R14-5158]. Deficiency of IL-36Ra has been associated with familial and sporadic GPP. Further genetic linkage between GPP and the IL36 pathway has been recently disclosed. For example, mutations in other genes linked to the IL36 pathway such as CARD14 [R16-0929] may also lead to GPP.

BI 655130 is a humanized antagonistic monoclonal IgG1 antibody that blocks human IL36R signalling. IL36R is a novel member of the IL1R family. The IL36R is formed as a heterodimeric complex of IL36R and 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. 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 NFκB and MAP kinase pathways in receptor-positive cell types, leading to enhanced production of downstream inflammatory cytokines/chemokines among which include IL8, IL6, and TNFα. BI 655130 could provide benefit as targeted therapy to GPP patients presenting with a flare of GPP by blocking the IL36 pathway and potentially reducing the severity and duration of disease-related symptoms.

Of note, it has been shown recently in children from families who had neonatal onset of sterile multifocal osteomyelitis, periostitis, and pustulosis that the absence of interleukin-1–receptor antagonist allows unopposed action of interleukin-1, resulting in life-threatening systemic inflammation with skin and bone involvement which responded to empirical treatment with the recombinant interleukin-1–receptor antagonist anakinra [P09-07583]. Strikingly, the patients showed an early response to targeted treatment of Anakinra with pustulosis resolving after days and even bone changes after only weeks. This latter disease model validates the relevance of therapeutic strategies relying on targeted inhibition of a unopposed, pathogenic IL1 family pathway.

1.2 DRUG PROFILE

1.2.4 Nonclinical pharmacokinetics

The pharmacokinetics of BI 655130 were studied in cynomolgus monkeys. In mice, pharmacokinetics were performed with the mouse-specific anti-IL36R antibody, BI 674304 [c03320876-01].

1.2.5 Clinical experience

A FIH (first-in-human) trial [c03361085-07] has been conducted according to a single-blind, partially randomized, single rising dose and placebo-controlled (within dose groups) design. The study explored safety, tolerability, pharmacokinetics and pharmacodynamics of intravenously administered BI 655130 in healthy male subjects. Subjects were to receive single ascending IV doses of 0.001 mg/kg, 0,003 mg/kg, 0.01 mg/kg, 0.03 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, 6 mg/kg and 10 mg/kg body weight or placebo. The first 3 subjects of dose group 5 received only half of the planned dose of BI 655130 (0.05 mg/kg instead of 0.1 mg/kg) due to a calculation error. This led to an additional intermediate dose group of 0.05 mg/kg for which data is available.
Overall the study included 78 male subjects with 59 subjects treated with BI 655130 and 19 subjects treated with placebo.

Safety and Tolerability

Based on preliminary evaluation, in the FIH study 27 of 78 subjects (34.6%) reported at least 1 treatment-emergent AE (TEAE). This included 19 of 59 subjects (32.2%) following administration of BI 655130 and 8 of 19 subjects (42.1%) following administration of placebo. Results are summarized in Table 1.2.5:1 below. There was no apparent relationship between the frequency of AEs and the dose. AEs categorized as related to treatment were observed in 3/19 (15.8%) subjects in the placebo group and in 7/59 (11.9%) subjects treated with BI 655130.

AEs were reported most frequently in the system organ classes (SOC) ‘gastrointestinal disorders' (4/59 subjects [6.8%] on BI 655130 and 1/19 subjects [5.3%] on placebo), 'nervous system disorders' (5/59 subjects [8.5%] on BI 655130 and 2/19 subjects [10.5%] on placebo), ‘infections and infestations’ (4/59 subjects [6.8%] on BI 655130 and 0/19 subjects [0%] on placebo), and ‘general disorders and administration site reaction’ (4/59 subjects [6.8%] on BI 655130 and 1/19 subjects [5.1%] on placebo). AEs reported most frequently were headache (5/59 subjects [8.5%] on BI 655130 and 2/19 subjects [9.5%] on placebo), and nasopharyngitis (3/59 subjects [5.1%] on BI 655130 and 0/19 subjects [0%] on placebo). There were two AEs of moderate intensity, both considered non related to the study drug, (injection site hematoma, headache), all remaining AEs were of mild intensity.

Table 1.2.5: 1 Frequency [N (%)] of subjects with related adverse events by treatment and preferred term

	Plac	BI 655130, Dose mg/kg body weight										
		0.001	0.003	0.01	0.03	0.1	0.3	1	3	6	10	0.05*
Number of subjects (%)	19 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	5 (100.0)	4 (100.0)	6 (100.0)	6 (100.0)	6 (100.0)	4 (100.0)	3 (100.0)
Total with related AEs	3 (15.8)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	2 (33.3)	0 (0.0)	1 (33.3)
Conjunctival hyperaemia	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	1 (33.3)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Injection site reaction	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)
Headache	2 (10.5)	1 (16.7)	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Subjects were planned to receive treatment of 0.1 mg/kg but received an actual treatment of 0.05 mg/kg

There were no relevant changes compared to placebo for laboratory safety, including clinical chemistry, hematology, coagulation parameters, and urinalysis. No clinically relevant changes were observed in 12 lead ECGs, vital signs, physical exams and cardio-monitoring.

Pharmacokinetics

PK data for all dose groups are available. PK parameters and the mean concentration-time plot are shown in Table 1.2.5:2 and Figure 1.2.5:1 below. In dose group 3, 2 subjects had PK concentrations that were below the limit of quantitation, resulting in n= 4.

Table 1.2.5: 2 Preliminary geometric mean (geometric CV%) PK parameters of BI655130 after IV Infusion

Dose Group#	**#1**	**#2**	**#3**	**#4**	**#5A**	**#5**
Dose	**0.001 mg/kg** N=6	**0.003 mg/kg** N=6	**0.01 mg/kg** N=4	**0.03 mg/kg** N=6	**0.05 mg/kg** N=3	**0.1 mg/kg** N=5
$AUC_{0\text{-}tz}$ (h•µg/m L)	NC	NC	0.00652 (121)	2.08 (29.0)	9.57 (5.90)	25.1 (15.5)
C_{max} (µg/mL)	NC	NC	0.0228 (33.5)	0.413 (21.2)	0.998 (15.7)	1.96 (11.9)
$t_{1/2}$ (day)	NC	NC	0.787 (150)	4.97 (17.3)	19.2 (23.0)	15.6 (24.0)
Dose Group#	**#6**	**#7**	**#8**	**#9**	**#10**	
Dose	**0.3 mg/kg** N=4	**1.0 mg/kg** N=6	**3.0 mg/kg** N=6	**6.0 mg/kg** N=6	**10.0 mg/kg** N=4	
$AUC_{0\text{-}tz}$ (h•µg/m L)	113 (5.86)	420 (13.3)	1050 (7.26)	2610 (11.7)	4130 (12.1)	
C_{max} (µg/mL)	6.63 (3.28)	20.3 (13.6)	60.6 (7.17)	153 (12.7)	235 (2.79)	
$t_{1/2}$ (day)	20.4 (11.9)	33.5 (55.4)	25.8 (13.3)	33.9 (18.7)	29.3 (26.3)	

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

BI 655130 is in development for the treatment of Generalized Pustular Psoriasis. The first trial to be conducted in GPP patients is an early stage development, proof-of-concept, phase I trial.

The rationale to perform this trial is based on the strong published human genetic linkage between the target disease GPP and the IL36 pathway targeted by BI 655130 [R15-1421] [R14-5158] and the high unmet clinical need in GPP. There is currently no drug specifically approved for the induction treatment of GPP flares. Patients presenting with a flare may progress to a life-threatening status without treatment and the current treatment options are not effective in reducing duration and severity of flares in GPP patients.

Recently, a FIH trial has been completed (see section 1.2.5) which explored safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 655130 following IV infusions of single rising doses of 0,001 mg/kg up to 10 mg/kg body weight in a healthy male population. BI 655130 was safe and well tolerated.

The objective of the first GPP trial is to evaluate safety, tolerability, PK and pharmacogenomics as well as exploratory efficacy of a single dose of BI 655130 administered to patients with a flare of GPP.

The results from this trial will be the basis for health authority interactions to discuss and design the further developmental program with this compound in this rare and high unmet clinical need indication.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and tolerability of BI 655130 following the intravenous administration of a single dose of 10 mg/kg in patients with a flare of GPP.

Secondary objectives are the assessment of the pharmacokinetics (PK) of BI 655130 after single dosing and the exploration of the efficacy in patients with a flare of GPP to establish proof-of-clinical-concept.

A description of the endpoints to be determined, and the observations along with specific information as how to collect the data for that information, is provided in Section 5.

2.3 BENEFIT - RISK ASSESSMENT

Treatment with BI 655130 has the potential to provide benefit to patients with a flare of GPP by reducing the severity and duration of disease-related symptoms.

The patients are exposed to the risks related to the exposure to the trial medication and the risks of the study procedures.

Procedure-related risks

The use of an indwelling venous catheter for the purpose of blood sampling may be accompanied by mild bruising and also, in rare cases, by transient inflammation of the wall of the vein and local infection. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paresthesia, reduced sensibility, and/or pain for an indefinite period. The same risks apply to venipuncture for blood sampling.

The total volume of blood withdrawn during the entire study should not exceed 400 mL per patient. This is less than the volume of a normal blood donation (500 mL). No health-related risk to the patients is expected from this blood withdrawal.

Drug-related risks and safety measures

The clinical safety and tolerability profile of intravenous single doses of BI 655130 has been comparable to placebo in male subjects with intravenous single doses up to 10 mg/kg body weight. There have been no withdrawals for adverse events or abnormal laboratory values. There has been no death or other serious adverse events. The adverse events reported had no apparent dose or exposure relationship. There have been no dose or exposure related abnormalities in safety laboratory parameters and no safety or tolerability concerns that would preclude further clinical development of BI 655130.

Nonclinical studies support repeat-dose clinical trials of up to 13 weeks duration. In a 13-week intravenous toxicity study of BI 674304 in mice, no adverse effects of IL36R

antagonism was seen at a dose (50 mg/kg, twice weekly) that was 5 fold higher than the dose that was protective in an experimental mouse colonic inflammation model.

We selected for the first trial in GPP patients 1368.11 a single dose of 10 mg/kg which was well tolerated in the previous single rising dose study and considered to be safe.

Based on the preceding FIH study, no specific drug-related risks are anticipated. Still, the following safety measures are/will be applied in this study in order to minimize the risk for the GPP patients:

- The IV administration allows to immediately discontinue further drug administration should any safety concern arise (please refer to Section 4.1.4).
- BI 655130 will be administered in a hospital setting and patients will be under close medical observation during their hospitalization (see section 6.2), as well as after their discharge and until the end of observation period. Safety will be closely monitored during site visits.
- Patients will be closely monitored for signs and symptoms of hypersensitivity reactions for 4 hours after the infusion at Visit 3. Hypersensitivity reactions should be treated according to medical standards.
- Extensive safety laboratory testing will be performed (Table 5.2.3:1).
- The investigator will have the possibility to treat the patient with a rescue medication of his/her choice. The decision to use a rescue medication will be based on the severity and progression of the disease (please refer to section 4.2.1).

Currently there are no data available to suggest interactions of BI 655130 [c03320876-01].

Retinoids (such as acitretin) and methotrexate will be permitted as background therapy (please refer to section 4.2.1).

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

Based on the findings in the nonclinical studies conducted to date and in accordance with international regulatory guidelines, the inclusion of women of childbearing potential in this study is justified [c03320876-01]. To minimize the risk of unintentional exposure of an embryo or fetus to the investigational drug, women of childbearing potential must agree to

the requirements for pregnancy testing (the day before the study drug administration, and every 4 weeks thereafter until the EOT Visit) and contraceptive methods described in the patient information. Male patients will be asked to use condoms to avoid exposure of the partner via seminal fluid and prevent the partner to become pregnant if she is of childbearing potential. Birth control methods must be used for 20 weeks after the infusion (corresponding to five BI 655130 half-lives).

Considering the medical need of the development of an effective and well tolerated drug for the therapy of GPP flares, the benefit of this trial is considered to outweigh the potential minimal risks and justifies the administration of a single dose of BI 655130 10 mg/kg to patients with a flare of GPP to investigate safety, tolerability, pharmacokinetics, and efficacy.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This single dose trial is designed as open label, exploratory, phase I, multi-centre, multi-national, single arm.

A maximum of 10 patients with a flare of GPP are planned to participate. Approximately 7 study sites in 7 countries worldwide will participate. They are all specialized referral centres experienced in the management of GPP.

Each patient will receive the active drug. Only one dose will be tested (10 mg/kg) and will be administered intravenously at Visit 3.

Patients will be hospitalized during at least 4 days following the study drug administration. Thereafter, the decision of patient's discharge will be left at the discretion of the investigator and based on the evolution of the GPP flare and the patient's health status.

Overall, 14 visits are planned. The observation period will last 20 weeks to cover the whole Residual Effect Period (refer to section 5.2.2.2; Figure 3.1:1). Women of childbearing potential will performed two additional visits (phone calls) to inform the site team of the result of the urine pregnancy test at Day 56 (Visit 12pc) and Day 112 (Visit 13pc).

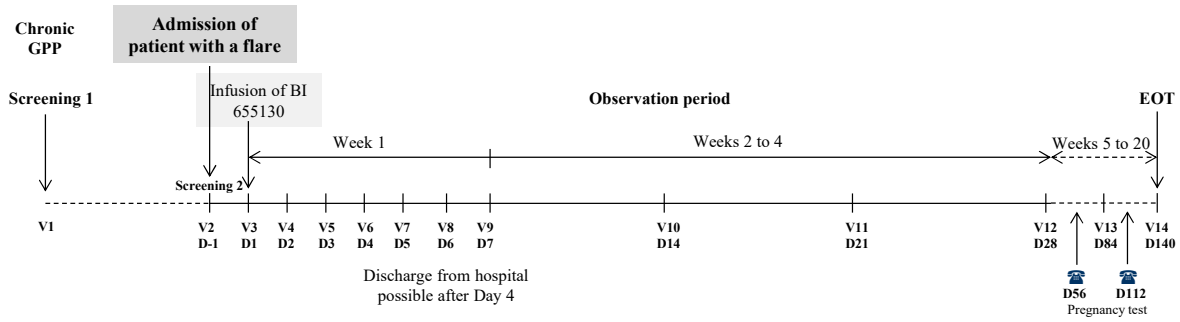

Figure 3.1: 1 Study design

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

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

BI has appointed a Trial Clinical Monitor, 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 local clinical monitors (CML), Clinical Research Associates (CRAs), and participating trial sites.

The trial medication will be provided by the Clinical Trial Supplies Unit (CTSU), BI Pharma GmbH & Co. KG, Biberach, Germany. An IRT vendor will be used in this trial. Details will be provided in IRT Manual available in ISF.

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

A central laboratory service (except for safety laboratory tests, which will be performed at the local laboratory of each site) and vendors for photodocumentation (skin lesions) and IRT (interactive response technology) will be used in this trial. Details will be provided in the applicable manuals available in the ISF.

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

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

Tasks and functions assigned in order to 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.

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

This phase I trial is the first study with BI 655130 to be conducted in GPP patients.

Current safety data about BI 655130 were obtained from a previous first-in-man phase I trial carried out in healthy volunteers. BI 655130 was safe and well tolerated in all dose groups tested in this trial up to the 10 mg/kg dose.

Non-clinical safety data are limited as BI 655130 could not be directly tested in preclinical toxicity studies (a surrogate antibody specific to mouse was used instead). The main objective of this phase I trial is to investigate safety and tolerability of BI 655130 in patients with a flare of GPP.

As a phase I trial, endpoints also include pharmacokinetics and pharmacogenomics.

Efficacy is an exploratory endpoint at this early stage of the development. Final data will be compared to baseline.

For the first trial in GPP (1368.11) it is planned to include patients with active disease regardless of the mutation status (while the status will be investigated during the trial) for the following reason:

- In addition to the described IL36RN mutation, other mutations in the same gene and other genes linked to the IL36 pathway (please see section 1.1 "Medical Background" above) have been described pointing to a general role of the IL36 pathway (and not only the IL36RN mutation) as disease trigger/driver
- Patients can be included without need for screening for mutation status (critical as onset of treatment, treatment of acute flares has to be fast)

No active control group is included in this trial as there is currently no drug approved for the induction treatment of flares. Secukinumab (Cosentyx®) and infliximab (Remicade®) are registered for the treatment of GPP in Japan, but not specifically for flares. For secukinumab, authorization was granted on the basis of long-term treatment data (52 weeks) derived from one clinical trial conducted in patients with chronic GPP, not necessarily presenting with a flare episode at the time of inclusion. This study did not specifically evaluate the efficacy of secukinumab during flares (primary endpoint was proportions of patients who achieved treatment success at week 16) [R16-1462].

In trial 1368.11, GPP patient with a known history of GPP presenting with a flare will be included with a condition in need of immediate treatment to prevent progression (disease may progress to a life threatening condition). Of note, it has been reported that flare recurrences appear to be the norm and occur promptly on withdrawing systemic therapy or even on stable maintenance treatment (with current treatment options such as retinoids or methotrexate). A placebo design (with BI 655130 as add-on to current treatment options as comparison) is considered not feasible (expert feedback) due to the objectives listed above and the fact that GPP is an extremely rare disease.

Ongoing background treatment with methotrexate or retinoids will be continued during the trial participation.
Seven countries have been invited to participate in order to minimize the risk of under recruiting and to meet the goal of a maximum of 10 patients enrolled within 6 months. Recruitment will be challenging due to the rareness of the disease and because patients must be included during a flare, which is difficult to predict. Moreover, the study will be performed in a competitive landscape. The selected countries seem to be the most appropriate countries to recruit.

The 10 mg/kg dose administered in this study was carefully selected on the basis of the first-in-man Single Rising Dose (SRD) study conducted in healthy volunteers (BI Trial No. 1368.1). This was the maximum dose administered in the SRD trial. This dose was safe and well tolerated and has been selected in this subsequent PoCC trial 1368.11 to maximize the

chance for a positive efficacy signal and treatment benefit for the patients. Please refer to section 4.1.3 for further details.

3.3 SELECTION OF TRIAL POPULATION

The objective is to enter a minimum of 6 patients but allow for a maximum of 10 patients. Once 6 patients have been included, the TMM can decide whether recruitment should be stopped or continued, dependent upon for example the rate at which patients are recruited into the trial.

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

3.3.1 Main diagnosis for study entry

The study will be performed in patients with a GPP flare.

3.3.2 Inclusion criteria

Patients will only be included into the trial, if they meet the following criteria:

1. Male or female patients, aged 18 to 75 years at screening (V2)

2. A known and documented history of Generalized Pustular Psoriasis regardless of the IL36RN mutation status, with previous evidence of fever, and/or asthenia, and/or myalgia, and/or elevated C-reactive protein, and/or leucocytosis with peripheral blood neutrophilia (above ULN)

3. Presenting with a flare of GPP with at least 10% of Body Surface Area (BSA) with erythema and pustules

4. A GPPGA score of at least moderate severity

5. GPP patients receiving maintenance treatment with retinoids and/or methotrexate for at least 4 weeks or GPP patients not receiving any maintenance therapy, at screening visit 2 (V2)

6. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation

7. Women of childbearing potential[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 patient information.

   Male patients must be ready and able to use condoms.

[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 sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
Birth control method must be continued up to 20 weeks after BI655130 administration.

3.3.3 Exclusion criteria

Patients will not be allowed to participate if any of the following general criteria apply:

1. 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 prevented from participating. They should refrain from breastfeeding up to 20 weeks after the study drug administration (see section 4.2.2.2).
2. Immediate life-threatening flare of GPP or requiring intensive care treatment, according to the investigator's judgement. Life-threatening complications mainly include, but are not limited to, cardiovascular/cytokine driven shock, pulmonary distress.
3. Identified, ongoing serious/severe infection
4. Acute generalized exanthematous pustulosis (AGEP)
5. Patient's clinical presentation being considered due to the differential diagnosis of toxic epidermal necrosis or Stevens-Johnson syndrome
6. Currently involved in or intending to participate in another investigational study during the course of this trial.
7. Previous enrolment in this trial
8. Use of any restricted medication as specified in Table 4.2.2.1:1, or any drug considered likely to interfere with the safe conduct of the study
9. Patients with dose escalation of their maintenance therapy with methotrexate and/or retinoids within the 4 weeks preceding V2 (second screening visit)
10. Background therapy with ciclosporin within the last 30 days preceding the second screening visit (V2)
11. Previous exposure to an IL36R inhibitor
12. Severe, progressive, or uncontrolled renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof, as judged by the investigator. Patients with less than 3-fold ULN increase in AST and/or ALT and/or alkaline phosphatase and/or with less than 2-fold ULN increase in total bilirubin at infusion day (V3) may be included, provided that no other cause of liver damage than GPP has been identified.
13. Known chronic or relevant acute infections including active tuberculosis, HIV or viral hepatitis; QuantiFERON® TB test will be performed at screening. If the result is positive, patients may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment should have been initiated and maintained according to local country guidelines.
14. Patient with a transplanted organ (with exception of a corneal transplant > 12 weeks prior to screening V2) or who have ever received stem cell therapy (e.g., Prochymal).

15. Known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
16. Any documented active or suspected malignancy or history of malignancy within 5 years prior to second screening visit (V2), except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
17. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than GPP, surgical procedure (i.e., organ transplant), medical examination finding (including vital signs and ECG), or laboratory value at the second screening visit (V2) outside the reference range, that is in the opinion of the investigator, is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data
18. History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients
19. Patient's refusal to be hospitalized for 4 days following the infusion

For study restrictions, refer to Section 4.2.2.

3.3.4 Removal of subjects from therapy or assessments

3.3.4.1 Removal of individual subjects

All patients have the right to withdraw from the study at any time without the need to justify their decision. The investigator has the right to remove patients from the study for non-compliance, administrative or other reasons. An excessive withdrawal rate can have a severe negative impact on the scientific value of the trial. Every effort should be made to keep patients in the trial as scheduled. This includes careful patient selection and appropriate explanation of the trial requirements and procedures prior to enrolment as well as an explanation of the consequences of premature withdrawal.

Removal from trial

An individual patient is to be removed from the trial if:

1. The patient withdraws consent for trial participation, without the need to justify the decision

An individual patient may be removed from the trial if:

1. The patient is no longer able to participate for other medical reasons
2. Development of a toxicity or adverse event which warrants BI 655130 discontinuation including but not limited to SAEs or SUSARs

In addition to these criteria, the physician may discontinue patients at any time based on his or her clinical judgment.

In case a patient has an elevation of AST and/or ALT and/or AP ≥3-fold ULN plus 2 time the baseline combined with an elevation of total bilirubin ≥2-fold ULN plus 1.5 time the baseline measured in the same blood sample (DILI, see section 5.2.2.1), it will be up to the discretion of the investigator to keep the patient in the trial as long as considers he/she can perform all planned procedures.

As there is only one drug administration, patients may be less motivated to adhere to the study visit schedule.
Investigator and site staff should work to detect early signs of lost interest and strongly encourage the patients to continue to attend regularly scheduled study visits until the trial ends. Should that not be acceptable to the patient, the following alternatives should be offered to the patient in a descending order:

- reduce the number of visits, with only the observation visits at Week 1 (Day 7, V9), Week 2 (Day 14, V10), Week 4 (Day 28, V12), and the End-Of-Trial assessment at Week 20 (Day 140, V14).
- conduct only the Visits 9, 10 and 12 in person and V14 over the phone.
- conduct all remaining study visits over the phone
- discontinue participation in remaining trial activities but collect vital status at V12 and the end of the trial.

Participation in the trial must be stopped if the patient withdraws his consent.

If a patient is removed from or withdraws from the trial prior to the administration of trial medication, the reason for withdrawal will be entered in the case report form (CRF) and trial database and will be reported in the clinical trial report (CTR). If a patient is removed from or withdraws from the trial after the administration of trial medication, this will be documented and the reason for discontinuation must be recorded in the CRF. The data will be included in the CRF/trial database and will be reported in the CTR. A complete V12 examination will be performed at the time of discontinuation and the information will be recorded in the CRFs. If the withdrawal occurs after V12, the patient should complete the EOT procedures. These discontinuations will be discussed in the CTR.

If a patient experiences a worsening of GPP during the course of the trial, he/she can receive rescue treatment and will be followed up as initially planned (refer to section 4.2.1.1). If a treated patient receives a prohibited treatment during the trial, he/she will continue the trial as initially planned and the prohibited treatment should be recorded as concomitant treatment.

If it is known that a patient becomes pregnant during the trial, she has to be followed until she has given birth or until the end of pregnancy. The patient's data are to be collected until the end of the trial (last visit of last patient) and reported in the clinical trial report. For reporting of pregnancy and all related events refer to Section 5.2.2.2.

Removal from treatment

In case the infusion of study drug is permanently discontinued before the whole amount of prepared solution has been administered to the patient, every effort should be made to keep

the patient in the trial and perform all study assessments. If not possible, assessments at Week 1, Week 2, Week 4, and Week 20 should be proposed to the patient. If still not possible, a complete V12 examination will be performed at the time of discontinuation and the information will be recorded in the CRFs. If the withdrawal occurs after V12, the patient should complete the EOT procedures. The discontinuation will be discussed in the CTR.

3.3.4.2 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 any of the following reasons:

1. New toxicological findings or serious adverse events invalidate the earlier positive benefit-risk-assessment. More specifically, the trial will be terminated if more than 50% of the patients show drug-related and clinically relevant adverse events of moderate or severe intensity, or if at least one drug-related serious adverse event is reported that is considered to be unacceptable.
2. The expected enrolment goals overall or at a particular trial site are not met
3. Violation of GCP, or the CTP by a trial site or investigator, disturbing the appropriate conduct of the trial
4. The sponsor decides to discontinue the further development of the investigational product.

3.3.5 Replacement of subjects

The objective is to enter a minimum of 6 patients but allow for a maximum of 10 patients. Once 6 patients have been included, the TMM can decide whether recruitment should be stopped or continued, dependent upon for example the rate at which patients are recruited into the trial.

A patient who has performed the first screening visit (V1) will not necessarily have a flare before the end of recruitment. Therefore, all screened patients will not necessarily have the possibility of receiving the study drug.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

The investigational product has been manufactured by BI Pharma GmbH & Co. KG.

4.1.1 Identity of BI investigational product and comparator product

The characteristics of the test product are given below:

Substance:	BI 655130
Pharmaceutical formulation:	Solution for infusion
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	
Posology:	1-0-0
Route of administration:	IV infusion
Duration of use:	Single dose

At the time of use, the IV solution for dosing will be prepared as detailed in the instruction given in the ISF.

There is no reference product in this non comparative trial.

4.1.2 Method of assigning subjects to treatment groups

There is only one treatment group in this trial.

4.1.3 Selection of doses in the trial

The dose of 10 mg/kg for this trial was selected for trial 1368.11 on the basis of the data obtained in the FIH single rising dose trial 1368.1. In this study, the intravenous dose of 10 mg/kg b.w. was safe and well tolerated. This support testing this dose in the subsequent PoCC trial 1368.11 to maximize the chance for a positive efficacy signal and treatment benefit for the patients.

All patients will receive a single dose of BI 655130 (10 mg/kg).

4.1.4 Drug assignment and administration of doses for each subject

The treatment to be evaluated is outlined in Table 4.1.4: 1 below. It will be assigned to each patient after the completion of the inclusion visit and verification of all inclusion and

exclusion criteria. The assignment will occur in an open label fashion via Interactive Response Technology (IRT).

All included patients will receive the BI 655130 on Day 1. For further details concerning timing see Flow Chart. Start- and end time of the infusion will be recorded.

Detailed instructions for the preparation of the infusion solution, the volume to be administered and the infusion rate is provided in the ISF.

After preparation, the solution for infusion may be stored at 2 - 8°C for up to 24 hours. After removal from 2 - 8°C storage or preparation, the solution must be administered within 60 minutes if stored at ≤ 25°C. Do not freeze.

Chemical and physical in-use stability has been demonstrated for 60 minutes at room temperature ≤ 25°C. In addition the time for infusion must not exceed 240 minutes at ≤ 25°C.

From a microbiological point of view the drug should be used immediately. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user, and would normally not be longer than 24 hours at 2 - 8°C (36 - 46°F), unless preparation has taken place in controlled and validated aseptic conditions.

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In all patients, the infusion solution will be intravenously administered over a period of 60 minutes. Infusion time can be extended up to 240 minutes provided that the maximum time between the start of preparation and completion of administration of the solution to the patient does not exceed 300 minutes (5 hours).

In case of safety concerns, e.g. due to 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 of the infusion and provided no further safety concern exists restarting at a slower rate. In any case, the total duration of infusion should not exceed 240 minutes (4 hours). Further based on medical judgment he/she will provide medications such as steroids, etc. as needed.

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

Table 4.1.4: 1 Preparation of final infusion solution containing BI 655130

Dose of BI 655130 (mg/kg)	In-line filter used?	Approximate pre-flush volume [mL]	Concentration of the ready to use IV bag BI 655130 [mg/mL]	Volume delivered [mL/kg b.w.]	Infusion time [min]
10	Yes	15	20	0.5	60 *

* Can be extended up to 240 minutes, provided that the maximum time between the start of preparation and completion of administration of the solution to the patient does not exceed 300 minutes (5 hours)

Patients will be kept under close medical surveillance during the 4 days of hospitalization following the study drug administration.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This Phase I trial will be handled in an open fashion throughout (that is, during the conduct, including data cleaning and preparation of the analysis).

4.1.5.2 Procedures for emergency unblinding

As this trial will be conducted open-label, the treatment information will be known. Therefore, no emergency envelopes/procedure will be provided.

4.1.6 Packaging, labelling, and re-supply

Drug supplies will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply consists of containers holding the trial medication which are labelled with trial identification. The required information according to the Annex 13/EU GMP Guideline will be provided on the containers. Smaller boxes within the clinical trial supply containers will be labelled with:

- BI trial number
- Name of product and strengths or identification code
- Pharmaceutical dosage form, quantity of dosage units
- Route and mode of administration
- Term ‘For Clinical Trial Use only’ (domestic language)
- Sponsor name and address
- Storage conditions
- Use-by date
- Patient or medication number
- Batch number
- Investigator

The telephone number of the sponsor and name, address and telephone number of the trial site are given in the patient information form. The EudraCT number is indicated on the title page of this protocol as well as on the patient information and informed consent forms. Examples of the labels will be available in the ISF.

No re-supply is planned. Each site will receive trial medication kits with the initial release and will have the possibility to request additional medication shipment from central/local depots.

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 (labelled) storage conditions. A temperature log must be maintained for documentation. If the storage conditions are found to be outside the specified

range, the local clinical monitor (as provided in the list of contacts) is to be immediately contacted.

The medication may only be dispensed to trial patients according to the CTP by authorized personnel as documented in the trial staff list.

4.1.8 Drug accountability

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

- Approval of the study protocol by the IRB / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre
- 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 or immediately imminent signing of the clinical trial protocol

Only authorized personnel as documented in the form 'Trial Staff List' may administer medication to trial patients. The trial medication must be administered in the manner specified in the CTP. All unused trial medication must be returned to the sponsor. All used and partially used medication must be destroyed locally by the trial site. Receipt, usage and return or disposal must be documented on the respective forms. Account must be given for any discrepancies.

The investigator / pharmacist / investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use for each patient, and the return to the sponsor of unused products or disposal by the site of used or partially used products.

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

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

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

4.2.1.1 Rescue medication

The use of a rescue medication should be based on the severity and progression of the disease and will be left at the discretion of the investigator in case of a worsening of the flare. It is recommended to wait until two weeks after the study drug administration before prescribing a rescue medication in case no improvement or no change in disease condition is observed (stable disease).

Even if the patient is dispensed rescue medication, he/she should stay in the trial and be followed-up as initially planned until Day 140.

The choice of the rescue medication will be left at the discretion of the investigator. The sponsor will not supply the sites with the rescue medication.

4.2.1.2 Emergency procedures

No special emergency procedures are to be followed.

4.2.1.3 Additional treatments

No additional treatment is planned.

However, in case of AEs in need of treatment, the investigator can authorise 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 eCRF.

Background treatment allowed

Patients receiving methotrexate or retinoids as background therapy for at least 4 weeks at second screening visit V2 can be included, if no escalation of dose occurred within the 4 weeks preceding V2. The therapy must be continued at the same dose during the study participation. Any change of dose is not permitted throughout the trial participation.

Patients who are not receiving methotrexate or retinoids at second screening visit V2 are not allowed to start such treatments during the trial (except in situations described in section 4.2.1.1).

Background treatment not allowed

Background therapy with ciclosporin or other biologics is not allowed throughout the trial. A patient with history of background treatment with ciclosporin can be included if the last intake was at least 30 days before Screening Visit 2. In this case, the dose that had been administered should be recorded in the eCRF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Table 4.2.2.1: 1 Restricted medications

Medication or class of medications	**Restriction duration (through EOT Visit [1])**
natalizumab, efalizumab, or agents that deplete B or T cells (e.g., rituximab, alemtuzumab, or visilizumab), briakinumab, secukinumab (Cosentyx®), ustekinumab (Stelara®), guselkumab, tildrakizumab	6 months prior to screening V2
IL36R inhibitors	not allowed neither before nor during trial participation
brodalumab, ixekizumab	4 months prior to screening V2
adalimumab (Humira®), infliximab (Remicade®) investigational products for psoriasis (non biologics)	12 weeks prior to screening V2
etanercept (Enbrel®) live virus vaccinations	6 weeks prior to screening V2
any investigational device or product (excludes psoriasis products) other systemic immunomodulating treatments except background therapy with methotrexate (e.g. ciclosporin A, corticosteroids[2], cyclophosphamide), tofacitinib (Xeljanz®), apremilast (Otezla®) other systemic psoriasis treatments except background therapy with retinoids (e.g. fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g., PUVA).	30 days prior to screening V2

Table 4.2.2.1: 1 Restricted medications (Cont.)

phototherapy (e.g., UVA, UVB) topical treatment for psoriasis or any other skin condition (e.g. corticosteroids[3], vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, anthralin, α -hydroxy, fruit acids)	14 days prior to screening V2
Anakinra	7 days prior to screening V2

[1] In case of worsening of the flare, the use of a rescue medication is left at the discretion of the investigator (refer to section 4.2.1.1); In case of any other acute setting after Day 28, the use of a restricted medication is permitted.

[2] There is no restriction on corticosteroids with only a topical effect (e.g. inhaled corticosteroids to treat asthma or corticosteroids drops administered in the eye or ear).

[3] Exception: topical steroids of US class 6 (mild, such as desonide) or US class 7 (least potent, such as hydrocortisone) for use on the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to trial visit in which GPPASI is assessed

In the event a patient with prior use of restricted medications (refer to Table 4.2.2.1:1) is enrolled, past medical records are required to document when these treatments were stopped.

All background, concomitant or rescue therapies will be recorded on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

Male and female patients of child bearing potential must maintain an adequate contraception throughout the course of the trial and up to 20 weeks after the study drug infusion.

Adequate birth control methods for female patients are:

- hormonal methods of contraception associated with inhibition of ovulation,
- intrauterine devices (IUD) or intrauterine hormone releasing systems (IUS),
- bilateral tubal ligation,
- vasectomized sexual partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided that partner is the sole sexual partner of the WOCBP participant),
- complete sexual abstinence as further described in the patient's information.

As monoclonal antibodies can be secreted in milk, women should refrain from breastfeeding once they receive the study drug and up to 20 weeks after, i.e. until BI 655130 is eliminated (approximately 5 half-lives). They can start nursing again after this period.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study center under supervision of the investigating physician or a designee. The measured plasma concentrations will provide additional confirmation of compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - CLINICAL PHARMACOLOGY

5.1.1 Endpoints of efficacy

Efficacy endpoints are secondary or further endpoints in this trial.

Secondary efficacy endpoints will be:

- Percent change from baseline in GPPASI total score at Week 2
- Proportion of patients with GPPGA total score of 0 (clear) or 1 (almost clear) at Week 2
- Change from baseline in FACIT-Fatigue scale score at Week 2
- Change from baseline in Pain VAS score at Week 2

5.1.2 Assessment of efficacy

The skin condition will be assessed by using the Generalized Pustular Psoriasis Area and Severity Index (GPPASI), Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) and the CGI-Improvement (CGI-I). Patients' questionnaires will also be used, fatigue scale (FACIT-Fatigue), Pain VAS, Psoriasis Symptom Scale (PSS) and other relevant scores as described in Section 5.1.1.

Methodological details for the evaluation of the scores/index are described in the ISF.

Generalized Pustular Psoriasis Area and Severity Index (GPPASI)

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

GPPASI score will be measured at Visits 3 (before study drug administration) to 10, 12 (Day 28), 13 (Day 84), and 14 (Day 140).

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 psoriatic lesions from 0 - 4. Each component is graded separately, the average is calculated and the final GPPGA is determined from this composite score. A lower score then indicates a lesser severity, with 0 being clear and 1 being almost clear. To receive a score of 0 or 1, the patient should be afebrile, in addition to skin presentation requirements.

GPPGA score will be measured at Visits 3 (before study drug administration) to 10, 12 (Day 28), 13 (Day 84), and 14 (Day 140).

FACIT-Fatigue scale

The FACIT-Fatigue scale is a brief and reliable instrument for monitoring fatigue and its effects on patients. It is a comprehensive compilation of questions that measure health-related quality of life in patients with chronic illnesses. It comprises 13 questions, the responses to which are each recorded on a 5-point Likert scale. Scores range from 0 to 52, with lower scores representing greater fatigue.

The FACIT fatigue scale score will be measured at Visits 3 (before study drug administration), and 9, 10, and 12 (Day 28).

Pain VAS

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

Pain VAS will be completed at Visits 3 (before study drug administration), and 9, 10, and 12 (Day 28).

Psoriasis Symptom Scale (PSS)

The PSS is a four-item patient-reported outcome (PRO) instrument that assesses the severity of pain, redness, itching and burning from psoriasis. Current symptom severity is assessed using a 5-point Likert-type scale ranging from 0 (none) to 4 (very severe) and a total score is calculated by adding all subscores. The PSS was developed based on published evidence supporting the development of two similar, proprietary patient-reported outcome instruments: the Psoriasis Symptom Inventory and the Psoriasis Symptom Diary. These measures were developed in accordance with FDA PRO Guidance and have published evidence of reliability, validity, and ability to detect change [R14-3562, R14-3559, R15-1219, R15-1410, R15-1411].

The PSS will be self-administered by the patient at Visits 3 (before study drug administration), and 9, 10, and 12 (Day 28).

CGI-Improvement

The CGI-I is an observer-rated scale which measures illness global improvement (CGI-I). It is rated on a 7-point scale, with the improvement of illness scale using a response ranging from 1 (very much improved) to 7 (very much worse).

The CGI-I test measure will be performed at Visits 9, 10, and 12.

5.2 SAFETY

5.2.1 Endpoints of safety

Primary endpoint to assess safety and tolerability of BI 655130 is the number [N (%)] of patients with adverse reactions, defined as drug-related AEs.

Further safety criteria of interest:

- AEs and SAEs
- Safety laboratory tests
- 12-lead ECG
- Vital signs (blood pressure, pulse rate, body temperature, body weight)
- Frequency and severity of injection site reactions

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability or incapacity, requires or prolongs hospitalisation, is a congenital anomaly/birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Cancers with new histology or exacerbation of an existing cancer are always considered serious.

For Japan: An AE which possibly leads to disability will be reported as an SAE. Every new occurrence of cancer will be reported as a SAE regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

Intensity of AEs

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Enough discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge,

confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the eCRFs.

Yes: there is a reasonable causal relationship between the investigational product administered and the AE
No: there is no reasonable causal relationship between the investigational product administered and the AE

Worsening of the underlying disease or pre-existing condition

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the eCRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination, and laboratory test results will be recorded as an (S)AE in the eCRF, if they are judged clinically relevant by the investigator.

Protocol-specified adverse events of special interest (AESIs)

Protocol-specified AESIs are events of medical concern requiring monitoring and rapid communication.

The following are defined as protocol-specified AESIs in this trial:

- Hepatic injury, as defined by the following alterations of hepatic laboratory parameters:
  - an elevation of AST and/or ALT and/or AP ≥3-fold ULN plus 2 time the baseline, combined with an elevation of total bilirubin ≥2-fold ULN plus 1.5 time the baseline, measured in the same blood sample.

Any patients with these lab abnormalities need to be followed up according to Section 10.1.2 of this CTP and the 'DILI checklist' provided in the ISF. In case of a DILI, it will be up to the investigator to keep the patient in the trial as long as considers he/she can perform all planned procedures.

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 serious timelines).

5.2.2.2 Adverse event and serious adverse event reporting

Upon enrolment into a trial, the patient's baseline condition is assessed (for instance, by documentation of medical history/concomitant diagnoses), and relevant changes from baseline are noted subsequently.

Patients will be required to report spontaneously any AEs and AESI as well as the time of onset, end, and intensity of these events. In addition, each patient will be regularly assessed by the medical staff throughout the clinical trial and whenever the investigator deems necessary. As a minimum, patients will be questioned for AEs, AESI (and concomitant

therapies) at the time points indicated in the Flow Chart. Assessment will be made using non-specific questions such as "How do you feel?" Specific questions will be asked wherever necessary in order to more precisely describe an AE.

A careful written record of all AEs and AESIs shall be kept by the investigator in charge of the trial. Records of AEs and AESIs shall include data on the time of onset, end time, and intensity of the event as well as any treatment or action required for the event and its outcome.

SAEs which occurred during the screening period are to be reported according to standard procedures.

All AEs, serious and non-serious, as well as AESI occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the End-Of-Trial visit) will be collected, documented and reported to the sponsor by the investigator on the appropriate CRF(s) / SAE reporting forms.

Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the ISF.

The residual effect period (REP) for BI 655130, when measurable drug levels or PD effects are still likely to be present, is 140 days (five half-lives). Therefore, all AEs reported within 140 days of the last trial medication will be considered on treatment.

For each AE, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

If not stipulated otherwise in the ISF, the investigator must report the following events via telephone/fax using the SAE form immediately (within 24 hours of awareness) to the sponsor: SAEs, AESIs, and non-serious AEs relevant to a reported SAE or AESI.

All (S)AEs, including those persisting after trial completion must be followed up until they have resolved, have been sufficiently characterised, or no further information can be obtained.

If the investigator becomes aware of an SAE that occurred after the patient completed the clinical trial (including any protocol required residual effect period and/or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator.

A list of AEs which are defined to be always serious is provided in the ICF. These events should always be reported as SAEs. In order to support the investigator in identifying these 'always serious AEs', if a non-serious AE is identified to be serious per BI definition, a query will be raised. The investigator must verify the description and seriousness of the event.

With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs, AESI and non-serious AEs must include a causal relationship assessment made by the investigator.

The SAE form is to be forwarded to the defined unique entry point identified (specific contact details will be provided in the ISF). This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal

relationship. It also applies if new information to existing SAEs or protocol-specified AESIs becomes available.

For Japan: All SAEs and AESIs must be reported immediately to the head of the trial site. 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.

Pregnancy

In the rare case that a female patient participating in this clinical trial becomes pregnant after having taken trial medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours of awareness) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the ISF). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of 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. On Day 1 (Treatment Visit), the results must be available before the study drug infusion, with the exception of serum tryptase.

The parameters that will be determined are listed in Table 5.2.3: 1. The laboratory tests will be performed at the local laboratory of each participating site.

Table 5.2.3: 1 Routine laboratory tests

Functional lab group	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 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[1]
Substrates	C-Reactive Protein (CRP) Serum albumin Creatinine Total bilirubin Direct bilirubin Total protein Total cholesterol Triglycerides Plasma glucose
Electrolytes	Sodium Potassium Chloride Calcium Phosphate
Urinalysis (Stix)	Urine nitrite Urine protein Urine glucose Urine ketone Urobilinogen Urine bilirubin Urine erythrocytes Urine leukocytes Urine pH
Infection screening[2]	Hepatitis B Surface Antigen (qualitative) Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON®-TB

Table 5.2.3: 1 Routine laboratory tests (Cont.)

Pregnancy test	Urine pregnancy test
Urine sediment (microscopic examination if urine analysis abnormal) (qualitative)	Only positive findings will be reported (for instance, the presence of sediment bacteria, casts in sediment, squamous epithelial cells, erythrocytes, leukocytes)

[1] Only at inclusion/treatment visit (V3)
[2] Only at first screening visit (V1)

A urine pregnancy test will be performed on all females of child-bearing potential at pre-treatment visit, and every 4 weeks thereafter (please refer to the flow chart). The patient will give the result by phone on Day 56 (Visit 12pc) and Day 112 (Visit 13pc). In case of a positive result at baseline, the test should be repeated for confirmation.

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.

5.2.4 Electrocardiogram

5.2.4.1 12-lead resting ECG

ECG measurements will always precede blood sampling to avoid impact of sampling on the ECG results.

In order to achieve a stable heart rate at rest and to assure high quality recordings at comparable resting phases, all ECGs will be recorded for a 10-sec duration after the patients have rested for at least 5 min in a supine position. The site personnel will be instructed to assure a relaxed and quiet environment so that all patients are at complete rest during the recordings. ECG assessment will always precede all other study procedures of the same time point (except blood drawing from an intravenous cannula which is already in place) to avoid impact of sampling on the ECG quality.

Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven.

Triple ECGs (recorded within 180 sec) will be recorded at the second screening visit (V2). At all other time points single ECGs will be recorded.

All locally printed ECGs will be evaluated by the investigator or a designee.

ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation). For time point with triple ECGs, all three single ECGs will be repeated.

Additional (unscheduled) ECGs may be collected by the investigator for safety reasons. These ECGs are assigned to the prior scheduled time point.

For the inclusion or exclusion (see Section 3.3) of a patient and for the assessment of cardiac safety during the study, the QT and QTcF according to Fridericia's formula

($QTcF = QT / RR^{1/3}$), and generated by the ECG machines or their manual corrections by the investigators will be used.

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at pre-treatment) if judged clinically relevant by the investigator. Any ECG abnormalities will be monitored carefully and, if necessary, the patient will be removed from the trial and will receive the appropriate medical treatment.

Assessed ECGs will comply with the ICH E14 guidance document and supplements [R05-2311, R13-0801, R13-4095] as well as the FDA requirements for annotated digital ECGs [R09-4830].

5.2.5 Assessment of other safety parameters

5.2.5.1 Vital signs

Vital signs evaluations will be performed at visits as shown in the flow chart. This includes body weight, temperature, pulse rate, systolic/diastolic blood pressure.

Body weight measurements should be done on the same scale for each patient. In order to get comparable body weight values, it should be performed in the following way:

- fasting (except for the screening visits)
- after the urine sampling (body weight after bladder voiding)
- shoes and coat/jackets should be taken off
- pockets should be emptied of heavy objects (i.e. keys, coins etc.)

Body temperature will be measured using a standard device. All recordings for a given patient should be made using the same instrument and at the same area (ear, mouth…).

Pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least five 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 dosing visit (V3), vital signs evaluations will be performed pre-dose.

5.2.5.2 Medical examinations

At the inclusion visit, the medical examination will include documentation of patient information, informed consent, demographics including height, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR, body weight and temperature), 12-lead ECG, laboratory tests, and a physical examination. At the End-Of-Trial examination, it will include review of vital signs, 12-lead ECG, physical examination, assessment of psoriatic lesions, and of the presence of edema.

Physical examinations will be performed at visits as described in the Flow Chart. Physical examination will include general appearance as well as evaluation of all relevant organ systems. Clinically relevant abnormal findings will be reported as baseline conditions or AEs.

Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 4 hours after the infusion at Visit 3. Hypersensitivity reactions should be treated according to medical standards.

5.2.5.3 Local tolerability

Local tolerability will be assessed by the investigator according to 'swelling', 'induration', 'heat', 'redness', 'pain', or 'other findings'.

5.3 OTHER

5.3.1 Photographs of skin lesions

Photography of skin lesions 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 per instructions in the ISF. The patient's consent must be obtained prior to take the photographs. Patients must be unrecognizable on the photos (refer to the procedure in the ISF).

5.4 APPROPRIATENESS OF MEASUREMENTS

The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG variables that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an intravenously administered drug, and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.5 are generally used assessments of drug exposure. The biomarkers, pharmacogenomic and efficacy parameters and measurements outlined in Sections 5.1, 5.6, and 5.7 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.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs.

Exact time points of plasma sampling will be documented in the CRFs by the site personnel or sent as electronic files to the trial data manager. The actual sampling times will be used for determination of pharmacokinetic parameters.

5.5.1 Pharmacokinetic endpoints

The following pharmacokinetic parameters will be determined if feasible:

5.5.1.1 Secondary endpoints

- $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity)

- C_{max} (maximum measured concentration of the analyte in plasma)

5.5.2 Methods of sample collection

Optional use of plasma aliquots: Plasma samples may be used for further methodological investigations (ex: for future stability testing). However, only data for measuring the analyte and antibody responses to the analyte will be generated by these investigations. The PK study samples will be discarded after completion of the investigations but not later than 3 years after the final study report has been signed. Following the finalization of the ADA

bioanalytical report, ADA aliquots will be transferred to long term storage for possible/optional ADA characterization in the future.

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 655130 plasma concentrations, blood will be taken from an antecubital or forearm vein into a K_2EDTA (ethylenediaminetetraacetic acid)-anticoagulant blood drawing tube at the time points indicated in the Flow Chart under PK plasma. Blood will be withdrawn by means of either an indwelling venous catheter or by venipuncture with a metal needle. Procedure for handling can be found in the Lab Manual (ISF).

5.5.2.2 Plasma sampling for ADA assessment

For ADA assessment, blood will be taken from an antecubital or forearm vein into a K_2EDTA anticoagulant blood-drawing tube at the time points listed in the Flow Chart under plasma ADA.

5.5.3 Analytical determinations

5.5.3.1 Analytical determination of BI 655130 plasma concentration

BI 655130 concentrations will be determined by a validated Enzyme Linked Immunosorbent Assay (ELISA).

5.6 BIOMARKER(S)

5.6.3 Methods of sample collection

Biomarkers sampling times and periods may be adapted during the trial based on information obtained during trial conduct (e.g. preliminary PK/PD data), including addition of samples and visits, as long as the total blood volume taken from each patient does not exceed 500 mL. Such changes would be implemented via non-substantial CTP Amendments.

Lesional skin biopsies (for histopathologic, immunohistopatholic and RNASeq) will be performed at baseline prior to receiving treatment (Day 1) and on Day 7 (Visit 9). Optional skin biopsies may be performed on Day 14 (Visit 10). They will be collected at the site of most inflammatory (deepest red erythema) lesion. Paired non-lesional skin biopsies will also be collected at baseline. Instructions on the skin biopsy samples preparation will be reviewed by site staff prior to the first biopsy (refer to ISF).

5.6.4 Analytical determinations

For histopathological evaluation, a histopathological score of the skin biopsies will be based on hematoxylin and eosin staining as the degree of parakeratosis, psoriasiform papillary pattern, vessel density, and dilation in the papillae, lymphocyte infiltration around the superficial plexes of vessels, and granulocyte infiltration in stratum corneum. The histopathologic score for each of the five patterns will be graded on a scale of Positive, Negative and Positive/Negative. At least one representative digital picture of each biopsy will be collected and provided to BI. For other endpoints, all sections stained with markers for presence of cytokines, leukocyte subsets, lymphocyte subsets, blood vessels, and other markers will be evaluated semi-quantitatively. Based on a semi-quantitative evaluation under the discretion of a consultant dermatologist, the staining level of each marker will be assessed

and reported. Characteristics of the analytical methods for the analysis of skin, serum and plasma biomarkers will be given in detail in the clinical trial report or in an accompanying technical/biomarker report.

Serum, plasma proteins and cell populations by flow cytometry will be analyzed using established parameters for each analyte (protein) and the corresponding matrix (serum and plasma) and cell subsets (flow cytometry).
Targeted re-sequencing and gene expression will be analyzed using standard molecular genetic methods and technologies such as Next Generation Sequencing (for whole genome sequencing) and TaqMan Real Time PCR and/or RNA sequencing for expression analysis.

5.7.1 Pharmacodynamic endpoints

Cf. section 5.6.1.

5.7.2 Methods of sample collection

Cf. section 5.6.3.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

No analysis of the relationship between pharmacokinetic and pharmacodynamic parameters is planned for this trial.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the flow chart. Investigators should encourage patient adherence to protocol specific activities. Each visit date (with its window) is to be counted from Day 1. The acceptable time windows for observation visits and End-Of-Trial are given in the Flow Chart. All deviations from the planned visit schedule will be documented. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

For planned individual plasma concentration sampling times refer to the Flow Chart. While these nominal times should be adhered to as closely as possible, the actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

If a patient misses an appointment, it will be rescheduled if possible. The relevance of measurements outside the permitted time windows will be assessed no later than at the Report Planning Meeting.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the flow chart and the respective protocol sections. Refer to Section 5 for explanations of procedures. Additional details on procedures at selected visits are provided below.

Included patients must be hospitalized for at least 4 days following the study drug administration. Patients will perform Visits 2 to 7 as inpatients. Visits 8 to 14 can be ambulatory or as inpatient if the patient is still hospitalized.

Measurement of vital signs should precede blood sampling and be assessed pre-dose at dosing visit.

The following sequence of procedures at each visit (where applicable) is recommended:

1. FACIT-Fatigue scale, pain VAS, and PSS
2. AE/local tolerability (at V3, local tolerability will be evaluated after the infusion) and concomitant therapy collection
3. Physical examinations / Vital signs / Body weight and temperature
4. GPPGA, GPPASI, CGI-I, presence of edema, pustular BSA
5. Photographs of skin lesions
6. ECG
7. Blood sampling for safety laboratory tests, PK, ADA, and biomarkers
8. Skin biopsies

Evaluation of GPPASI, GPPGA, CGI-I, presence of edema, and pustular BSA for a given patient should be performed by the same physician throughout the study.

The patient's questionnaires (FACIT-Fatigue, PSS, pain VAS) should be completed by the patient himself without any help. In case of impossibility, they should not be completed.

6.2.1 Screening period

6.2.1.1 Screening Visit 1

The study requirements, including the procedure for the follow-up of prematurely withdrawn patients must be fully explained to the patient and written informed consent obtained prior to initiating any study-related evaluation. The importance of staying in the trial until completion of all study requirements will be emphasized.

No trial procedures should be done unless the patient has consented to taking part in the trial.

Once consented, the patient is considered to be enrolled in the trial and have started screening. The patient should be recorded on the enrolment log and be registered in IRT as a screened patient.

Screening (Visit 1) should normally take place several days, weeks before a flare of GPP, and be terminated the day before the treatment administration at Visit 3 (a second screening visit will take place the day the patient is admitted for a flare of GPP (Visit 2)).

Infection screening
Refer to exclusion criteria Section 3.3.3 with study participation directive for patients with a positive QuantiFERON®TB test TB.

Mutation status
Information on the presence or absence of IL36RN mutation will be collected in patient's historical data and reported in the eCRF.

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.

Review of inclusion/exclusion criteria
Selection criteria will be reviewed carefully.

IRT
All patients that are screened must be registered with IRT. If the patient results in a screen

failure, IRT should be notified as soon as possible. Details of IRT procedures can be found in the IRT manual located in the ISF.

6.2.1.2 Screening Visit 2

The patient will be asked to confirm that he/she is still willing to participate in the trial. Eligibility will be assessed during this visit.

Re-screening will not be permitted: patients who fail screening following Visits 1 or 2 assessments should be registered as a screen failure in IRT. Details of IRT procedures can be found in the IRT manual located in the ISF.

All procedures described in the Flow Chart for this visit will be performed.

6.2.2 Treatment Visit (V3) and observation period

Treatment Visit 3 should be performed the day after Visit 2.

The BI655130 will be administered only at Visit 3. The observation period is from Visit 4 to EOT Visit (V14).

All procedures described in the Study Flow Chart and PK Flow Chart for this visit will be performed.

Study measurements and assessments scheduled to occur ‘before’ trial medication administration on Day 1 are to be performed and completed within a 4 h-period prior to the trial drug administration (including blank values for PK, ADA and biomarkers).

For information regarding laboratory tests, ECG, vital signs, and physical examination, refer to Sections 5.2.3 to 5.2.5.

Fasting condition is not required for blood sampling. Pharmacogenomic genotyping for targeted GPP causing mutations (IL36RN, CARD14, AP1S3) will be performed in all patients (for details see Sections 5.6.2 and 5.6.3). DNA banking is optional and will only be performed in patients who give their consent for it.

Skin lesions photographs will be taken at all visits on site except visits 7 and 8. Skin biopsies will be performed at visits 3, and 9 (one additional biopsy at visit 10 is optional). For indications, refer to ISF.

Skin biopsies and venipuncture (i.e. safety laboratories, PK, ADA, biomarkers) should be the last procedure prior to study drug administration.

Study drug allocation via IRT and administration of study medication should be the last activity at Visit 3.

A urine pregnancy test will be performed at Day 28 (Visit 12), Day 56, Day 84 (Visit 13), Day 112, and Day 140 (Visit 14). The patient will inform the site of the results of the tests performed at Day 56 and Day 112 by phone.

All abnormal values (including laboratory parameters) that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved.

6.2.3 Early trial termination

Trial termination should be completed at EOT visit. In case a patient prematurely discontinues the treatment or the trial, every effort should be made to perform assessments at Day 7 (Visit 9), Day 14 (Visit 10), Day 28 (Visit 12), and Day 140 (EOT Visit) as initially planned (please refer to section 3.3.4.1).

If a patient cannot or will not continue in the trial as defined above, then the patient should complete V12 procedures at the time of discontinuation. If the withdrawal occurs after V12, the patient should complete the EOT procedures.

For Japan: In the case of a patient's discontinuation from the trial, the patient will be followed-up until the investigator or sub-investigator is convinced of the patient's safety. When follow-up is not possible or comes to an end, it should be formally completed after discussion with the sponsor. If a patient stops attending trial assessments, the investigator should assess the patient's status as comprehensively as possible and the well-being of the patient should be monitored. However, if the patient withdraws from the trial, it is the patient's choice whether or not to participate; he or she cannot be compelled.

6.2.4 End-Of-Trial (Visit 14)

Completion is defined as a patient having reached the EOT visit within the specified window per the Flow Chart.

Adverse events persisting after trial completion must be monitored until they have normalised or have been sufficiently characterised.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

The study design is described in Section 3 and trial objectives are listed under Section 2.2. The safety, efficacy and PK endpoints will be evaluated descriptively; for efficacy endpoints 95% confidence intervals may be presented in addition.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in a confirmatory sense. Instead, the endpoints will be described in their entirety and evaluated by descriptive statistical methods.

Confidence intervals will be computed and will have to be interpreted in the perspective of the exploratory character of the study, i.e. confidence intervals are considered as interval estimates for effects.

7.3 PLANNED ANALYSES

Adherence to the protocol (such as inclusion/exclusion criteria, times of measurement, compliance with intake of trial medication, treatment dispensing errors, prohibited concomitant medication, completeness and consistency of data) will be checked. Important protocol violations (IPVs) will be identified in the TSAP.

7.3.1 Primary analyses

Analysis of safety and tolerability is described in Section 7.3.4.

7.3.2 Secondary analyses

The continuous secondary efficacy endpoints, such as GPPASI total score, Pain VAS, and FACIT-Fatigue score at week 2, will be evaluated descriptively, including the original as well as change from baseline values where applicable, along with exact 95% confidence intervals, if feasible. For the GPPASI total score, the percentage change from baseline at week 2 will be displayed.

The binary efficacy endpoint, GPPGA response of 0 (clear) or 1 (almost clear), will be described using patient frequencies and percentages. Exact 95% confidence intervals will additionally be provided for the proportion of patients with a response, if feasible.

The patient set for the evaluation of efficacy endpoints (FAS) will include all treated patients who had a baseline and at least one post-baseline measurement available for either GPPASI or GPPGA. Baseline is defined as the last measurement collected prior to administration of the trial treatment.

The secondary PK parameters (refer to Section 5.5.1) will be calculated according to the BI Standard Operating Procedure (SOP) 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472). Analyses will be performed for parent drug.

Pharmacokinetic parameters of a patient will be included in the analysis unless the patient has an important protocol violation relevant for the evaluation. Whether a protocol violation is important will be decided no later than in the Report Planning Meeting.

Reasons for exclusion of single pharmacokinetic parameters may be:

- Time deviations
- Use of restricted medications

The patient set for the evaluation of PK endpoints (PKS) will include all treated patients that provide at least one observation for at least one secondary PK endpoint without important protocol violations with respect to the statistical evaluation of PK endpoints. It will be decided in the Report Planning Meeting which patients are to be included in the PKS. Excluded patients will be listed with their individual plasma concentrations and individual pharmacokinetic parameters, however, will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical PK assessment.

7.3.3 Further analyses

Analysis of the further efficacy endpoints will be performed using similar methods to those described in section 7.3.2 for the secondary analyses. Patient frequencies and percentages will be used to describe each category of the CGI-I at each visit.

7.3.4 Safety analyses

Safety will be assessed for the endpoints listed in Section 5.2.1. All treated patients (that is, all patients who received at least one dose of the study drug), will be included in the safety evaluation. Safety analyses will be descriptive in nature and will be based on BI standards.

Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatment (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to intake of trial medication will be assigned to 'screening', and those between trial medication intake until the end of REP will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, intensity and causal relationship of AEs will be tabulated by treatment, primary system organ class and preferred term. SAEs, AESIs (see Section 5.2.2.1) and other significant AEs (according to ICH E3) will be listed separately.

Laboratory data will be compared to their reference ranges. Values outside the reference range will be flagged. Additionally, differences from baseline will be evaluated.

For vital signs, the differences from baseline will be evaluated.

Relevant ECG findings will be reported as AEs.

7.3.5 Interim analyses

The analysis of the efficacy and safety data collected up to week 4 will be performed once all entered patients have completed the first 4 weeks of study (through visit 12); at that time-point, a preliminary database lock will be done. Since the study is planned to continue through an additional 16 weeks of further follow-up, a logistics plan will be developed in order to describe the processes to be implemented for protecting the integrity of the ongoing trial through the final week 20 analysis. Details of the analyses to be performed for the final week 4 data, as well as for the completed study through 20 weeks, will be described in the trial statistical analysis plan (TSAP). Both the TSAP and logistics plan will be finalized prior to database lock for the final week 4 analysis.

Efficacy and safety data will be reviewed on an ongoing basis at the Medical Quality Review Meeting to ensure data quality and patient's safety.

7.3.6 Pharmacokinetic analyses

The pharmacokinetic parameters listed in Section 5.5.1 for drug BI 655130 will be calculated according to the BI SOP 'Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics' (001-MCS-36-472).

Patients who are not included in the PKS (refer to Section 7.3.1.) will be reported with their individual plasma concentrations and individual pharmacokinetic parameters; however, they will not be included in descriptive statistics for plasma concentrations, pharmacokinetic parameters or other statistical PK assessment.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report, (that is, to the same number of decimal places provided in the bioanalytical report).

If a predose concentration value is greater than 5% of C_{max}, the patient's pharmacokinetic data will be not included in any PK statistical evaluations, in accordance with international guidances. The individual pharmacokinetic parameters of such a patient will be calculated and listed separately. If a predose concentration is above BLQ, but less than or equal to 5% of the patient's C_{max} value, the patient's data without any adjustments will be included in all pharmacokinetic measurements and calculations.

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

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

7.4.2 Plasma drug concentration - time profiles

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472).

Drug concentration data identified with NOS (no sample available), NOR (no valid result), NOA (not analyzed), BLQ (below the lower limit of quantification), or NOP (no peak detectable) will be displayed as such and not replaced by zero at any time point (this rule also applies also to the lag phase, including the predose values).

7.4.3 Pharmacokinetic parameters

Handling of missing PK data will be performed according to the relevant SOP of the Sponsor (001-MCS-36-472).

For the non-compartmental analysis, concentration data identified with NOS, NOR or NOA will generally not be considered. Concentration values in the lag phase identified as BLQ or NOP will be set to zero. All other BLQ/NOP values of the profile will be set to missing. The lag phase is defined as the period between time zero and the first time point with a concentration above the quantification limit.

7.4.4 Biomarker assessment

No imputations are planned for any missing biomarker data.

7.4.5 Efficacy

The following rules will be used to impute for missing data:

- For continuous endpoints, and for the CGI-Improvement, under the assumption that the disease is self-limiting and will gradually improve over time, the Last Observation Carried Forward (LOCF) approach is intended to be used;

- For binary endpoints, the following will be performed:

- If there are data at visits both before and after the visit with a missing outcome, then impute as success only if both neighboring visits also represent a success;

- Otherwise, impute as a failure to achieve a response (i.e. NRI [No Response Imputation]).

For patients that take a rescue medication during the course of the study, efficacy outcomes subsequent to the time-point at which the medication was taken will be set to missing and will be imputed using the steps described above.

For continuous endpoints, the data will additionally be displayed in the original form without any imputation for missing data performed.

Details on the handling of missing item scores for the FACIT will be based on FACIT Administration and Scoring Guidelines (version 4) and provided in the TSAP.

Further imputation strategies for missing data will be considered in the TSAP.

7.5 RANDOMISATION

No randomisation is planned in this trial, as it is an open-label trial with one treatment arm. All patients will receive the same treatment. A (medication) randomisation list will only be provided for logistical reasons with a block size of 1, i.e., a list of consecutive numbers is provided.

7.6 DETERMINATION OF SAMPLE SIZE

It is planned to enter a minimum of 6 patients but allow for a maximum of 10 patients. The planned sample size is not based on a power calculation but on feasibility and practical considerations to explore safety and tolerability as well as PK and efficacy of BI 655130 in GPP patients.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs, and for Japan, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

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

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study patients against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP, and for Japan, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in a separate agreement between the investigator or the trial site and the sponsor. As a general rule, no trial results should be published prior to finalisation of the CTR.

According to local requirements: The terms and conditions of the insurance coverage must be given to each patient and are made available to the investigator via documentation in the ISF.

8.1 STUDY APPROVAL, PATIENT INFORMATION, AND 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 a patient's participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient information form are to be retained by the investigator as part of the trial records. A copy of the signed and dated written informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative.

For Japan:

The investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent. Re-consenting may become necessary

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

The following items need to be included:

1. That the clinical trial is aimed at testing.
2. Objectives of the trial.
3. The name, title, and address of the investigator to contact.
4. Trial procedures.
5. Anticipated benefits of the investigational products and anticipated disadvantages to the patient.
6. Matters concerning other therapeutic measures.
7. Duration of participation in the clinical trial.
8. That the patient may withdraw from the trial at any time.
9. That patient's refusal of or withdrawal from participation in the trial does not cause any disadvantage to him or her.
10. That the monitors, the auditors, and the institutional review board are given access to the relevant source documents on condition that confidentiality of the patient is fully secured.
11. That privacy of the patient is kept.
12. The office of the medical institution to contact in the event of trial-related injury.
13. That necessary treatment is available to the patient in the event of trial-related injury.
14. Matters concerning compensation in the event of any trial-related injury.
15. The type of the IRB which is used for the reviews and deliberations on the matters such as appropriateness of conducting the clinical trial, the matters to be reviewed and deliberated by each IRB, and other matters concerning the IRBs involved in the clinical trial.
16. Other necessary matters concerning the clinical trial.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his or her medical records may be examined by authorised monitors (Clinical Monitor Local/Clinical Research Associate) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees, by IRBs/IECs, 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.

The data management procedures to ensure the quality of the data are described in detail in the trial data management and analysis plan (TDMAP) available in the TMF.

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

All data reported in the CRFs must be consistent with the source data or the discrepancies must be explained.

The investigator may need to request previous medical records or transfer records, depending on the trial.

8.3.2 Direct access to source data and documents

The investigator/institution will permit trial-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes (if applicable) and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate/on site monitor and auditor may review all CRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.3.3 Storage of records

Trial sites:

The trial sites must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor:

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular AE is 'listed', i.e. is a known side effect of the drug. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For BI 655130 this is the current version of the Investigator's Brochure [c03320876-01]. The current version of this reference document is to be provided in the ISF. No AEs are classified as listed for study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

8.5 STATEMENT OF CONFIDENTIALITY

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

The sponsor will take measures to protect the confidentiality and security of patients' pharmacogenomics samples and patient's data and privacy in accordance with current local laws. Samples collected for the purpose of potential future genetic research will be labelled with the same unique code number as used for patient's data in the main clinical trial. This number will be used in place of patient's name and other personally identifiable information that directly and easily identifies the patient, for example, his/her name and birth date. Only the trial site will have the link between patient's name and the code number.

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

8.6 COMPLETION OF TRIAL

For Japan: when the trial is completed, the investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient/patient out, unless specified differently in Section 6.2.5 of the CTP) or early termination of the trial.

8.7 PROTOCOL VIOLATIONS

For Japan: The investigator should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to trial subjects or for other medically compelling reason, the principal investigator should prepare and submit the records explaining the reasons thereof to the sponsor, and retain a copy of the records.

8.8 COMPENSATION AVAILABLE TO THE PATIENT IN THE EVENT OF TRIAL RELATED INJURY

For Japan: in the event of health injury associated with this trial, the sponsor is responsible for compensation based on the contract signed by the trial site.

9. REFERENCES

9.1 PUBLISHED REFERENCES

P09-07583 Aksentijevich I, et al. An autoinflammatory disease with deficiency of the interleukin-1-receptor antagonist. N Engl J Med 2009. 360(23):2426-2437.

R05-2311 ICH E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs (ICH harmonised tripartite guideline, recommended for adoption at step 4 of the ICH process on 12 May 2005 by the ICH Steering Committee). www.emea.eu.int 2005:1-14.

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R13-0801 E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs - Questions and Answers (R1). October 2012. website.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm323656.htm

R13-4095 European Medicines Agency (EMA). Committee for Medicinal Products for Human Use (CHMP): ICH guideline E14 - questions and answers: step 5 (May 2012, EMA/CHMP/ICH/310133/2008). website.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002878.pdf

R14-3559 Revicki DA, Jin Y, Wilson HD, Chau D, Viswanathan HN. Reliability and validity of the psoriasis symptom inventory in patients with moderate-to-severe psoriasis. J Dermatol Treat 2014. 25(1):8-14.

R14-3562 Bushnell DM, Martin ML, McCarrier K, Gordon K, Chiou CF, Huang X, Ortmeier B, Kricorian G. Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. J Dermatol Treat 2013. 24(5):356-360.

R14-5158 Marrakchi S, et al; Interleukin-36-receptor antagonist deficiency and generalized pustular psoriasis; N Engl J Med 365 (7), 620 -628 (2011)

R15-1219 Martin ML, McCarrier KP, Chiou CF, Gordon K, Kimball AB, Voorhees AS van, Gottlieb AB, Huang X, Globe D, Chau D, Viswanathan HN, Kricorian G. Early development and qualitative evidence of content validity for the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure of psoriasis symptom severity. J Dermatol Treat 2013. 24(4):255-260.

R15-1399 Blumberg H1, Dinh H, Dean C Jr, Trueblood ES, Bailey K, Shows D, Bhagavathula N, Aslam MN, Varani J, Towne JE, Sims JE.; IL-1RL2 and its ligands contribute to the cytokine network in psoriasis.; J Immunol. 2010 Oct 1;185(7):4354-62. doi: 10.4049/jimmunol.1000313. Epub 2010 Sep 10

R15-1410 Lebwohl M, Swensen AR, Nyirady J, Kim E, Gwaltney CJ, Strober BE. The psoriasis symptom diary: development and content validity of a novel patient-reported outcome instrument. Int J Dermatol 2014. 53(6):714-722

R15-1411 Strober BE, Nyirady J, Mallya UG, Guettner A, Papavassilis C, Gottlieb AB, Elewski BE, Turner-Bowker DM, Shields AL, Gwaltney CJ, Lebwohl M. Item-level psychometric properties for a new patient-reported psoriasis symptom diary. Value Health 2013. 16(6):1014-1022.

R15-1420 Towne JE, Sims JE.; IL-36 in psoriasis; Curr Opin Pharmacol. 2012 Aug;12(4):486-90. doi: 10.1016/j.coph.2012.02.009. Epub2012 Mar 5. Review

R15-1421 Onoufriadis A1, Simpson MA, Pink AE, Di Meglio P, Smith CH, Pullabhatla V, Knight J, Spain SL, Nestle FO, Burden AD, Capon F, Trembath RC, Barker JN.; Mutations in IL36RN/IL1F5 are associated with the severe episodic inflammatory skin disease known as generalized pustular psoriasis; Am J Hum Genet. 2011 Sep 9;89(3):432-7. doi: 10.1016/j.ajhg.2011.07.022. Epub 2011 Aug 11

R15-1432 Blumberg H1, Dinh H, Trueblood ES, Pretorius J, Kugler D, Weng N, Kanaly ST, Towne JE, Willis CR, Kuechle MK, Sims JE, Peschon JJ.; Opposing activities of two novel members of the IL-1 ligand family regulate skin inflammation; J Exp Med. 2007 Oct 29;204(11):2603-14. Epub 2007 Oct 1

R15-1447 Tortola L1, Rosenwald E, Abel B, Blumberg H, Schäfer M, Coyle AJ, Renauld JC, Werner S, Kisielow J, Kopf M.; Psoriasiform dermatitis is driven by IL-36-mediated dc-keratinocyte crosstalk; J Clin Invest. 2012 Nov;122(11):3965-76. doi: 10.1172/JCI63451. Epub 2012 Oct 15

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 Feb;26(1):23-31.

R16-0929 Berki DM, Liu L, Choon SE, Burden AD, et al. Activating CARD14 mutations are associated with generalized pustular psoriasis but rarely account for familial recurrence in psoriasis vulgaris. J Invest Dermatol 2015. 135:2964-2970

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 Jun;53(6):676-84. doi: 10.1111/ijd.12070. Epub 2013 Aug 22.

R16-1461 Varman KM, Namias N, Schulman CI, Pizano LR. Acute generalized pustular psoriasis, von Zumbusch type, treated in the burn unit. A review of clinical features and new therapeutics. Burns. 2014 Jun;40(4).

R16-1462 Imafuku S, Honma M, Okubo Y, Komine M, Ohtsuki M, Morita A, Seko N, Kawashima N, Ito S, Shima T, Nakagawa H. 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 Feb 26. doi: 10.1111/1346-8138.13306. [Epub ahead of print]

R16-1463 Borges-Costa J, Silva R, Gonçalves 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. 2011 Aug 1;12(4):271-6.

R16-2698 Augey F, Renaudier P, Nicolas JF. Generalized pustular psoriasis (Zumbusch): a French epidemiological survey. Eur J Dermatol. 2006 Nov-Dec;16(6):669-73.

R16-2960 Viguier M, Aubin F, Delaporte E, Pagès C, Paul C, Beylot-Barry M, Goujon C, Rybojad M, Bachelez H; Groupe de Recherche sur le Psoriasis de la Société Française de Dermatologie. Efficacy and safety of tumor necrosis factor inhibitors in acute generalized pustular psoriasis. Arch Dermatol. 2012 Dec;148(12):1423-5

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 Apr;23(4):415-9.

R95-0013 Broom C. Design of first-administration studies in healthy man. Early Phase Drug Evaluation in Man. O'Grady J, Linet OI (Eds.), Macmillan Press: London, 1990, 206 213.

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

9.2 UNPUBLISHED REFERENCES

c03320876-01 Investigator's Brochure BI 655130

c03361085-07 Clinical Trial Protocol 1368.1 Single-blind, partially randomised, placebo-controlled Phase I study to investigate safety, tolerability, harmacokinetics and pharmacodynamics of single rising intravenous doses of BI 655130 in healthy male volunteers; 27 January 2016

001-MCS-36-472 Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics

10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Protocol-specified AESIs), are to be further evaluated using the following procedures:

10.1.2 Procedures

Repeat the following laboratory tests: ALT, AST, AP, and bilirubin (total and direct) - within 48 to 72 h. If it is confirmed that AST and/or ALT and/or AP ≥3-fold ULN plus 2 time the baseline occurs in conjunction with an elevation of total bilirubin ≥2-fold ULN plus 1.5 time the baseline, the laboratory parameters listed below (clinical chemistry, serology, hormones, haematology) must be determined and made available to the investigator and to BI as soon as possible.

In addition,

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the 'DILI checklist' provided in the ISF
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the 'DILI checklist' provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the 'DILI checklist' provided in the ISF;

and report these via the CRF.

Clinical chemistry
Alkaline phosphatase, albumin, PT or INR, CK, CK-MB, coeruloplasmin, α-1 antitrypsin, transferin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody

Hormones, tumormarker
TSH

Haematology
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.
- Initiate close observation of patients by repeat testing of ALT, AST, AP and total bilirubin (total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then monitor further as specified in the CTP. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

10.2 RECONSTITUTION INSTRUCTION(S)

Please refer to ISF for details about the preparation of the infusion solution.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		09 Nov 2016
EudraCT number		2016-001236-35
BI Trial number		1368.11
BI Investigational Product(s)		BI 655130
Title of protocol		Multi-centre, open-label, single arm, phase I study to investigate safety, tolerability, pharmacokinetics, pharmacogenomics and efficacy of a single intravenous dose of BI 655130 in patients with active generalized pustular psoriasis.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1. Flow charts, sections 2.3, 3.1, 5.1.1, 5.1.2, 5.2.1, 5.2.2.2, 5.2.3, 5.2.5.2, 6.1, 6.2.2, 6.2.4 2. Section 1.2.5 3. Synopsis, section 3.3.3 4. Synopsis, section 5.2.1 5. Section 3.3.2 6. Sections 3.3.2, 4.2.2.2 7. Sections 3.3.3, 4.2.2.2 8. Section 4.1.4 9. Section 4.1.4 10. Flow Chart, section 4.1.4 11. Section 6.2 12. Section 7.3.5 13. Section 7.3.2

Number of global amendment		1
		14. Sections 4.2.1.3, 5.2.3, 6.2 15. Sections 3.3.4.1, 6.2.3 16. Synopsis, 3.1, 3.2
Description of change		1. Update of study flow charts Observation period was extended until 20 weeks after study drug administration (End of Trial visit is now at Week 20) Additional visit at Week 12 with time-window was included Additional urinary pregnancy tests were included (due to extended observation period, results will be provided by phone) 2. PK data of FIH trial have been updated 3. Exclusion criteria n°4 was clarified 4. The primary endpoint was specified 5. The definition of women of childbearing potential was added 6. Period of use of birth control method was extended until 20 weeks after study drug administration. Birth control methods were updated 7. Information that women who stop breastfeeding can participate in the trial has been added. The time when they can start nursing again after their participation has also been specified. 8. In-use stability data were updated 9. Infusion time was prolonged to 60 minutes 10. Weight of infusion set before and after study drug administration was deleted 11. Statement that patient's questionnaires should be completed by the patient himself was added 12. Interim analysis was added 13. The definition of FAS was specified 14. Correction of inconsistencies and typing errors in safety lab tests and others sections were performed 15. Statements regarding removal of patients were rephrased for better understanding 16. One country was removed (UK)
Rationale for change		1. PK results from 1368.1 trial suggest a

Number of global amendment		1
		for doses tested in the study. The evaluation is ongoing. However as precautionary measure we have extended the observation period to Day 140 to cover 2. PK data for all dose groups are available 3. Exclusion criteria n°4 was clarified for better understanding 4. The definition of an adverse reaction was specified for clarification 5. Information was missing 6. We have extended the period of use of contraception methods to cover the residual effect period We have updated the birth control methods according to the new BI SOP 7. Information was missing 8. Updated In-Use Stability Data with date from 26 Sept 2016 9. Updated In-Use Stability Data with date from 26 Sept 2016 10. After Pre-Trial Contact Visits, the procedure seemed to be less reliable than collecting the infused volume indicated on infusion pump 11. Statement was missing 12. The final analysis of the efficacy and safety data collected up to Week 4 will be performed once all entered patients have completed the first 4 weeks of study (through Visit 12); at that time-point, a preliminary database lock will be done 13. The definition of FAS was specified for clarification 14. A few inconsistencies and typing errors were corrected 15. Text about removal of patients has been rephrased to avoid misunderstanding 16. Investigator was excluded because moved to another site

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Team Member Medicine		09 Nov 2016 17:26 CET
Author-Trial Clinical Monitor		09 Nov 2016 17:49 CET
Approval-Therapeutic Area		09 Nov 2016 18:58 CET
Author-Trial Statistician		10 Nov 2016 15:35 CET
Verification-Paper Signature Completion		10 Nov 2016 17:23 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed