

Clinical Trial Protocol

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EudraCT No.:	2016-004573-40	
BI Trial No.:	1368.15	
BI Investigational Product(s):	BI 655130	
Title:	Multi-center, double-blind, randomised, placebo-controlled, phase IIa study to investigate efficacy, safety, tolerability, pharmacokinetics and pharmacogenomics of multiple intravenous doses of BI 655130 in patients with Palmoplantar Pustulosis (PPP)	
Lay Title:	Initial Dosing of BI 655130 in Palmoplantar Pustulosis patients	
Clinical Phase:	IIa	
Trial Clinical Monitor:	Phone: _____ Fax: _____	
Coordinating Investigator:	Phone: _____ Fax: _____	
Status:	Final Protocol (Revised Protocol (based on Global Amendment No. 1 and No. 2))	
Version and Date:	Version: 3.0	Date: 08 May 2018
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		Boehringer Ingelheim	
Name of finished product:		Not Applicable	
Name of active ingredient:		BI 655130	
Protocol date: 03 February 2017	Trial number: 1368.15		Revision date: 08 May 2018
Title of trial:	Multi-center, double-blind, randomised, placebo-controlled, phase IIa study to investigate efficacy, safety, tolerability, pharmacokinetics and pharmacogenomics of multiple intravenous doses of BI 655130 in patients with Palmoplantar Pustulosis (PPP)		
Coordinating Investigator	Phone: _____ Fax: _____		
Trial site(s):	Multi-centre study		
Clinical phase:	IIa		
Objective(s):	The primary objective of this trial is to investigate the safety and efficacy of BI 655130 in patients with PPP following multiple intravenous administrations of either 900 mg or 300 mg compared to placebo		
Methodology:	Randomised, parallel-design, multiple-doses, placebo-controlled, double-blind		
No. of patients:			
total entered:	60 patients		
each treatment:	20 patients per treatment arm		
Diagnosis :	Palmoplantar Pustulosis defined as primary, persistent (>3months duration), sterile, macroscopically visible pustules on the palms and/or soles, without or with plaque psoriasis		
Main criteria for inclusion:	<ul style="list-style-type: none"> • Male or female patients, aged 18 to 65 years at screening • Diagnosed with Palmoplantar Pustulosis with a minimum ppPASI score of 12 and pppPGA of at least moderate severity 		

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	at baseline <ul style="list-style-type: none"> Patients with associated plaque psoriasis $\geq 10\%$ of the body surface area are excluded 		
Test product	BI 655130		
dose:	900 mg and 300 mg every 4 weeks at Day 1, 29, 57 and 85		
mode of administration:	Intravenous (i.v.)		
Comparator products:	placebo		
dose:	0 mg (placebo) every 4 weeks at Day 1, 29, 57 and 85		
mode of administration:	i.v.		
Duration of treatment:	12 weeks		
Endpoints	Primary Endpoint <ul style="list-style-type: none"> Efficacy: ppPASI50 at week 16 Safety: Number of patients with drug-related AEs Secondary Endpoint(s) <ul style="list-style-type: none"> Treatment success defined as achieving a clinical response of 0 or 1=clear/almost clear via PPP Physicians Global Assessment (pppPGA) at week 16 ppPASI75 at week 16 Percent change from baseline in the ppPASI at week 16 		
Safety criteria:	Physical examination, vital signs, 12-lead Electrocardiogram (ECG), laboratory tests, adverse events, serious adverse events and tolerability. The intensity grading of AEs and abnormal laboratory values will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0.		
Statistical methods:	Randomisation will be stratified by the presence or absence of plaque psoriasis. For the primary endpoint, the unadjusted risk difference		

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<p>based on the observed proportion of patients with ppPASI50 at week 16 for BI 655130 and placebo will be assessed descriptively, for the Full Analysis Set (FAS), and 95% Wilson confidence intervals (CIs) will also be provided. The FAS comprises all participants who were randomised, received at least one dose during the trial, and had a baseline measurement for the primary endpoint. The influence of the stratification variable on the primary endpoint will be characterized in exploratory analyses.</p> <p>Safety data will be presented using descriptive methods.</p>			

FLOW CHART

Trial Periods	Screening ¹	Randomised Treatment Period										Post treatment follow-up	
		2 ²	3	4	5	6	7	8	9	10	11 PE ³	12	13 EOT ⁴
Visit	1												
Week	-4 to -1				2	4	6	8	10	12	16	24	32
Day	-28 to -7	1	4±2	8±3	15±3	29±3	43±3	57±3	71±3	85±3	113±3	169±7	225±7
Informed Consent	X												
Inclusion/exclusion criteria	X	X											
Demographics, Medical History	X												
Physical Examination	X ^{12,C}	X ^T	X ^T	X ^T	X ^T	X ^T	X ^T	X ^T	X ^T	X ^T	X ^C	X ^T	X ^{12,C}
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy testing ⁵	X ^s	X ^{u,(s)}				X ^{u,(s)}		X ^{u,(s)}		X ^{u,(s)}	X ^{u,(s)}	X ^{u,(s)}	X ^{u,(s)}
Safety Laboratory tests	X	X	X	X	X	X	X	X	X	X	X	X	X

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Trial Periods	Screen- ing ¹	Randomised Treatment Period										Post treatment follow-up		
		1	2 ²	3	4	5	6	7	8	9	10	11 PE ³	12	13 EOT ⁴
Week	-4 to -1					2	4	6	8	10	12	16	24	32
Day	-28 to-7	1	4±2	8±3	15±3	29±3	43±3	57±3	71±3	85±3	113±3	169± 7	225±7	
Assign/Administer study drug		X					X		X		X			

Palmoplantar Pustular Psoriasis Area and Severity Index (ppPASI)	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PPP Physician Global Assessment (pppPGA)	X	X	X	X	X	X	X	X	X	X	X	X	X	X

12-lead ECG	X	X				X		X		X	X	X	X	X
Local Tolerability		X				X		X		X				
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Completion of participation ⁴														X

Footnotes:

¹ The time window for Visit 1 may be extended at the discretion of the Local Clinical Monitor (CML) in conjunction with the TCM (Trial Clinical Monitor) on a case by case basis.

² Day of Randomisation / Day of first administration of randomised medication.

³ PE – Primary Endpoint Visit.

⁴ EOT End of Trial. If the patient withdraws from the trial prematurely following randomisation, instructions in [Sections 3.3.4](#) and [6.2.3](#) should be followed.

⁵ Only applicable for women of childbearing potential. S – serum pregnancy test (performed at screening). U – urine pregnancy tests will be performed at all other visits indicated in the [Flow chart](#). Urine pregnancy testing should be done prior to administration of study drug in case there is dosing at study visits. Study drug should only be administered in case of a negative test result. (S) - in case of a positive urine pregnancy test, a serum pregnancy test will be done. Women who underwent tubal ligation are still considered of childbearing potential and pregnancy testing is necessary just as for other women of childbearing potential.

C=complete physical examination; T=targeted physical examination. At the screening physical examination, patient height and weight will be collected (see [Section 5.3.1](#)).

¹³ For the patients with concurrent plaque psoriasis, the percent body surface area (BSA) involved with plaque-type psoriasis lesions will be captured.

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ABBREVIATIONS

ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AMP	Auxiliary Medicinal Product
API	Active Pharmaceutical Ingredient
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BSA	Body Surface Area
CDC	Complement-Dependent Cytotoxicity
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organisation
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DEDP	Drug Exposure During Pregnancy
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Desoxyribo Nucleid Acid
ECG	Electrocardiogram
EDTA	Ethylendiaminetetraacetic Acid
e.g.	Example given
ELISA	Enzyme Linked Immunosorbent Assay
EOT	End of Trial
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FcRn	Neonatal Fc receptor
FIH	First-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPP	Generalized Pustular Psoriasis
HIV	Human Immunodeficiency Virus
HV	Healthy Volunteer
IB	Investigator's Brochure
IBD	Inflammatory Bowel Disease
i.e.	id est
IEC	Independent Ethics Committee
IgG	Immunglobulin G

IL	Interleukin
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
ITE	Indirect Target Engagement
i.v.	Intravenous
kDA	Kilodalton
kg	Kilogram
LPDD	Last Patient Drug Discontinuation
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
mm	Millimeter
MMRM	Mixed Model Repeated Measures
MoA	Mode of action
MRD	Multiple rising dose
NCE	New chemical entity
NIMP	Non-Investigational Medicinal Product
NRI	No Response Imputation
OPU	Operative Unit
PD	Pharmacodynamics
PGA	Physicians Global Assessment
PK	Pharmacokinetics
PoCC	Proof of Clinical Concept
PPP	Palmoplantar Pustulosis
pppPGA	Palmoplantar Pustulosis Physicians Global Assessment
ppPASI	Palmoplantar Pustular Psoriasis Area and Severity Index
PROs	Patient Reported Outcomes
PUVA	Psoralen plus UV-A
RCTC	Rheumatology Common Toxicity Criteria
RDC	Remote Data Capture
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RNA	Ribonucleid Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
s.c.	subcutaneous
SD	Standard Deviation
SOP	Standard Operating Procedures
SRD	Single rising dose
SUSARs	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TMDD	Target Mediated Drug Disposition
TNF	Tumor necrosis factor
TSAP	Trial Statistical Analysis Plan

WBC	White Blood Count
WFI	Water For Injection
WOCBP	Women of Childbearing Potential

1.0 INTRODUCTION

1.1 MEDICAL BACKGROUND

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

PPP may be considered a rare disease. PPP is characterized by the presence of sterile pustules on palms and/or soles [[R16-0927](#)]. Despite the limited area of skin involvement in PPP, the disease is very debilitating with a large impact on quality of life including ability to work. PPP symptoms include pruritus, burning sensations, and pain. In severe cases, the skin affliction makes walking or other activities of daily living challenging if not impossible. No approved treatment is available for PPP further highlighting the high need for an effective treatment option. There are 2 subpopulations of patients with palmoplantar pustulosis. Those patients with pure pustulosis where patients only have the sterile pustules on the palms of their hands and/or soles of their feet and those patients in addition having plaque psoriasis which for this study would be on less than 10% of their body surface area. For the sake of clarity in this study both subpopulations of patients would be referred to as having palmoplantar pustulosis (PPP).

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

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

It is planned to enroll PPP patients irrespective of their mutation status of these three genes.

Currently there is no standard of care available for the treatment of PPP (i.e., no approved therapy). PPP is notoriously difficult to treat. Patients usually end up being treated with the

currently available systemic treatment options including retinoids, PUVA, methotrexate, ciclosporine and topical corticosteroids. Unfortunately, these options are usually not effective in reducing duration and severity of PPP.

Thus, there is high unmet medical need for PPP.

Secukinumab (anti-IL17A; EU) and guselkumab (anti-IL23; Japan) are the only treatments currently being tested in the clinic for the PPP indication. No data for palmoplantar pustulosis are currently available for these treatments. No anti-IL36R treatments are known to have been tested or are being tested in the clinic.

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

2.0 RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

BI 655130 is in development for the treatment of Palmoplantar Pustulosis. The first trial to be conducted in PPP patients is a proof-of-concept, phase IIa trial. The rationale to perform this trial is based on the published human genetic linkage between the target disease PPP and the IL36 pathway targeted by BI 655130 [[R16-0950](#); [R16-3561](#)], the functional linkage between the IL36 pathway and PPP [[R16-3543](#)] and the high unmet medical need in PPP.

There is currently no drug specifically approved for the treatment of PPP and it is notoriously difficult to treat. Patients usually end up being treated with the currently available systemic treatment options including retinoids, PUVA, methotrexate, ciclosporine and topical corticosteroids. Unfortunately, the current treatment options are not effective in reducing duration and severity of PPP. Thus, there is high unmet medical need for PPP.

The results from this trial will enable the design of the further developmental program and in case that positive efficacy signals can be confirmed the results will form the basis for discussions with regulatory agencies.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to investigate the safety and efficacy of BI 655130 in patients with PPP following multiple intravenous administrations of either 900 mg or 300 mg compared to placebo.

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

Procedure-related risks

The use of an indwelling venous catheter for the purpose of infusion 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 when drawing blood samples prior to the start of infusion.

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 (AEs) or abnormal laboratory values. There have been no deaths or other serious adverse events (SAEs). The adverse events reported had no apparent dose or exposure relationship. There have been no dose or exposure related abnormalities in safety laboratory parameters, no clinically relevant laboratory abnormalities on treatment with BI 655130 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.

Still, the following safety measures are/will be applied in this study in order to minimize the risk for the PPP patients:

- The i.v. administration allows for immediate discontinuation of further drug administration should any safety concern arise (please refer to [Section 4.1.4](#)).
- BI 655130 will be administered under close medical observation (see [Section 6.2](#)) during patient visits.
- Patients will be closely monitored for signs and symptoms of hypersensitivity reactions. Hypersensitivity reactions should be treated according to medical standards.
- Extensive safety laboratory testing will be performed ([Table 5.3.3:1](#)).

Currently there are no data available to suggest interactions of BI 655130 with other drugs ([c03320877](#)).

In order to mitigate any safety signals as early as possible, an independent Data Monitoring Committee (DMC) will oversee this study (see [Sections 3.1.](#) and [7.4](#) for further details). Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety, see also [Section 5.3.6.1](#).

Participation in this study may help generate future benefit for larger groups of patients with PPP if BI 655130 proves to be successful in treating this disease since an unmet medical need will be addressed as described in [Section 1.1](#).

Treatment with BI 655130 has the potential to provide benefit to patients with palmoplantar pustulosis by reducing the severity and duration of disease-related symptoms. However, no direct benefit for all individual participants in this study can be assumed, because efficacy of BI 655130 has not been confirmed in palmoplantar pustulosis and because some patients will be randomised to the placebo arm.

It is important to have a placebo control to address potential confounding factors, such as placebo effect, potential investigator bias in safety and efficacy assessment or regression to the mean in endpoint scoring as well as in order to characterize both the efficacy and safety background rates in this trial population. Currently there are no clinical trial data available in the published literature that describes a placebo response on the ppPASI50 in the population of patients with palmoplantar pustulosis.

Considering the medical need for development of an effective and well tolerated drug for the therapy of PPP, the benefit of this trial is considered to outweigh the potential minimal risks and justifies the administration of multiple doses of BI 655130 to patients with PPP to investigate efficacy, safety, tolerability and pharmacokinetics.

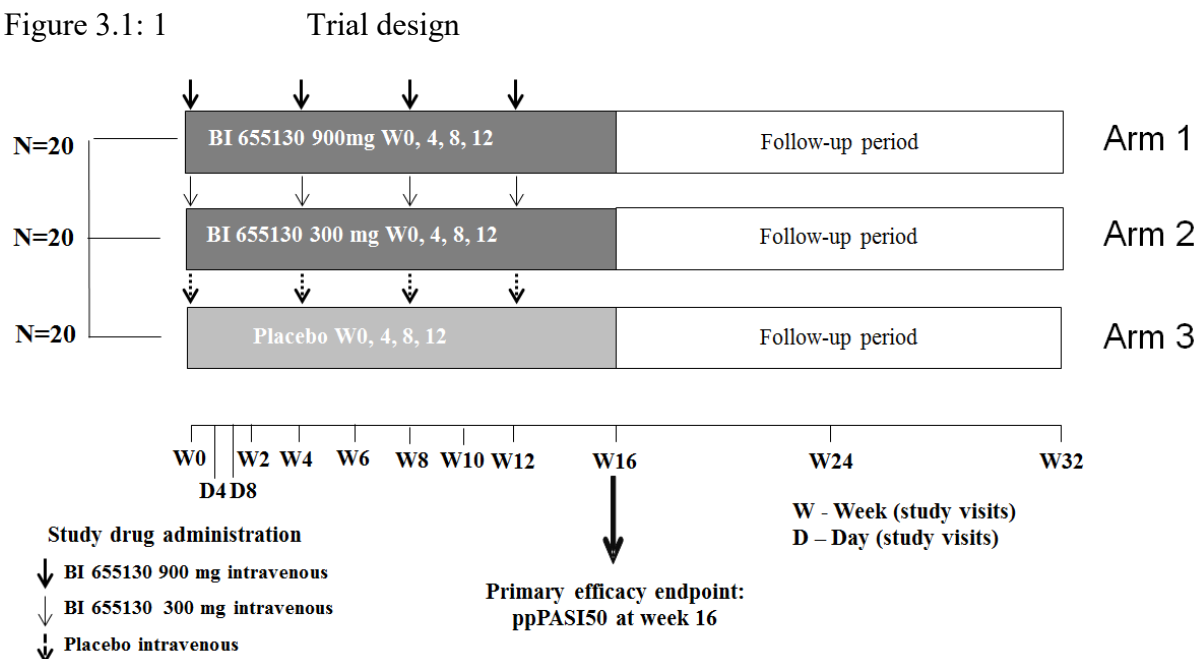
3.0 DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a randomised, double-blind, placebo-controlled, parallel-design study. This design is appropriate for providing proof-of-concept and assessing the efficacy and safety of BI 655130 compared to placebo in patients with PPP.

There will be two active dosing arms in this study along with a placebo control arm as follows:

Figure 3.1: 1



The final analysis of the efficacy and safety data collected up to week 16 will be performed once all randomised patients have completed the first 16 weeks of study; at that time-point, a database lock will be done. The final analysis of the entire trial data collected through week 32 will be performed once all patients have completed the last scheduled trial visit.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).

Boehringer Ingelheim 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 Standard Operating Procedures (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial; and
- ensure appropriate training and information of local clinical monitors (CMLs), Clinical Research Associates (CRAs), and Investigators of participating countries.

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

A Coordinating Investigator is responsible to coordinate Investigators at different centers participating in this multicenter trial. Tasks and responsibilities are defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in the ISF.

A partially external Data Monitoring Committee will be established to assess the safety of BI 655130 in this clinical trial at specified intervals through the final time-point (week 32). At least 3 members of this DMC will be independent of the sponsor, including the DMC Statistician and the Chair. Measures will be put in place to ensure blinding of the sponsor and all other trial participants. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings. In addition, an optional interim analysis, to be performed on the primary efficacy endpoint once 50% of the total required number of patients has completed 16 weeks of study, will be performed by the DMC (see [Section 7.4](#) for further details).

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

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

A central laboratory service and an Interactive Response Technology (IRT) vendor will be used in this trial. Details will be provided in IRT Manual and Central Laboratory Manual, available in ISF.

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

This phase IIa trial is the first study with BI 655130 to be conducted in PPP patients. Current safety data about BI 655130 were obtained from a previous first-in-man single dose phase I trial 1368.1 and the multiple raising dose trial 1368.2 both carried out in healthy volunteers. BI 655130 was safe and well tolerated in all dose groups tested in 1368.1 and in all dose group tested so far in 1368.2 (10 mg/kg multiple dosing and 20 mg/kg single dose. 20 mg/kg multiple dose group has been approved and is currently ongoing.

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 IIa trial is to investigate proof of concept (safety and efficacy) and tolerability of BI 655130 in patients with PPP. Pharmacokinetics and pharmacogenomics will also be evaluated.

Both patients who have a pure palmoplantar pustulosis (PPP) presentation and those patients with a mixed pustulosis and psoriasis presentation on less than 10% of the BSA will be included in this study.

A placebo control group is necessary and is included in this trial because there are currently no clinical trial data available in the published literature that describes a placebo response on the primary efficacy endpoint in the population of patients with palmoplantar pustulosis.

3.3 SELECTION OF TRIAL POPULATION

3.3.1 Main diagnosis for trial entry

The study will be performed in adult patients diagnosed with Palmoplantar Pustulosis defined as presence of primary, persistent (> 3months duration), sterile, macroscopically visible pustules on the palms and/or soles, without or with plaque psoriasis.

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

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

3.3.2 Inclusion criteria

1. Signed and dated written informed consent in accordance with Good Clinical Practice (GCP) and local legislation prior to the start of any screening procedures.
2. Male or female patients, 18 to 65 years of age at screening.
3. Palmoplantar Pustulosis defined as presence of primary, persistent (> 3months duration), sterile, macroscopically visible pustules on the palms and/or soles, without or with plaque psoriasis on less than 10% of the body surface area.
4. Presence of active pustulation (yellow pustules) on palms and /or soles.
5. A minimum ppPASI score of 12 and pppPGA of at least moderate severity at baseline.
6. Women of childbearing potential (WOCBP)¹ and men able to father a child must use highly effective methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

¹ A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.

Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

Tubal ligation is NOT a method of permanent sterilisation.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

3.3.3 Exclusion criteria

1. Patients with associated plaque psoriasis $\geq 10\%$ of the body surface area.
2. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.
3. Severe, progressive, or uncontrolled renal, hepatic, haematological, endocrine, pulmonary, cardiac, neurologic, cerebral, or psychiatric disease, or signs and symptoms thereof.
4. Presence or known history of anti-TNF-induced PPP-like disease.
5. Patients with SAPHO (Synovitis–acne–pustulosis–hyperostosis–osteitis) syndrome.
6. Patient with a transplanted organ (with exception of a corneal transplant > 12 weeks prior to screening) or who have ever received stem cell therapy (e.g., Prochymal).
7. Known history of lymphoproliferative disease, including lymphoma, or signs and symptoms suggestive of possible lymphoproliferative disease, such as lymphadenopathy and/or splenomegaly.
8. Any documented active or suspected malignancy or history of malignancy within 5 years prior to the screening visit, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
9. Patients who have previously undergone allergy immunotherapy for prevention of anaphylactic reactions.
10. 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, as assessed by the investigator.
11. Plans for administration of live vaccines during the study period or within 6 weeks prior to randomisation.
12. History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients.
13. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomisation, as assessed by the investigator.
14. Chronic or relevant acute infections including human immunodeficiency virus (HIV), viral hepatitis and (or) active or latent tuberculosis (patients with a positive QuantiFERON TB test are excluded. Patients with suspected false positive or undeterminable QuantiFERON TB result may be re-tested).
15. Major surgery performed within 12 weeks prior to randomisation or planned within 32 weeks after randomisation (e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator.
16. Total white blood count (WBC) $< 3,000/\mu\text{L}$, or platelets $< 100,000/\mu\text{L}$ or neutrophils $< 1,500/\mu\text{L}$, or hemoglobin < 8.5 g/dL at screening.
17. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $> 2x$ the upper limit of normal, or total bilirubin $> 1.5x$ the upper limit of normal (patients with Gilbert's syndrome are not excluded) at screening.

18. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s).
19. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable study subject or unlikely to complete the trial.
20. Previous randomisation in this trial.

3.3.4 Withdrawal of patients from therapy or assessments

Patients may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see [Sections 3.3.4.1](#) and [3.3.4.2](#) below.

Every effort should be made to keep the randomised patients in the trial: if possible on treatment, or at least to collect important trial data.

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

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

3.3.4.1 Withdrawal from trial treatment

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

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication. Please refer to [Section 4.2.2](#) for restricted medication during this trial.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to stick to the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for the remaining scheduled visits and follow up as outlined in the [Flow Chart](#).

Should the patient not agree to continue the remaining trial visits as scheduled after the premature treatment discontinuation, all efforts should be made to bring the patient to the primary endpoint visit at Week 16 (Day 113, V11), and/or at least to the End of Trial at Week 32 (Day 225, V13).

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

3.3.4.2 Withdrawal of consent for trial participation

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

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.

If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see [Section 3.3.4.1](#) above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for any of the following reasons:

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

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

4.0 TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The investigational product has been manufactured by BI Pharma GmbH & Co. KG. The BI 655130 molecule is a heterodimer with a molecular weight of approximately 146 kDa. BI 655130 drug product is formulated at a concentration of 20 mg/mL. Active Pharmaceutical Ingredient (API) in a buffer consisting of 25 mM sodium citrate, 200 mM sucrose, 0.04% w/v polysorbate 80 at pH 6 and water for injection (WFI). All excipients are of compendium quality (e.g. USP, Ph.Eur.).

4.1.1 Identity of the Investigational Medicinal Products

The characteristics of the test product are given below:

Table 4.1.1:1 Test product BI 655130:

Substance:	BI 655130
Pharmaceutical formulation:	
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	150mg/7.5 mL
Posology:	900mg or 300 mg every 4 weeks at Day 1, 29, 57 and 85.
Route of Administration:	i.v. infusion
Duration of Use:	12 weeks

Table 4.1.1:2 Placebo

Substance	Placebo
Pharmaceutical formulation	A buffer of 25 mM sodium citrate, 200 mM sucrose, 0.04% w/v polysorbate 80 at pH 6 and water for injection.
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	0 mg/7.5 mL
Posology	0 mg every 4 weeks at day 1, 29, 57 and 85.
Route of Administration	i.v. infusion
Duration of Use	12 weeks

At the time of use the i.v. solutions for dosing will be prepared as detailed in the instruction in the ISF.

4.1.3 Method of assigning patients to treatment groups

An Interactive Response Technology will be used to screen and randomise eligible patients, perform subsequent drug assignment, manage initial/re-supply ordering of drug supplies and handle emergency un-blinding. The investigator will receive all necessary instructions to access IRT from the Sponsor or chosen provider. Detailed IRT functions and procedures will be documented in the user requirement specifications mutually agreed to by the sponsor and the IRT vendor. Patients will be randomly assigned to any of the treatment groups through the assignment of medication which will be treatment group-specific (c.f. [Section 3.1](#) for the treatment groups of the trial). For technical and statistical features of the treatment allocation process, please c.f. [Sections 4.1.4](#) and [7.5](#).

4.1.4 Drug assignment and administration of doses for each patient

During visit 2 on Day 1 eligible patients will be randomised to receive one of three treatments in a 1:1:1 ratio according to a randomisation plan. Randomisation will be stratified by the presence or absence of plaque psoriasis. The assignment will occur in a blinded fashion via IRT.

The treatments to be evaluated are outlined in [Table 4.1.4: 1](#) below. Treatment will be assigned to each patient after the completion of the screening visit and verification of all inclusion and exclusion criteria.

For further details concerning the timing of dosing patients with investigation product see [Flow Chart](#). Start and end time of the infusion will be recorded in eCRF.

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

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. Further based on his 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 its preparation, if correct dosage cannot be ensured otherwise. Prior to each administration of study drug, a urine pregnancy test will be performed on site. If this test has a positive result, the administration of study drug should not proceed and this urine test should be confirmed by a serum pregnancy test.

Table 4.1.4: 1 Schedule for dosing patients

Total BI 655130 Dose (mg)	Visit 2 Day 1	Visit 6 Day 29	Visit 8 Day 57	Visit 10 Day 85
	Number of patients			
900	20	20	20	20
300	20	20	20	20
0 (placebo)	20	20	20	20

4.1.5 Blinding and procedures for un-blinding

4.1.5.1 Blinding

Patients and investigators involved in trial conduct will remain blinded with regard to the randomised treatment assignments until after the final trial database lock. The randomisation code will be kept secret by Clinical Trial Support up to the final database lock. For the primary analysis which is to be performed at week 16 once all randomized patients have completed the 16-week visit, the blind status of study personnel through the remainder of the trial will be clarified in a logistics plan which is to be finalized prior to the unblind for the week 16 analysis. Please refer to [Section 7.4](#) for further details.

A partially external DMC will perform an un-blinded safety and efficacy assessment at specified intervals in order to ensure that patients are protected from potential harm, please refer to [Section 3.1.1](#). An optional interim analysis, to be performed on the primary efficacy endpoint once 50% of the total required number of patients has completed 16 weeks of study, will also be performed by the DMC. Furthermore, an interim analysis on primary, secondary and selected further efficacy endpoints, to be performed by an external vendor once 75% of the total required number of patients has completed 16 weeks of study, will additionally be done. Please refer to Section 7.4 for further details.

4.1.5.2 Unblinding and breaking the code

An emergency code break through IRT will be available to the Investigator / Pharmacist / investigational drug storage manager. This code break may only be opened in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. If the code break for a patient is opened, the sponsor must be informed immediately. The reason for opening the code break must be documented on the envelope and/or appropriate CRF page along with the date and the initials of the person who broke the code.

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

Formal treatment unblinding will be performed prior to each DMC meeting as a prerequisite for generation of the applicable DMC summaries required, as well as subsequent to database lock for the interim analyses at week 16, subsequent to database lock for the week 16 primary analysis, as well as subsequent to the final trial database lock. Treatment unblind will be officially released once the final trial database lock has been performed. Procedures to protect the integrity of the trial including the blind of patients, investigators, and study personnel through the final trial database lock will be implemented and are further described in [Section 7.4](#).

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany. The investigational product consists of a carton holding a single vial of the trial medication. The required information according to the Annex 13/EU GMP Guideline is provided on the vial and carton. Each carton will have a unique medication number.

The investigational product will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For description of the label, refer to the ISF.

4.1.7 Storage conditions

Investigational Medicinal Product (IMP) will be kept in original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the sponsor must be contacted immediately. Refer to ISF. Trial medication must be securely stored, e.g. in a locked refrigerator or at a pharmacy. The medication may only be dispensed to trial patients

according to the Clinical Trial Protocol (CTP) by authorized personnel as documented in the trial staff list. IMP will only be prepared for infusion just prior to infusion.

4.1.8 Drug accountability

The Investigator, Pharmacist or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB) / ethics committee
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal Investigator,
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the principal Investigator

The Investigator, Pharmacist or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

4.2.1.1 Rescue medication

The use of a rescue medication will be left at the discretion of the investigator and should be based on the severity and progression of the disease. It is recommended to wait until at least four weeks after the study drug administration (week 16) before prescribing a rescue medication in case no improvement or no change in disease condition is observed (stable disease). In case a rescue medication is prescribed, the patient will stay in the trial and will be followed-up as initially planned until week 32 (End of Trial Visit). The sponsor will not supply the sites with the rescue medication.

4.2.1.2 Emergency Procedures

In case of infusion reactions emerging during or after infusion of study drug, the investigator should consider in accordance with severity of the reaction and local standard of care to

- Immediately interrupt the infusion
- Treat with systemic anti-histamines and intravenous steroids

Based on patient's clinical course and medical judgment, the infusion may be re-initiated in case of mild or moderate reactions (according to RCTC grading in ISF) at lower speed with gradual increase to complete the infusion as detailed in the Instructions for Preparation and Handling of BI 655130/placebo in the Investigator Site File.

4.2.1.3 Additional treatments

No additional treatment is planned. However, in case of adverse events in need of treatment, the investigator can authorize symptomatic therapy. In those cases, patients will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

Background therapy is not allowed throughout the trial.

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 be taken for the time periods as specified.

Table 4.2.2.1:1 Restricted Medications

Medication or class of medications	Restriction duration (through Primary Endpoint Visit at Week 16) ¹
IL36R inhibitors other than the study drug	not allowed neither before nor during trial participation
Secukinumab (Cosentyx®), ustekinumab (Stelara®), guselkumab, ixekizumab, tildrakizumab, brodalumab Adalimumab, infliximab Natalizumab or agents that deplete B or T cells (e.g. rituximab, alemtuzumab or visilizumab) Investigational products for psoriasis	12 weeks or 5 half-lives, whichever is greater, prior to randomisation

Table 4.2.2.1:1 Restricted Medications (cont'd)

Medication or class of medications	Restriction duration (through Primary Endpoint Visit at Week 16) ¹
Etanercept Live virus vaccinations ⁴	6 weeks prior to randomisation
Other systemic immunomodulating treatments (e.g. corticosteroids ² , methotrexate, fumaric acid esters, acitretin, ciclosporin, apremilast Any investigational device or product (excludes psoriasis products)	4 weeks prior to randomisation
Phototherapy (e.g., UVA, UVB), topical treatment for psoriasis or any other skin condition (e.g. corticosteroids ³ , vitamin D analogues, salicylic acid, tar, anthralin)	14 days prior to randomisation.
Anakinra	7 days prior to randomization

¹ In case of worsening of the PPP and/or psoriasis, 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 indication after the Primary Endpoint Visit at Week 16, 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 ppPASI is assessed.

⁴ Live virus vaccination should be restricted until the end of the trial.

In the event a patient with prior use of systemic steroids, TNF α inhibitors, IL17/IL12/23 inhibitors, or anakinra is enrolled, past medical records are required to document when these treatments were stopped. All concomitant or rescue therapies will be recorded (including time of intake and dose on study days) on the appropriate pages of the CRF.

4.2.2.2 Restrictions on diet and life style

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

4.2.2.3 Restrictions regarding women of childbearing potential

Women of child bearing potential must maintain an adequate contraception throughout the course of the trial as described in patient information and up to 20 weeks after the last study drug infusion.

4.3 TREATMENT COMPLIANCE

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

Patients who are non-compliant (for instance, who do not appear for scheduled visits) may be removed from the trial and the CRFs completed accordingly (for further procedures, please see [Section 3.3.4.1](#)).

5.0 VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint(s)

- Efficacy: ppPASI50 at week 16
- Safety: Number of patients with drug-related AEs

5.1.2 Secondary Endpoint(s)

- Treatment success defined as achieving a clinical response of 0 or 1=clear/almost clear via PPP Physicians Global Assessment (pppPGA) at week 16
- ppPASI75 at week 16
- Percent change from baseline in the ppPASI at week 16

5.2 ASSESSMENT OF EFFICACY

Palmoplantar Pustulosis Physician Global Assessment (pppPGA)

pppPGA relies on clinical assessment of the patient's skin presentation on the palms and soles and will be measured at the timepoints scheduled in the [Flow Chart](#). The investigator

(or qualified site personnel) scores the lesions on the most severely affected palmoplantar surface from 0 – 4 as clear, almost clear, mild, moderate or severe (cf Table 5.2: 1; [R17-0324](#)). Further practical guidance will be available in the ISF.

Table 5.2:1 PPP Physician Global Assessment (pppPGA)

Score	Wording	Detailed description
0	Clear	No signs of PPP; no scaling or crusts or pustule remains
1	Almost clear	Slight scaling and/or erythema and / or slight crusts; very few new (yellow) and / or old (brown) pustules
2	Mild	Scaling and/or erythema and/or crusts; visible new (yellow) and/or old (brown) pustules of limited number and extent
3	Moderate	Prominent scaling and/or erythema and / or crusting; prominent new (yellow) and / or old (brown) pustules covering most of the area involved
4	Severe	Severe scaling and/or erythema and / or crusting; numerous new (yellow) or old (brown) pustules with and/or without major confluence covering the entire area of at least 2 palmoplantar surfaces

Palmoplantar Pustulosis Psoriasis Area and Severity Index (ppPASI)

The ppPASI is an investigator assessment of the extent and severity of pustular and plaque lesions on the palms and soles presenting in PPP patients. The adaptation from PASI, an established measure of severity and area of psoriatic lesions in patients with psoriasis, by Bhushan et.al [[R16-5334](#)] will be used in this trial (cf Table 5.2: 2).

This tool provides a numeric scoring for patients overall PPP disease state, ranging from 0 to 72. It is a linear combination of the percent of surface area of skin that is affected on the palms and soles of the body and the severity of erythema, pustules, and scaling (desquamation).

The ppPASI will be measured at the timepoints scheduled in the [Flow Chart](#).

Table 5.2:2 Palmoplantar Pustulosis Psoriasis Area and Severity Index

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

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

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

5.3 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events (including drug-related AEs)
- Serious adverse events
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to ISF for details)
- Safety laboratory tests
- Physical examination
- Vital signs (blood pressure, pulse rate, body temperature)
- 12-lead ECG

5.3.1 Physical examination

Complete and target physical examinations will be performed at visits as described in the [Flow Chart](#). Height and weight of the patient will be recorded at the screening visit.

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

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

5.3.2 Vital Signs

Vital signs evaluations will be performed at visits as shown in the Flow Chart. This includes measuring temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least 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 visits with study drug administration vital signs will be assessed pre-dose, at 5 minutes and approximately 120 minutes after study drug administration.

Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the study drug administration. Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further injections might be considered and will be agreed on between investigator and BI clinical monitor.

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death [R11-4890]. To be able to prospectively define and assess any potential cases of anaphylaxis, the clinical criteria for diagnosis of anaphylaxis defined in [Section 10.1](#) are to be considered.

5.3.3 Safety laboratory parameters

The laboratory tests listed in Table 5.3.3: 1 will be performed at the central laboratory service provider. Samples will be taken and sent for testing at the central lab however in cases of immediate patient safety concerns a local laboratory may be used for selected testing.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in ISF. For time points of laboratory sampling, see [Flow Chart](#).

Laboratory results (i.e. all safety laboratory and clinical laboratory data relevant for current clinical practice) of the patients will be available in real time to the respective investigator (via laboratory reports) and to the sponsor (via the central laboratory website) and selected abnormal laboratory alerts will be flagged to the site and sent to sponsor in real time.

Clinically relevant abnormal findings will be reported as baseline conditions or AE's. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results should be confirmed using an unscheduled visit laboratory kit and should be repeated until normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria [R13-3515].

Table 5.3.3: 1 Laboratory tests

Category	Test name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hbc (HbA1c) (only at screening) Red Blood Cell Count Reticulocyte Count White Blood Cells / Leukocytes Platelet Count/ Thrombocytes
Diff. Automatic	Neutrophils (relative count) Eosinophils (relative count) Basophils (relative count) Monocytes (relative count) Lymphocytes (relative count)

Table 5.3.3: 1 Laboratory tests (cont`d)

Category	Test name
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/ γ -GT) Lactic Dehydrogenase (LDH) Amylase Lipase Serum tryptase ¹
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine eGFR (estimated by CKD-EPI formula) (only at screening) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (Reflex, in case of elevated CK) Protein, Total Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol
Specific gamma-globulin quantification	IgE ³
Urine Pregnancy test ² . At the drug administration visits, the test will be performed prior to the administration of study drug	Human Chorionic Gonadotropin in urine
Serum Pregnancy test ² (only for female patients of childbearing potential)	Human Serum Chorionic Gonadotropin
Hormones (only at screening)	TSH (free T3 and free T4 in case of abnormal TSH result)
Autoantibodies (only at screening)	Rheumatoid Factor anti-CCP antibodies

Table 5.3.3: 1 Laboratory tests (cont'd)

Category	Test name
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH Urine creatinine
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urine (only at screening)	Albumin (quantitative)
Infections screening (only at screening)	Hepatitis B Surface Antigen (qualitative), Hepatitis C Antibodies (qualitative), HIV-1, and HIV-2 Antibody (qualitative), QuantiFERON®

¹performed only at the randomisation visit (visit 2).

²Urine and serum pregnancy testing will be performed as indicated in the [Flow Chart](#).

³IgE will be taken in case of infusion reaction together with ADA (anti-drug antibodies) sample

5.3.4 Electrocardiogram

The 12-lead ECGs will be performed as scheduled in the Flow Chart.

ECGs will be recorded after the patients have rested for at least 5 minutes in a supine position and will always precede blood sampling to avoid impact of sampling on results. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six pre-cordial leads (V1–V6), according to Wilson, will be used.

ECGs may be repeated for quality reasons (like alternating current artefacts, muscle movements, electrode dislocation).

Additional ECGs may be collected for safety reasons. Clinically relevant, abnormal findings will be reported as AEs.

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

5.3.5 Other safety parameters

5.3.5.1 Medical examination

At the screening visit, the medical examination will include documentation of patient information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (BP, PR), 12-lead ECG, laboratory tests, and a physical examination. Details about the timing of the examinations during the trial are included in the [Flow Chart](#).

5.3.5.2 Local tolerability

Local tolerability will be assessed by the investigator according to ‘swelling’, ‘induration’, ‘heat’, ‘redness’, ‘pain’, or other findings’ at the times indicated in the Flow Chart.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event

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

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

Adverse reaction

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

Serious adverse event

A serious adverse event is defined as any AE which:

- results in death,
- is life-threatening, this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalisation or
- prolongation of existing hospitalisation,

- results in persistent or significant disability or incapacity, or
- 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.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered “Always Serious”

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

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

The latest list of “Always Serious AEs” can be found in the Remote Data Capture (RDC) system. A copy of the latest list of “Always Serious AEs” will be provided upon request.

Adverse events of special interest (AESIs)

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

The following are considered as AESIs:

Hepatic injury

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

- an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the “DILI checklist” provided in the RDC.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the Investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

Intensity of AEs

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

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

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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.

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

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

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

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

5.3.6.2 Adverse event collection and reporting

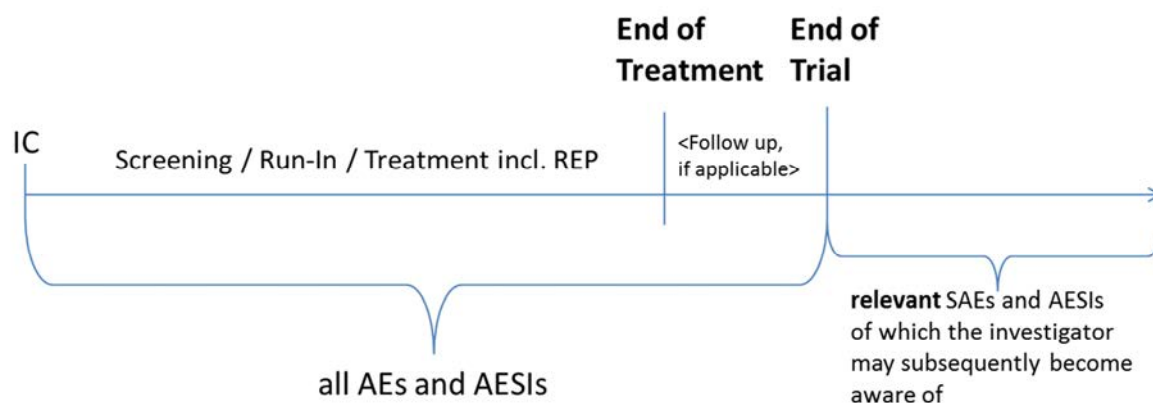
AE Collection

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

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

- From signing the informed consent onwards through the residual effect period (REP), until individual patient's end of trial:
 - All AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
 - The investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which he may become aware of.

If an individual patient discontinues trial medication prematurely but stays in the trial (i.e. if further visits are planned), the Investigator must report all AEs and all AESIs until the individual patient's end of the trial.



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

AE reporting to sponsor and timelines

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

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

Information required

For each AE, the Investigator should provide the information requested on the appropriate CRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drug(s) and a Non-Investigational Medicinal Product (NIMP) / Auxiliary Medicinal Product (AMP).

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

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

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

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

Pregnancy

In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and B).

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

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and are to be performed in order to monitor patients' efficacy, safety and other parameters in an appropriate way. 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.

Efficacy and parameters are outlined in [Section 5.1](#)

6.0 INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the [Flow Chart](#). Investigators are to encourage adherence by the patient to protocol specific activities. Each visit date (with its window) is to be counted from Day 1. The acceptable time windows for follow-up visits and end of trial examination 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.

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 last Blinded Report Planning Meeting.

Study measurements and assessments are scheduled to occur 'before' trial medication administration at dosing visits and are to be performed and completed prior to the trial drug administration. For planned individual plasma concentration sampling times refer to the Flow Chart. At non-dosing visits sampling should be done after other study procedures have concluded. Sampling times will be recorded and used for determination of pharmacokinetic parameters.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and respective protocol sections. Additional details on procedures at selected visits are provided below.

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

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

2. AE/local tolerability and concomitant therapy collection
3. Physical examinations
4. pppPGA, ppPASI

6. ECG
7. Blood sampling,

6.2.1 Screening and run-in period(s)

Screening Period

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

Once consented, the patient is considered to be enrolled in the trial and has started screening. The patient should be recorded on the enrolment log and be registered in IRT as a screened patient. Patients will be assigned a study patient number by the RDC system once the consent is signed.

Baseline conditions and medical history will be assessed during screening.

Screening (Visit 1) should normally take place no more than 28 days before Visit 2 and be completed no less than 7 days prior to Visit 2. Visit 1 procedures may be completed over multiple physical visits, if needed.

The time window for Visit 1 may be extended at the discretion of the CML in conjunction with the TCM on a case by case basis.

Patients who have a laboratory test value that makes their participation uncertain may have the test repeated to determine eligibility; however, the result must be available prior to Visit 2 (Day 1).

Patients who fail screening following Visit 1 assessments should be registered as a screen failure in IRT. Re-screening is allowed in this trial.

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

6.2.2 Treatment period(s)

When eligibility of the patient to participate in the trial is confirmed, randomisation via IRT will be performed at Visit 2. The treatment period is from Visit 2 to Visit 10, followed by the primary endpoint visit at week 16 (Visit 11). Procedures described in the Flow Chart for each visit should be performed.

At visits during the treatment period, venepuncture (i.e. safety laboratories, should be the last procedures performed prior to study drug administration. Only after all blood specimens are collected, will each eligible patient receive a dose of the assigned trial medication. Trial medication will be administered as i.v. infusion by the Investigator or his designee. Details and procedures of administration of study drug are described in [Section 4.1.4](#) and in the ISF.

6.2.3 Follow Up Period and Trial Completion

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

For patients completing the randomized trial treatment regularly at week 16, safety follow-up visits will be performed at week 24 (FU1 visit) and at week 32 (End of Trial, EOT visit).

Early treatment discontinuation

Patients who discontinue treatment prematurely prior to the week 12 (last planned treatment visit), should follow the scheduled visits as defined in the [Flow Chart](#) until the End of Trial Visit at week 32.

Trial completion:

Trial completion is defined as a patient having reached the EOT visit (Week 32).

7.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN – MODEL

This trial is a study of proof of concept in patients with palmoplantar pustulosis. It is designed as a randomised, double-blind, and placebo-controlled trial with 3 parallel groups (2 doses of BI 655130 and placebo).

The primary objective of this trial is to assess the safety and efficacy of BI 655130 in comparison to placebo in patients with palmoplantar pustulosis.

Baseline refers to the measurement recorded at randomisation (Visit 2); if data at Visit 2 is missing, then data from Visit 1 will be considered baseline. The percent reduction from baseline of the primary endpoint, at all follow-up visits, is calculated as:

$\% \text{ ppPASI reduction from baseline} = ((\text{ppPASI at baseline} - \text{ppPASI at Visit X}) / \text{ppPASI at baseline}) * 100.$

Achieving a response of X% or larger decrease from baseline in ppPASI score is denoted as ppPASIX (where X = 50). This trial is designed to demonstrate an increase in the proportion of patients who achieve a ppPASI50, the primary endpoint, for BI 655130 relative to Placebo via the unadjusted risk difference estimate at week 16.

Randomisation will be stratified by the presence or absence of plaque psoriasis. However, due to the low number of patients to be recruited into this trial, the effects of the stratification variable on the primary endpoint will be assessed only in exploratory analyses.

7.2 NULL AND ALTERNATIVE HYPOTHESES

There will be no formal hypothesis testing performed in this trial. As an exploratory Phase II trial in patients with palmoplantar pustulosis, inferences concerning the efficacy of BI 655130 will be based on the magnitude of the observed difference(s) versus Placebo on the proportion of patients who achieve a 50% reduction from baseline in the ppPASI score (ppPASI50) at Week 16, as well as on other efficacy endpoints, such as the % change in ppPASI from baseline, ppPASI75, etc.

The study has 3 treatment arms (BI 655130 900 mg, BI 655130 300 mg and placebo), and there are 2 scenarios of interest, as described below:

- (1) Scenario 1: Examines the maximum effect of (BI 655130 900 mg or 300 mg) versus Placebo
- (2) Scenario 2: Examines the effect of BI 655130 300 mg versus Placebo

A sample size justification regarding the scenarios of interest and potential decision boundaries for comparison can be found in [Section 7.7](#).

7.3 PLANNED ANALYSES

The efficacy analyses will be performed for the FAS which is based on the intent-to-treat principle, and comprises all participants who were randomised, received at least one dose during the trial, and had a baseline measurement for the primary endpoint. Efficacy analyses will be based on the planned treatment (i.e., the treatment assigned at randomisation). Safety analyses on patients who were randomised and received at least one dose during the trial will be based on the actual treatment received at the randomisation visit; this set of patients is called the Safety Analysis Set (SAF). All efficacy analyses will be conducted on the FAS. All safety analyses will be conducted on the SAF.

Important violations of the protocol will include key inclusion and exclusion violations, incorrect medications taken, compliance with study medication, concomitant use of restricted medications, and any other violations of the protocol deemed important by the study team. All decisions concerning important protocol violations will be made prior to un-blinding of the database for the final week 16 analysis. A per-protocol set (PPS) will be defined as a subset of the FAS which excludes all patients with a violation that potentially affects the Week 16 efficacy assessment.

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

For continuous secondary endpoints, mean changes from baseline will be analysed using a restricted maximum likelihood (REML)-based repeated measures approach. Analyses will include the fixed, categorical effects of treatment and visit, presence or absence of plaque psoriasis (yes/no), as well as the treatment-by-visit interaction, and continuous, fixed covariates of baseline “endpoint” and baseline-by-visit interaction. An unstructured covariance structure will be used to model the within-patient measurements. Exploratory confidence intervals will be based on least-squares mean differences to Placebo using a two-sided $\alpha = 0.05$.

This is an exploratory trial and formal confirmatory statistical testing will not be performed.

7.3.1 Primary endpoint analyses

The achievement of ppPASI50 at Week 16 is the primary endpoint in this trial and represents a binary variable with values of 0 (= non-response) or 1 (=response). Prior to treatment unblinding for the optional week 16 interim analysis, it may be decided to use the ppPASI75 as the primary endpoint (instead of ppPASI50 which will then be considered as a secondary endpoint); if applicable, such decision will be documented in the Trial Statistical Analysis Plan (TSAP).

The primary analysis of the unadjusted absolute risk difference versus Placebo will be calculated simply as the difference in the observed proportion of patients with ppPASI50 at week 16 for each treatment scenario, for the FAS. A 95% Wilson confidence interval around this difference will also be provided. In addition, a parametric bootstrap 95% confidence interval will be generated by sampling from the binomial distribution on each treatment with

number of patients and observed proportion of responders per treatment representing the sampling parameters. A hierarchical approach to the testing of both scenarios for BI 655130 versus Placebo will, however, be performed for the primary analysis in order to control for multiplicity arising as a result of the multiple treatment comparisons.

Further details will be provided in the TSAP.

7.3.2 Secondary endpoint analyses

For the secondary binary endpoints, for the FAS, the unadjusted absolute risk difference versus Placebo will be calculated and a 95% Wilson confidence interval around this difference will also be provided. In addition, a parametric bootstrap 95% confidence interval will also be generated.

For secondary continuous endpoints, mean changes from baseline will be analysed using a restricted maximum likelihood (REML)-based repeated measures approach (see [Section 7.3](#)).

7.3.4 Safety analyses

The safety set, described in [Section 7.3](#), will be used to perform all safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered ‘treatment-emergent’. The REP is defined as 20 weeks after the last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’. Drug related AEs will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

In addition, the frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of MedDRA.

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

7.4 INTERIM ANALYSES

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

An interim analysis, on the primary endpoint only, will be performed if the period for randomization of the entire patient population exceeds approximately 4 months. The purpose will be to facilitate further substance development and project planning. There will be no changes to the design of the trial as a result of the performance of this optional interim analysis. If performed, the interim database lock and subsequent analysis will be done once the first 50% of the total required number of patients has completed 16 weeks of study. The efficacy decision that will be communicated to the sponsor will be formulated with regard to the conditional probability for achieving at least a target difference in the treatment effect at week 16 based upon the primary endpoint and the decision boundary as described in DMC

charter. Further details on the communication strategy will be provided in the DMC charter. The interim analysis will be performed by the DMC, independent of the trial team, in order to prevent the potential introduction of operational bias. Details regarding the analyses required for this interim, if required, will be described in the DMC SAP. An interim logistics plan, outlining the procedures to be implemented to ensure that all members of the trial team, including the investigators and patients, remain blinded to study treatments, will also be prepared and approved prior to achieving interim database lock in accordance with the sponsor's SOP. This logistics plan will include a list of the sponsor representatives who will have access to the un-blinded interim data via knowledge of the interim results for subsequent project planning.

An additional interim analysis will be performed once the first 75% of patients have completed 16 weeks of the study for the purpose of planning the subsequent trial(s) in PPP. This analysis will include primary, secondary, and selected further efficacy endpoints and biomarkers as well as the PK concentration data, and details of the statistical analysis will be specified in the trial statistical analysis plan. In order to protect the integrity of the continuing trial, this 75% interim analysis will be performed by a team who are external and fully independent from the trial team. The information resulting from this analysis will not be shared with patients, investigators, or with sponsor-involved trial team members. An interim analysis logistics and access plan will be prepared which will outline the team who will perform the analysis, the procedures to protect the blind, the unblinding process, and the individuals who will have access to the results and to any individual unblinded data. There are no changes to the design of the trial planned as a result of the performance of this additional interim analysis.

Once all randomised patients have completed the first 16 weeks of study, a partial database lock may be performed in order that a fast track analysis of primary and selected secondary and safety endpoints be done; a second data lock would then be done for the remaining efficacy and safety data collected up to week 16. If fast-track analysis is not performed, a single database lock will be done for safety and efficacy data collected up to week 16. At this time, the final analysis of these data through week 16 will be performed. Since the study is planned to continue through an additional 16 weeks of further follow-up, and will remain blinded, a week 16 logistics plan will be developed in order to protect the integrity of the ongoing trial data and reporting subsequent to treatment un-blind for both the fast track and the complete week 16 primary analysis. Details of the analysis to be performed for the week 16 data will be described in the TSAP which is planned to be finalized prior to achieving database lock for the optional week 16 interim analysis.

An analysis of the entire trial data will be performed once all randomized patients have completed the 32 weeks of study. At this time, the database will be locked, and official unblinding of the trial will be performed. Details of the analysis to be performed for the completed trial through 32 weeks (End of Trial Visit) will also be described in the TSAP which is planned to be finalized prior to achieving database lock for the optional week 16 interim analysis.

All analyses are planned to be documented in a clinical trial report which is to be prepared at the end of the trial.

7.5 HANDLING OF MISSING DATA

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

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

For all binary endpoints (i.e. endpoints that are either 1 (patient responded) or 0 (patient did not respond)), 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 neighbouring visits also represent a success;
- Otherwise, impute as a failure to achieve a response (i.e. NRI [No Response Imputation]).

If a patient takes a rescue medication for the treatment of palmoplantar pustulosis prior to observing the primary endpoint for this trial, then all data subsequent to the intake of such rescue will be considered to represent a failure to achieve a response. Further details on what constitutes a rescue intake with potential impact on efficacy outcomes will be described in the TSAP.

For secondary efficacy endpoints which are continuous in nature, the use of a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach will ensure that missing data are handled implicitly, via a missing at random assumption, by the statistical model.

7.6 RANDOMISATION

Patients will be randomised in blocks to double-blind treatment. Approximately equal numbers of patients will be randomised to each treatment group using a 1:1:1 allocation ratio. BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented.

Randomisation will be stratified by the presence or absence of plaque psoriasis.

7.7 DETERMINATION OF SAMPLE SIZE

The study is intended to show an increase for BI 655130 over placebo in terms of the proportion of patients achieving a ppPASI50 response at Week 16. There is currently no clinical trial data available in the published literature that describes a placebo response on the ppPASI50 in the population of patients with palmoplantar pustulosis. The success probability for the primary endpoint on this PoCC trial has, therefore, been derived under the assumption that the difference between BI 655130 and Placebo is 0.30 and that a total N of 60 patients (fixed according to feasibility considerations) will be studied in a 1:1:1 ratio (i.e. 20 patients per treatment group).

Simulations in SAS[®] were used to derive estimates of the probability that a single trial would demonstrate an observed difference in proportions between BI 655130 and Placebo that was equal or greater than a defined threshold under a positive scenario whereby the expected difference in proportions is 0.3 in favour of BI 655130. For identifying such a target threshold, a minimum probability of 0.80 was defined. For each trial simulation, the response for each patient on each treatment was generated using a binomial distribution utilizing the expected treatment response rates as noted in [Table 7.7:1](#) below. The trial observed proportions for each treatment were calculated and then the treatment comparisons, according to scenario 1 and scenario 2, were each compared against a range of threshold values using a hierarchical approach. A total of 100,000 trial simulations were performed. In addition, the probability of a false positive declaration being made given the specified target threshold(s), so-called negative scenario, was also determined.

Table 7.7:1 Probability to Achieve the Threshold Difference in Treatments given Expected Treatment Response Rates on ppPASI50 and a Total Sample Size of 60 Patients

Population Response Rate			Expected Response Difference (BI vs PLC)	Threshold (Observed Difference)	Probability Threshold Exceeded ¹	False Positive Rate (%) ²
Low Dose BI	High Dose BI	Placebo				
SCENARIO 1 (maximum of [BI 655130 900 mg or 300 mg] vs. Placebo)						
0.45	0.45	0.15	0.3	0.20	93%	11%
0.50	0.50	0.20	0.3	0.20	92%	15%
0.55	0.55	0.25	0.3	0.20	91%	18%
0.60	0.60	0.30	0.3	0.20	91%	20%
SCENARIO 2 (BI 655130 300 mg vs. Placebo)						
0.45	0.45	0.15	0.3	0.15	87%	7%
0.50	0.50	0.20	0.3	0.15	86%	10%
0.55	0.55	0.25	0.3	0.15	85%	12%
0.60	0.60	0.30	0.3	0.15	85%	14%

Hierarchical testing: scenario 2 only tested if outcome on scenario 1 \geq specified threshold.

¹ Positive scenario: Assuming the expected response rate difference, the probability that the BI 655130 response rate exceeds that of Placebo by at least the threshold amount is displayed.

² Negative scenario: The probability that the BI 655130 response rate exceeds that of Placebo by at least the threshold amount assuming that treatments are equal.

In summary, for a total N of 60 patients, a 1:1:1 allocation ratio to BI 655130 900 mg, BI 655130 300 mg, and Placebo, then under the assumption of a target difference between each dose of BI 655130 and Placebo of 0.30 [positive scenario] for the proportion of responders on the primary endpoint at week 16, this trial will be able to show:

- An observed difference in response rates of at least 0.20, for the maximum of (BI 655130 900 mg and BI 655130 300 mg) versus Placebo, with 91% probability (assuming a Placebo response rate from 0.15 through 0.30). The false positive decision probability in this case ranges from approx. 11%-20% under the assumption of no treatment difference;
- An observed difference in response rates of at least 0.15, for BI 655130 300 mg versus Placebo, with 85% probability (assuming a Placebo response rate from 0.15 through 0.30). The false positive decision probability in this case ranges from approx. 7%-14% under the assumption of no treatment difference.

The hierarchical nature of the comparisons, with rejection of the maximum of (BI 655130 900 mg or BI 655130 300 mg) versus Placebo (scenario 1) required prior to proceeding to the test of BI 655130 300 mg versus Placebo (scenario 2), warrants that the overall success probability is at least 85% while the overall false positive rate [under negative scenario] is controlled at 20% (one-sided).

8.0 INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014 and other relevant regulations.

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

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

Prior to patient participation in the trial, written informed consent must be obtained from each patient (or the patient's legally accepted representative) according to ICH / GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the Investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."

The Investigator or a designee must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator or designee obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator or designee must sign (or place a seal on) and date the informed consent form.

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

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

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

Case Report Forms for individual patients will be provided by the sponsor. See [Section 4.1.5.2](#) for rules about emergency code breaks. For drug accountability, refer to [Section 4.1.8](#).

8.3.1 Source documents

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

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

Before providing any copy of patients' source documents to the sponsor the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

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

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

- Patient identification: gender, date or year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of Patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))

- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of Patient's Participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient eligible for the clinical trial.

8.3.2 Direct access to source data and documents

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

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

8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to 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 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below and in [Section 5.5.3](#).

Patient privacy will be ensured by using patient identification code numbers.

Data protection and data security measures are implemented for the collection, storage and

processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial.

The **end of the trial** is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").

The "**Last Patient Drug Discontinuation**" (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPDD at their site.

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

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

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

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

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

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9.2 UNPUBLISHED REFERENCES

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10.0 APPENDICES

10.1 DIAGNOSIS OF ANAPHYLAXIS

Clinical Criteria for diagnosing anaphylaxis [[R11-4890](#)]

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

PEF, Peak expiratory flow; BP, blood pressure.

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

11.0 DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1.0
Date of CTP revision		01 August 2017
EudraCT number		2016-004573-40
BI Trial number		1368.15 (1368-0015)
BI Investigational Product(s)		BI 655130
Title of protocol		Multi-center, double-blind, randomised, placebo-controlled, phase IIa study to investigate efficacy, safety, tolerability, pharmacokinetics and pharmacogenomics of multiple intravenous doses of BI 655130 in patients with Palmoplantar Pustulosis (PPP)
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	X	
Section to be changed		Flowchart, Footnotes 10 and 12
Description of change		

Section to be changed		
Description of change		
Rationale for change		
Section to be changed		
Description of change		The following change was done (highlighted)
Rationale for change		Correction to align protocol description with the actual instructions given to the patients.

Number of global amendment		2.0
Date of CTP revision		08 May 2018
EudraCT number		2016-004573-40
BI Trial number		1368.15 (1368-0015)
BI Investigational Product(s)		BI 655130
Title of protocol		Multi-center, double-blind, randomised, placebo-controlled, phase IIa study to investigate efficacy, safety, tolerability, pharmacokinetics and pharmacogenomics of multiple intravenous doses of BI 655130 in patients with Palmoplantar Pustulosis (PPP)
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	X	
Section to be changed		Section 4.1.5.1 Blinding
Description of change		Text highlighted in yellow was added: A partially external DMC will perform an un-blinded safety and efficacy assessment at specified intervals in order to ensure that patients are protected from potential harm, please refer to Section 3.1.1. An optional interim analysis, to be performed on the primary efficacy endpoint once 50% of the total required number of patients has completed 16 weeks of study, will also be performed by the DMC. Please refer to Section 7.4 for further details.
Section to be changed		Section 4.1.5.2 Unblinding and breaking the code
Description of change		The following change was done (highlighted)

		Formal treatment unblinding will be performed prior to each DMC meeting as a prerequisite for generation of the applicable DMC summaries required, as well as subsequent to database lock for the interim analysis at week 16, subsequent to database lock for the week 16 primary analysis, as well as subsequent to the final trial database lock. Treatment unblind will be officially released once the final trial database lock has been performed. Procedures to protect the integrity of the trial including the blind of patients, investigators, and study personnel through the final trial database lock will be implemented and are further described in Section 7.4.
Section to be changed		Section 7.4 Interim Analyses
Description of change		The following has been added:
Rationale for changes		In order to facilitate the project development and design planning of the subsequent trial in PPP.

APPROVAL / SIGNATURE PAGE**Document Number: c09935708****Technical Version Number:3.0****Document Name: clinical-trial-protocol-version-03**

Title: Multi-center, double-blind, randomised, placebo-controlled, phase IIa study to investigate efficacy, safety, tolerability, pharmacokinetics and pharmacogenomics of multiple intravenous doses of BI 655130 in patients with Palmoplantar Pustulosis (PPP)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area		08 May 2018 13:23 CEST
Approval-Trial Clinical Monitor		08 May 2018 13:33 CEST
Approval-Team Member Medicine		08 May 2018 13:35 CEST
Author-Trial Clinical Pharmacokineticist		08 May 2018 13:39 CEST
Approval-Biostatistics		08 May 2018 14:12 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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