Clinical Trial Protocol

	Document Number:	**c08943535-02**
BI Trial No.:	1311.38	
BI Investigational Product:	risankizumab, BI 655066	
Title:	A phase II/III, randomised, double-blind study to evaluate efficacy and safety of two different dose regimens of BI 655066 (risankizumab) and placebo and maintenance of response of BI 655066 (risankizumab) administered subcutaneously in Japanese patients with moderate to severe chronic plaque type psoriasis.	
Lay Title:	BI 655066 (risankizumab) compared to placebo in Japanese patients with moderate to severe chronic plaque psoriasis	
Clinical Phase:	Phase II/III	
Trial Clinical Monitor:	[redacted]	
Coordinating Investigator:	[redacted]	
Status:	Final Protocol (Revised Protocol based on global amendment #1)	
Version and Date:	**Version: 2.0**	**Date: 08 Jun 2017**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product: Not applicable			
Name of active ingredient: risankizumab, BI 655066			
Protocol date: 05 Sep 2016	**Trial number:** 1311.38		**Revision date:** 08 Jun 2017

Title of trial:	A phase II/III, randomised, double-blind study to evaluate efficacy and safety of two different dose regimens of BI 655066 (risankizumab) and placebo and maintenance of response of BI 655066 (risankizumab) administered subcutaneously in Japanese patients with moderate to severe chronic plaque type psoriasis.
Coordinating Investigator	[redacted]
Trial sites:	Multi-centre trial
Clinical phase:	II/III
Objectives:	The main objective of this study is to assess the efficacy and safety of two different dose regimens of BI 655066 (risankizumab) compared to placebo in patients with moderate to severe chronic plaque psoriasis.
Methodology:	Placebo controlled, double-blind, double-dummy, randomised, parallel-design comparison of two different dose regimens of BI 655066 (risankizumab).
No. of patients:	
total entered:	Approximately 168
each treatment:	BI 655066 (risankizumab) 75 mg: 56 patients BI 655066 (risankizumab) 150 mg: 56 patients placebo: 56 patients

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Name of finished product: Not applicable			
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Diagnosis :	Moderate to severe chronic plaque psoriasis
Main criteria for inclusion:	• Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient. • Have stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis at both Screening and Baseline (Randomisation): a. Have an involved BSA ≥10% and b. Have a PASI score ≥12 and c. Have an sPGA score of ≥3. • Age ≥20 years at screening
Test product:	BI 655066 (risankizumab)
dose:	75 mg (1 syringe and 1 placebo) or 150 mg (2 syringes, 75 mg each) at Week 0, 4 and every 12 weeks
mode of administration:	subcutaneous
Comparator products:	placebo at Weeks 0 and 4
dose:	not applicable
mode of administration:	subcutaneous
Duration of treatment:	40 weeks

Name of company:		**Boehringer Ingelheim**	
Name of finished product: Not applicable			
Name of active ingredient: risankizumab, BI 655066			
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Endpoints	Primary endpoint: - Achievement of ≥90% reduction from baseline PASI score (PASI 90) at Week 16 Secondary endpoints: • Achievement of ≥90% reduction from baseline PASI score (PASI 90) at Week 52 • Achievement of an sPGA score of clear or almost clear at Week 16 • Achievement of an sPGA score of clear or almost clear at Week 52 • Achievement of ≥75% reduction from baseline PASI score (PASI 75) at Week 16 • Achievement of ≥75% reduction from baseline PASI score (PASI 75) at Week 52 • Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16 • Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 52 • Achievement of American College of Rheumatology (ACR) 20 response at Week 16 • Achievement of ACR 20 response at Week 52
Safety criteria:	Physical examination, vital signs, 12-lead electrocardiogram, laboratory tests, adverse events, serious adverse events, and local tolerability

Name of company:		**Boehringer Ingelheim**	
Name of finished product: Not applicable			
Name of active ingredient: risankizumab, BI 655066			
Protocol date: 05 Sep 2016	**Trial number:** 1311.38		**Revision date:** 08 Jun 2017
Statistical methods:	Primary analysis: The achievement of PASI 90 at Week 16 is the primary endpoint and is binary variables with values of 0 or 1. The difference in proportion responding between the BI 655066 (risankizumab) arm and placebo arm will be estimated and tested using the Cochran-Mantel-Haenszel risk difference estimate stratified by the randomisation factors of concomitant disease of PsA at baseline (Yes versus No), and body weight (≤90 kg versus >90 kg) with weights proposed by Greenland & Robins. Secondary analysis: The same methods as the primary analyses will be used to analyse all binary secondary. Change from baseline in Psoriasis Symptoms Scale (PSS) at Week 16 will be analysed by the van Elteren test between the BI 655066 (risankizumab) arm and placebo arm. In order to maintain the full significant level of 5%, two null hypotheses of each BI 655066 (risankizumab) arm vs Placebo will be tested using fixed-sequence method.		

FLOW CHART

Trial Periods	**Screening**	**Randomised Treatment**									**Follow-Up**		
Visit	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**EOT**	**FU1**	**FU2/ EOO**	**FU3/ EOO**
Week			**4**	**8**	**12**	**16**	**22**	**28**	**34**	**40**	**46**	**52**	**56**
Day	**-42 to -14**	**1**	**29**	**57**	**85**	**113**	**155**	**197**	**239**	**281**	**323**	**365**	**393**
Visit window (days)			**±3**	**±7**	**±7**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**
Informed consent	X												
Demographics	X												
Medical history	X												
Smoking/alcohol history	X												
Psoriasis therapy history	X												
Psoriatic arthritis history	X												
CASPAR[1]	X												
In-/exclusion criteria	X	X											
% BSA involvement	X	X											
Height	X												
Weight/waist circumference[2]	X					X				X			
Physical examination[3]	X_C	X_T	X_T	X_T	X_T	X_C	X_T	X_T	X_T	X_C	X_T	X_C	
Vital signs[4]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection screening[5]	X											X	
X-ray[5]	X											X	
Pregnancy testing[6]	X	X	X			X		X		X		X	X
Safety laboratory tests[7]	X	X		X		X		X		X		X	
12 lead-ECG	X	X	X			X		X		X		X	
PK sampling[8]		X	X		X	X		X	X	X		X	
ADA sampling[8]		X	X			X		X		X		X	
Biomarker sampling[9]		X	X			X		X		X		X	
Local tolerability			X	X	X	X	X	X	X	X			
PASI	X	X	X	X	X	X	X	X	X	X	X	X	
sPGA	X	X				X		X		X		X	

Tender and Swollen Joint Counts (TJC 68, SJC 66)[10]		X				X		X		X		X	
Physician's global assessment of disease activity (VAS)[10]		X				X		X		X		X	
PSS		X				X		X		X		X	
DLQI		X				X		X		X		X	
Patient's assessment of pain (VAS)		X				X		X		X		X	
Patient's global assessment of disease activity (VAS)		X				X		X		X		X	
HAQ-DI		X				X		X		X		X	
Optional DNA banking		X											
Randomisation		X											
Contact IRT	X	X	X			X		X		X		X	
Admin. of trial drugs		X	X			X		X		X			
Termination of trial med.[11]										X			
Trial completion[12]												X	X
Open label extension [13]												X	
Vital status[14]													X

Abbreviations: EOT=end of treatment, EOO=end of observation, FU= Follow-up, CASPAR=ClASsification of Psoriatic Arthritis, BSA= body surface area, ADA=anti-drug antibodies, HAQ-DI= Health Assessment Questionnaire Disability, PASI=Psoriasis Area and Severity Index, sPGA=static physician global assessment, TJC= Tender Joint Counts, SJC= Swollen Joint Counts, VAS= Visual Analog Scale, PSS= Psoriasis Symptoms Scale, DLQI= Dermatology Life Quality Index, V= Visit

1. At selected study sites, patients with a positive history of PsA or suspected to have PsA will be evaluated via CASPAR (ClASsification of Psoriatic Arthritis) criteria for psoriatic arthritis (PsA). Refer to Appendix 10.3.
2. Refer to Section 5.3.1 for weight and waist circumference procedures.
3. Physical examination: C=complete, T=targeted. Refer to Section 5.3.1.
4. Vital signs should precede blood sampling and be assessed pre-dose at all dosing visits. Additional vital signs assessments at approximately 5 minutes post-dose (5 minutes after last injection and 60 minutes post-dose (60 minutes after last injection) at Visit 2 and Visit 3. Monitor for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at Visit 2 and for approximately 1 hour after the last injection at all other visits with drug administration. Refer to Section 5.3.2.
5. The result of T-SPOT®, PPD, and X-ray will not be included in the clinical data base. Refer to Table 5.3.3: 1

6. Serum pregnancy testing must be done at screening and if urine pregnancy test is positive. Urine pregnancy testing will be done prior to administration of study drug at all dosing visits and at Follow-Up (FU) Visit.
7. Blood samples should be taken after patient has fasted for at least 8 hours (except screening visit). If not fasted mark on laboratory requisition form.
8. On dosing visits, pharmacokinetic (PK) and ADA samples should be taken approximately within 1 hour prior to administration of study drug.
9. Biomarker sampling should be done prior to administration of study drug at dosing visits. Refer to Section 5.5.
10. At selected study sites, patients diagnosed with PsA by CASPAR criteria will perform PsA assessments as detailed in Appendix 10.3.
11. Patients that terminate trial medication (med.) early should remain in the trial if possible and complete all remaining Treatment Period Visits, as well as FU1 and FU2 Visits. Termination of trial medication should be completed in the eCRF and treatment discontinuation registered in IRT. Refer to Section 6.2.3 for more details.
12. Patients who finish the randomised treatment period, will complete either of the follow-up visit schedules dependent on extension trial participation (refer to Section 6.2.3):
    - Not participating in extension trial: FU1, FU2/EOO, FU3/EOO (final 1311.38 visit)

      or
    - Participating in extension trial: FU1, FU2/EOO (final 1311.38 visit), enter extension trial
13. Patients who have completed the study and who meet the eligibility criteria will be offered to participate in an extension trial. Refer to Section 6.2.3 and ISF.
14. For randomised patients leaving the study before the planned EOO, their vital status should be collected at Week 56.

TABLE OF CONTENTS

ABBREVIATIONS

ACR	American College of Rheumatology
ADA	anti-drug antibodies
AE	adverse event
AESI	adverse event of special interest
AUC	area under the concentration-time curve of the analyte
BI	Boehringer Ingelheim
BSA	body surface area
CASPAR	CIASsification of Psoriatic Arthritis
CK	creatinine kinase
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
DILI	drug induced liver injury
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
DNA	deoxyribonucleic acid
eCRF	electronic case report form
ECG	electrocardiogram/electrocardiography
eGFR	estimated glomerular filtration rate
EOO	end of observation
EOT	end of treatment
FAS	full analysis set
FU	follow-up
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire Disability
HIV	human immunodeficiency virus
IB	investigator's brochure
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IgG	immunoglobulin G
IRB	institutional review board
IRT	interactive response technology
ISF	investigator site file
i.v.	intravenous(ly)
LOCF	last observation carried forward
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
PASI	Psoriasis Area and Severity Index
PD	pharmacodynamics
PK	pharmacokinetics
PPD	purified protein derivative

PRO	patient reported outcome
PsA	psoriatic arthritis
PSS	Psoriasis Symptoms Scale
RCTC	Rheumatology Common Toxicity Criteria
REP	residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SAE	serious adverse event
s.c.	subcutaneous(ly)
SOP	standard operating procedures
sPGA	static physician global assessment
VAS	Visual Analog Scale

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Psoriasis is a chronic inflammatory disease with raised, well-demarcated erythematous oval plaques with adherent silvery scales (R11-1257). It is the most prevalent immune mediated skin disease, affecting 2% of the world population (R08-1089). Twenty-five percent of patients have moderate to severe disease with considerable negative impact on psychosocial and economic status (R11-1259). It is increasingly recognised that psoriasis is more than a superficial disease, with 30% of patients having joint involvement and a high correlation between psoriasis and obesity, diabetes, depression, metabolic syndrome and cardiovascular risk (R15-1393).

While the majority of psoriasis patients are managed initially with topical therapies, those with severe and/or refractory disease may require phototherapy and/or systemic therapy. Oral systemic agents provide modest efficacy, but increasingly patients are treated with biological agents, such as TNF-alpha inhibitors (adalimumab and infliximab) and the p40 IL-12/23 inhibitor (ustekinumab) (R14-5159). While the clinical efficacy of ustekinumab indicates a role for both IL-12 and IL-23 in the pathogenesis of psoriasis, more recent data suggest that IL-23 is disproportionately involved in the maintenance of chronic psoriasis (R11-1547). IL-23 is thought to be involved in the pathophysiology of psoriasis via induction and maintenance of Th17 type cells, including type 17 T cells and other IL-23 responsive cells. This is supported by recent clinical data indicating that monoclonal antibodies that block IL-17, the cytokine produced by Th17 cells, have high efficacy in psoriasis.

There is still clinical need for increased efficacy as the most effective anti-TNF and IL-12/23 agents provide only 75% improvement in psoriasis in about 60 -70% of patients and these responses tend to be lost over time. While the anti-IL-17 agents (i.e., secukinumab) provide better efficacy, they require monthly injections, thus their long term utility is still undetermined.

A 48-week phase II dose ranging trial of BI 655066 (risankizumab) versus ustekinumab indicates a 37% greater improvement for BI 655066 (90 mg and 180 mg, pooled data) than ustekinumab in the proportion of patients achieving 90% reduction in psoriasis area and severity index (PASI 90) at Week 12.

1.2 DRUG PROFILE

BI 655066 is a fully humanised monoclonal antibody (mAb) of the IgG1 subclass directed towards IL-23p19 [redacted]

The toxicology data suggest BI 655066 can be safely administered to humans, as supported by chronic administration to monkeys for up to [redacted] weeks. The monkey was identified as the most relevant toxicology species with a no observed adverse effect level (NOAEL) of [redacted] mg/kg/dose, corresponding to an exposure (combined sex) of [redacted] µg/mL for the C_{max} and [redacted] µg*h/mL for AUC[redacted], respectively.

BI 655066 has been studied in approximately 500 patients without any unexpected adverse events (AEs) or signal of a safety issue.

In Study 1311.1 (c02434648), a Phase I single rising dose trial in 39 patients with chronic plaque psoriasis, administration of BI 655066 either intravenously (i.v.) or subcutaneously (s.c.) was well tolerated. Over the 24 weeks following a single i.v. or s.c. administration of BI 655066, 65% (20/31) of patients experienced an AE compared with 88% (7/8) of patients receiving placebo. The most frequently reported AEs were mild to moderate upper respiratory tract infections, mild nasopharyngitis and mild to moderate headache.

In patients receiving BI 655066 either i.v. (N=18) or s.c. (n=13), 87% achieved at least 75% reduction in PASI (PASI 75) by Week 12, compared to none in the placebo group. Twenty four weeks after a single administration of BI 655066, 71% of patients maintained at least a PASI 75; nearly half (48%) had 90% reduction in PASI (PASI 90) and 29% had complete resolution of lesions (PASI 100). A protocol amendment allowed an optional extension of follow-up beyond Week 24 for patients in the s.c. dose cohort; six of thirteen originally enrolled patients maintained a PASI 100 improvement for at least 41–66 weeks after treatment.

[redacted]

In Study 1311.16, a Phase I single rising dose trial in 80 healthy male adult volunteers (40 Japanese, 24 Chinese, and 16 Caucasian), administration of BI 655066 ([redacted] mg, [redacted] mg, [redacted] mg) or placebo either s.c. or i.v. is ongoing. Among the safety data available at the interim analysis of the safety data was conducted from subjects who had received administration of BI 655066 s.c. at least 4 weeks prior to the cut-off as of November 9, 2015, 9 out of 55 subjects had AE. Those intensity was almost mild and it was well tolerated.

After a single s.c. administration, Japanese exposure were numerically slightly higher than Caucasian exposure but were comparable after adjustment of body weight (preliminary interim result in Study 1311.16).

For a more detailed description of the BI 655066 profile please refer to the current investigator's brochure (IB, c01569420) which is included in the investigator site file (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Psoriasis is a chronic inflammatory disease with significant impact on patient quality of life and associated with significant systemic disease. It is considered that 0.1-0.2% of Japanese population has psoriasis. BI 655066 (risankizumab) is a humanised monoclonal antibody with high affinity for the p19 component of human IL-23A that specifically neutralizes IL-23. Proof of clinical concept (PoCC) for BI 655066 was demonstrated in a single dose phase I trial in 39 patients with moderate to severe plaque psoriasis where 87% of patients achieved PASI 75 with no safety concerns (Trial 1311.1, c02434648).

The current trial is being performed to assess the efficacy and safety of BI 655066 to support registration in Japan for the treatment of moderate to severe chronic plaque psoriasis in adult patients.

2.2 TRIAL OBJECTIVES

The objectives of this study are to assess the efficacy and safety of two different dose regimens of BI 655066 compared to placebo in patients with moderate to severe chronic plaque psoriasis. The primary efficacy evaluation will be performed at 16 weeks and an assessment of maintenance of response will be performed at 52 weeks.

In the subset of enrolled patients with concomitant psoriatic arthritis, the signs and symptoms of psoriatic arthritis will be evaluated to assess improvement during the trial.

This trial will assess PK and the emergence of anti-drug antibodies (ADA) and their effect on efficacy and safety. Moreover, it will be explored how the use of BI 655066 may influence protein expression levels and disease specific protein markers.

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study may help to generate future benefit for larger groups of patients with psoriasis if BI 655066 proves to be successful in treating this disease. BI 655066 has been studied in approximately 200 patients with moderate to severe plaque psoriasis. In these

studies, the majority of patients receiving BI 655066 achieved 90% improvement of their disease. The most common AEs reported in these trials were mild nasopharyngitis, headache, back pain, and arthralgia, which showed no dose dependency. Local reactions following subcutaneous administration of BI 655066 were uncommon, and limited to redness, swelling or induration at the injection site.

As with any immune modulating agent, BI 655066 may impair immune function resulting in a risk of infection. This will be monitored by collection of all AEs during the treatment and observation periods. Patients with clinically important active infection will not be included in the study. Patients with positive QuantiFERON® TB test, positive T-SPOT® test, or a positive PPD (purified protein derivative) skin test for tuberculosis must fulfil entry criteria as specified in Section 3.3.3, item 6. There is not enough information at this time to rule out a risk of cancer with BI 655066, but this risk is considered small with this type of compound as experience with the anti-IL-12/23 mAb ustekinumab has not suggested significant risk for cancer/serious infection. The investigators will perform physical examination at each visit and will monitor for signs and symptoms of malignancy.

Increases in major adverse cardiovascular events (MACE) including myocardial infarction, cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents, such as ustekinumab, have not been observed in longer-term studies. In Phase I study and phase II study of BI 655066, 3 cases were considered to be possible MACE. While the likelihood of increased MACE with treatment by BI 655066 is small, all suspected cardiovascular events (serious or non-serious) observed in this study will be adjudicated by an independent MACE adjudication committee.

A patient will have an about 33% (1 in 3) chance in being randomised to the placebo arm. Patients assigned to placebo will not receive an active treatment through Week 16, but after that patients will receive BI 655066. The knowledge gained from the placebo treatment group in a relatively short period of time will be used to control for confounding factors for an unbiased estimate of effect size. The delay in starting treatment does not diminish the potential benefit of treatment because of active treatment. If the patient experiences an intolerable increase of psoriasis the patient will be discontinued from the trial to receive rescue treatment.

Patients will be monitored with study visits every 4 weeks through the end of the placebo period at Week 16.

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.

In order to recognize any safety signals as early as possible, an independent data monitoring committee (DMC) will monitor all studies where patients are receiving BI 655066.

In conclusion, the benefit-risk profile is considered appropriate for this stage of clinical development.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This randomised, double-blind, double-dummy, placebo controlled, parallel design study compares two different dose regiments of BI 655066 (risankizumab) with placebo. In total, approximately 168 patients with moderate to severe chronic plaque psoriasis will be randomised in this trial.
Patients are included in the trial once they have signed the informed consent. Patients suitable after screening will be eligible to participate in the 40-week treatment period and will be randomised at a ratio of 2:2:1:1 to one of 4 treatment arms (BI 655066 75 mg, BI 655066 150 mg, placebo with BI 655066 75 mg, after Week 16, and placebo with BI 655066 150 mg after Week 16) as shown in Figure 3.1: 1. Randomisation will be stratified by concomitant PsA at baseline (Yes versus No) and body weight (≤90 kg versus >90 kg) as listed in Section 7.6.

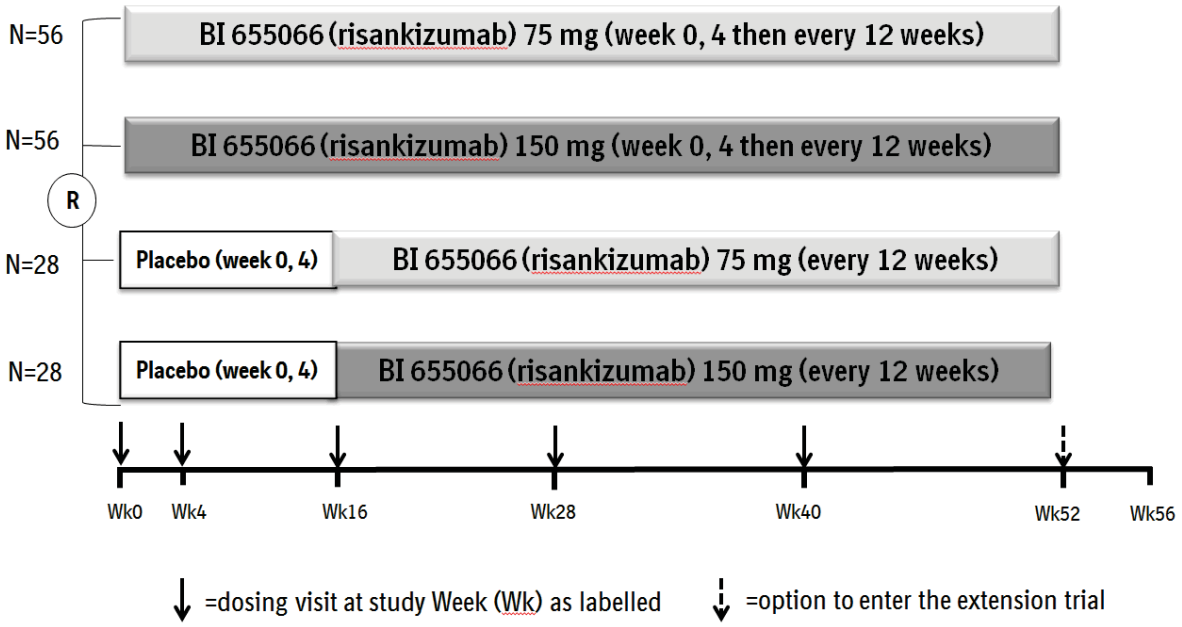


Figure 3.1: 1 Trial design

Individual patient participation is concluded when the patient has completed the last planned visit. The "last-patient-last-visit-primary-endpoint" is the last scheduled primary endpoint visit at Week 16 completed by the last patient.
Patients will be offered to roll over into an extension trial, if they have completed the study and meet the inclusion criteria for the extension trial.

Patients who will not participate in the extension trial will be followed up for AE assessment 16 weeks after having received their last dose.

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI).
BI has appointed a trial clinical monitor, responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), clinical research associates (CRAs), and investigators of participating countries.

A coordinating investigator will be responsible to coordinate activities of investigators at different centres participating in this multi-centre trial. Tasks and responsibilities will be 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.

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

A central laboratory service and vendors for ECG, electronic clinical outcome assessment, and IRT (interactive response technology) will be used in this trial. Details will be provided in the applicable manuals available in the ISF.

The organisation of the trial will be performed by the Nippon Boehringer-Ingelheim 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 CML will be appointed responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI Japan.

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 Japanese information can be found in the ISF.

3.1.2 Data Monitoring Committee (DMC)

A project-based DMC, independent of the sponsor will be established to assess the progress of the clinical trial, including unblinded safety assessment at specified intervals, and to recommend to the sponsor whether to continue, modify, or stop the trial. Any efficacy data provided to the DMC will only be used for DMC's obligation to assess the full benefit-to-risk of the treatments. Thus, no statistical penalty will be imposed since efficacy analyses will not be the basis for any potential early trial termination. Measures are in place to ensure blinding of the sponsor and all other trial participants. The sponsor will remain blinded until after database lock. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

3.1.3 MACE Adjudication Committee

A project-based independent adjudication committee will be used to adjudicate all observed cardio- and cerebro-vascular events and thrombotic events reported during the conduct of the study to assure consistent assessment of MACE. This review will be blinded to treatment allocation; the events that are adjudicated and the adjudication process will be detailed in the MACE Adjudication Committee Charter.

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

This is a randomised, double-blind, double-dummy, placebo controlled, parallel design trial. The trial design is appropriate for assessing the efficacy and safety of two different dose regiments of BI 655066 compared to placebo in patients with moderate to severe chronic plaque psoriasis. While there is a low rate of response with placebo treatment, it is important to have a placebo control early in the study. In order to facilitate patient participation, the trial design will allow patients initially assigned to placebo to receive active treatment. Thus, only AEs reported during the first 16 weeks of the trial can be directly compared to placebo.

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 168 patients will be randomised in the current trial. A sufficient number of patients will be screened to meet this randomised goal. Patients will be recruited at multiple investigative sites. Recruitment will be competitive.

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.

3.3.1 Main diagnosis for trial entry

Patients must have moderate to severe chronic plaque psoriasis.
Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.2 Inclusion criteria

1. Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient.
2. Have stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis at both Screening and Baseline (Randomisation):
    a. Have an involved BSA ≥10% and
    b. Have a PASI score ≥12 and
    c. Have an sPGA score of ≥3.
3. Age ≥20 years at screening

4. Male or female patients. Women of childbearing potential* must be ready and able to use highly effective methods of birth control per ICH M3(R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.

   *Women of childbearing potential are defined as:

   - having experienced menarche and are
   - not postmenopausal (12 months with no menses without an alternative medical cause) and are
   - not permanently sterilised (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

5. Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator
6. Signed and dated written informed consent prior to admission to the study in accordance with GCP and Japanese legislation

3.3.3 Exclusion criteria

1. Patients with
   a. non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular)
   b. current drug-induced psoriasis (including an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium)
   c. active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis that might confound trial evaluations according to investigator's judgment
2. Previous exposure to BI 655066
3. Currently enrolled in another investigational study or less than 30 days (from screening) since completing another investigational study (participation in observational studies is permitted)
4. 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
5. Major surgery performed within 12 weeks prior to randomisation or planned within 12 months after screening (e.g., hip replacement, aneurysm removal, stomach ligation).
6. Known chronic or relevant acute infections including active tuberculosis, human immunodeficiency virus (HIV) or viral hepatitis based on infection screening; QuantiFERON® TB test, T-SPOT® test or PPD skin test. And X-ray will be performed. If the result is positive, patients may participate in the study if further work-up (according to Japanese practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment should have been initiated and maintained according to local country guidelines.
7. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
8. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than psoriasis, surgical procedure (i.e., organ transplant),

medical examination finding (including vital signs and ECG), or laboratory value at the screening visit outside the reference range that is in the opinion of the investigator, is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data.

9. History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients
10. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
11. Previous enrolment in this trial

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

All patients have the right to withdraw from the study at any time without the need to justify their decision. The investigator has the right to remove patients from the study for noncompliance, administrative, or other reasons. It should be clearly understood that an excessive rate of withdrawals can render the study results uninterpretable. The sponsor reserves the right to remove any study patient from the trial for non-compliance.

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

- The patient withdraws consent for trial treatment or trial participation, without the need to justify the decision.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy)
- Development of a toxicity or AE which warrants BI 655066 discontinuation including but not limited to SAEs or suspected unexpected serious adverse reactions (SUSARs).
- If prohibited treatment is used during the study for any indication, the patient must discontinue use of the prohibited treatment if he/she wishes to continue in the study. In case of undue safety risk for the patient, the patient should discontinue study treatment at the discretion of the investigator. If the patient received a live virus vaccination during the study, the patient must discontinue study treatment.
- If the patient experiences an intolerable increase of psoriasis during the course of the trial the patient will be discontinued from the trial to receive rescue treatment as deemed appropriate by the investigator.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and CML, is not willing or able to stick to the trial requirements in the future.

Discontinuation of study medication should not lead to withdrawal from the study. If possible the patient should complete all study visits and procedures as initially planned.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart and Section 6.2.3. If a patient becomes pregnant, refer to Section 5.3.6.2 for instructions.

Patients who discontinue the trial after receiving the first dose of study medication at Visit 2

will not be replaced.

For randomised patients leaving the study before the planned end of observation (EOO), their vital status should be collected at Week 56.

For randomised patients the reason for withdrawal (e.g., AEs) must be recorded in the case report form (CRF). These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

BI/AbbVie reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial, or any other administrative reason (e.g., discontinuation of development of BI 655066)
3. Violation of Good Clinical Practice (GCP), the clinical trial protocol (CTP), or the contract disturbing the appropriate conduct of the trial

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

Two different dose regimens of BI 655066 (risankizumab) and placebo to match BI 655066 will be administered subcutaneously. All products will be supplied by BI.

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Description of test product BI 655066

Substance:	BI 655066
Pharmaceutical form:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-23p19 mAb
Molecular weight	Approximately 148 kDa
Unit Strength:	75 mg BI 655066 in a pre-filled syringe, concentration 90 mg/mL
Route of administration:	Subcutaneous injection
Posology:	Week 0, Week 4, then every 12 weeks
Duration of use:	40 weeks

Table 4.1.1: 2 Description of test product placebo to BI 655066

Substance:	Placebo to BI 655066
Pharmaceutical form:	0.9% sodium chloride solution presented in a 1 mL syringe pre-filled with 0.87 mL. Dispensed volume is 0.83 mL.
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Not applicable
Molecular weight	Not applicable
Unit Strength:	Not applicable
Route of administration:	Subcutaneous injection
Posology:	Week 0 and Week 4 then every 12 weeks for placebo with BI 655066 75 mg arm, Week 0 and Week 4 for placebo with BI 655066 150 mg arm Week 0, Week 4, then every 12 weeks for BI 655066 75 mg arm
Duration of use:	4 weeks for placebo arm for placebo with BI 655066 150 mg arm, 40 weeks for placebo with BI 655066 75 mg arm, and BI 655066 low dose arm

4.1.2 Selection of doses in the trial

A dose of 150 mg has been selected for global phase III trials of BI 655066 for psoriasis. The dose selection strategy for global phase III involved analyses of data from the completed phase I study (Trial 1311.1, c02434648), the phase II study (Trial 1311.2, c03272682) and PK-PD modelling of all available data from the phase I and II studies. In Study 1311.16, Japanese exposure were numerically slightly higher than Caucasian exposure but were comparable after adjustment of body weight. Therefore, the dose of 150 mg was adopted in this trial and expected as an approved dose to be launched in Europe and the United States.

[redacted]

In conclusion, above two doses (75 mg and 150 mg) are selected for this trial.

4.1.3 Method of assigning patients to treatment groups

Through the utilisation of IRT, patients will be randomised to receive BI 655066 75 mg, BI 655066 150 mg, placebo (BI 655066 75 mg after Week 16), or placebo (BI 655066 150 mg after Week 16) in a ratio of 2:2:1:1 (See Section 3.1).

After the eligibility criteria are confirmed, the investigator or designee will randomise the patient on Day 1 (Visit 2) through IRT call or website entry. At visits where study medication is to be administered, study sites will be required to complete the medication resupply module in the IRT. Details regarding the use of the IRT are described in the site-user manual available in the ISF.

4.1.4 Drug assignment and administration of doses for each patient

An IRT will be used to allocate medication to patients through medication numbers. These visits where study medication is to be administered are specified in the Flow Chart.

At randomisation as well as subsequent medication administration visits, IRT will assign medication numbers. Site personnel will enter the medication numbers in the eCRF.

Study drugs will be administered subcutaneously. Injections will be given in a double-blind/double-dummy fashion with each patient receiving 2 injections at each dosing visit: 2 injections of BI 655066, one injection of BI 655066 and one injection of matching placebo or 2 injections of matching placebo depending on randomized dosing group. Syringes will be administered per Flow Chart schedule as assigned by IRT.

The injections at each visit, including injections of placebo necessary in order to assure blinding are presented in Table 4.1.4: 1.

BI 655066 and/or matching placebo will be administered as a subcutaneous injection in the abdomen, thighs, gluteal regions, or upper arms (contra-lateral to that used for PK/ADA samples). Injections should be at least 2cm apart and should not be close to a vein. The injection sites should avoid sites of psoriasis involvement as well as sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses. The 2 injections at each dosing visit should be administered within approximately 5 minutes. Further information regarding injection details will be provided in the ISF.

Table 4.1.4: 1 Dosing schedule

Dosing Visit[1]	BI 655066 low dose arm	BI 655066 high dose arm	Placebo arm (BI 655066 low dose after Week 16)	Placebo arm (BI 655066 high dose after Week 16)
Day 1 (Visit 2)	1 x active BI 1 x placebo	2 x active BI	2 x placebo	2 x placebo
Week 4 (Visit 3)	1 x active BI 1 x placebo	2 x active BI	2 x placebo	2 x placebo
Week 16 (Visit 6)	1 x active BI 1 x placebo	2 x active BI	1 x active BI 1 x placebo	2 x active BI
Week 28 (Visit 8)	1 x active BI 1 x placebo	2 x active BI	1 x active BI 1 x placebo	2 x active BI
Week 40 (EOT Visit)	1 x active BI 1 x placebo	2 x active BI	1 x active BI 1 x placebo	2 x active BI

BI=BI 655066 **(**risankizumab**), EOT=** end of treatment
[1] Each patient will receive a total of 2 injections per dosing visit.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

After randomisation at Visit2, patients, Investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomised treatment assignments until after final database lock.

The randomization code will be kept secret by clinical trial support up to final database lock.

The randomisation codes will be provided to bioanalytics prior to last patient out to allow them to exclude PK samples of placebo patients from the bioanalytical analyses. Bioanalytics will not disclose the randomisation code or the results of their measurements until the trial is officially unblinded. Serum drug levels and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation and analysis in accordance with sponsor's standard procedures.

The randomisation code will be unblinded to personnel involved in the interim analysis.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the principal investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of

trial participants. Each principal investigator receives a manual from the IRT provider that contains instructions on how to unblind the treatment of a patient via the IRT. If the code break for a patient is accessed, the sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented in the source documents and/or the appropriate eCRF page along with the date and the initials of the person who broke the code. In case third party needs to break the code, however, when the Investigator cannot be reached, the code can be opened by calling emergency code manager (Refer trial identification card).

Due to the requirements to report SUSARs, it may be necessary for a representative from BI's Pharmacovigilance group to access the randomisation code for individual patients during trial conduct. The access to the code will only be given to authorised pharmacovigilance representatives and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.
For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

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

If the storage conditions are found to be outside the specified range, the 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 CTP by authorised personnel as documented in the trial staff list.

4.1.8 Drug accountability

The investigator/pharmacist who is documented in the trial staff list/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)
- Availability of a signed and dated clinical trial contract between the sponsor and the head of the investigational site,
- Notification of the regulatory authority, e.g., competent authority,
- Availability of the curriculum vitae of the principal investigator,
- Availability of a signed and dated CTP,

- Availability of the proof of a medical license for the principal investigator

The investigator/pharmacist who is documented in the trial staff list/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 who is documented in the trial staff list/investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator/pharmacist who is documented in the trial staff list/investigational drug storage manager must verify that no remaining supplies are in the Investigator's possession.
All unused medication must be returned to the sponsor.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

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

In the event that a patient experiences an intolerable increase of psoriasis, as deemed by the investigator, during the course of the trial the patient will be discontinued from the trial to receive rescue treatment.

In case of AEs in need of treatment symptomatic therapy according to investigator judgment will be permitted. All concomitant and/or rescue therapies will be recorded on the appropriate pages of the eCRF.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Table 4.2.2.1: 1 Restricted medications

Medication or class of medications	Restriction duration (through EOO Visit)
guselkumab , tildrakizumab	not allowed prior or during trial participation
briakinumab, ustekinumab (sterala®), secukinumab (Cosentyx®)	6 months prior to randomisation
Brodalumab (Lumicef®), ixekizumab (Taltz®)	4 months prior to randomisation
adalimumab (Humira®) , infliximab (Remicade®) investigational products for psoriasis (non-biologics)	12 weeks prior to randomisation
etanercept (Enbrel®) live virus vaccinations	6 weeks prior to randomisation
any investigational device or product (excludes psoriasis products) other systemic immunomodulating treatments (e.g., methotrexate, cyclosporine A, corticosteroids[1], cyclophosphamide, tofacitinib (Xeljanz®), apremilast) other systemic psoriasis treatments (e.g., retinoids, fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g., PUVA)	30 days prior to randomisation
phototherapy (e.g., UVA, UVB) topical treatment for psoriasis or any other skin condition (e.g., corticosteroids[2], vitamin D analogues, vitamin A analogues, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea,α-hydroxy [fruit acids])	14 days prior to randomisation

[1] No restriction on corticosteroids with only a topical effect for non-skin indications (e.g., inhalative corticosteroids to treat asthma or corticosteroid drops used in the eye or ear).

[2] Exception: Topical steroids of medium such as Locoid or weak such as prednisolone for use on the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to trial visit in which PASI is assessed.

4.2.2.2 Restrictions on diet and life style

Patients should be fasted for at least 8 hours prior to collection of the safety laboratory samples, starting from Visit 2. Moisturizers/emollients containing retinoids and the use of tanning beds are not allowed during the study.

4.2.2.3 Restrictions regarding women of childbearing potential

Female patients of childbearing potential should use the contraception methods described in Section 3.3.2 and the patient information.

4.3 TREATMENT COMPLIANCE

Study medication will be administered in accordance with the protocol by authorised study personnel (e.g., investigators and study nurse). The measured plasma concentrations will provide additional information about compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoints in this trial is the achievement of ≥90% reduction from baseline PASI score (PASI 90) at Week 16

5.1.2 Secondary Endpoints

Secondary Endpoints are:

- Achievement of ≥90% reduction from baseline PASI score (PASI 90) at Week 52
- Achievement of an sPGA score of clear or almost clear at Week 16
- Achievement of an sPGA score of clear or almost clear at Week 52
- Achievement of ≥75% reduction from baseline PASI score (PASI 75) at Week 16
- Achievement of ≥75% reduction from baseline PASI score (PASI 75) at Week 52
- Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16
- Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 52
- Achievement of an American College of Rheumatology (ACR) 20 response at Week 16
- Achievement of an ACR20 response at Week 52

5.1.3 Further Endpoints

The further endpoints are as follows:
- Achievement of ≥50% reduction from baseline PASI score (PASI 50) at Weeks 16 and 52
- Time until the first achievement of PASI 50, PASI 75, PASI 90, PASI 100 and sPGA 0 or 1
- Time until loss of PASI 75, PASI 90, PASI 100 and sPGA 0 or 1 response
- Change from baseline in PASI score at Weeks 16 and 52
- Percent change from baseline in PASI at Weeks 16 and 52
- Absolute PASI of <3 at all visits collected
- Achievement of an sPGA score of clear at Weeks 16 and 52
- Change from baseline in psoriasis symptoms evaluated using the total score on the Psoriasis Symptoms Scale (PSS) at Weeks 16 and 52
- Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Weeks 16 and 52
- Achievement of total score on the PSS of 0 at Weeks 16 and 52
- Change from baseline in DLQI at all Weeks 16 and 52

5.2 ASSESSMENT OF EFFICACY

The skin condition will be assessed by using the PASI, sPGA, and other relevant scores as described in Section 5.1 and the ISF.
Symptoms, quality of life, and physical function will be assessed by PSS and DLQI.
PsA assessment will be assessed by using ACR 20.
Details of the efficacy assessments are listed in Appendix 10.

5.3 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:
- Adverse events
- Serious adverse events
- Clinical laboratory values (haematology, clinical chemistry, and urinalysis)
- Intensity of AEs will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to ISF for details)

5.3.1 Physical examination

Complete and targeted physical examinations will be performed at visits as described in the Flow Chart. Complete physical examination will include vital signs assessment and general appearance as well as evaluation of all relevant organ systems. Targeted physical examination will include vital signs 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.

5.3.1.1 Waist circumference

Waist circumference measurements should be made around a patient's bare midriff, after the patient exhales while standing without shoes and with both feet touching and arms hanging freely. The tape should be placed perpendicular to the long axis of the body and horizontal to the floor and applied with sufficient tension to conform to the measurement surface. Waist circumference should be determined by measuring the midpoint between the lowest rib and the iliac crest.

5.3.1.2 Body Weight

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

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

5.3.2 Vital Signs

Vital signs evaluations will be performed at visits as shown in the Flow Chart. This includes systolic/diastolic blood pressure, pulse rate, temperature, and respiratory rate. Blood pressure, pulse rate, and respiratory rate will be measured after patients have been sitting comfortably for at least five minutes. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements. At dosing visits vital signs

evaluations will be performed pre-dose and at Visit 2 and Visit 3 additional evaluations will be taken at approximately 5 minutes post-dose (5 minutes after last injection) and approximately 60 minutes post-dose (60 minutes after last injection).

Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at Visit 2 and for approximately 1 hour after the last injection at all other visits with 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.

5.3.3 Safety laboratory parameters

The laboratory tests listed in Table 5.3.3: 1 will be performed by the central laboratory service provider. A local laboratory may be used for selected tests in exceptional cases. Patients should be fasting for at least 8 hours prior to the blood sample being taken (except screening visit).

Instructions regarding sample collection, sample handling/processing, and sample shipping are provided in the Laboratory Manual in the 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 must be confirmed using an unscheduled visit laboratory kit and should be repeated until normalisation or stabilisation 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 Hemoglobin (Hb) Glycosylated Hbc (HbA1c) Red Blood Cell Count/Erythrocytes Reticulocyte Count White Blood Cells/Leukocytes Platelet Count/Thrombocytes
Differential Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Basophils (relative and absolute count) Monocytes (relative and absolute count) Lymphocytes (relative and absolute count)

Table 5.3.3: 1 (continued) Laboratory tests

Category	Test name
Differential Manual (if Diff erential Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen
Enzymes	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN Uric acid Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (reflex, in case of elevated CK) Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol
Urine Pregnancy test (only for female patients of childbearing potential; test done in clinic)	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (only for female patients of childbearing potential at screening or if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Hormones (only at screening)	TSH, (free T3and T4 in case of abnormal TSH)
Autoantibodies (only at screening)	Rheumatoid Factor

Table 5.3.3: 1 (continued) Laboratory tests

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-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	Albumin (quantitative) Creatinine Albumin/creatinine ratio
Infection screening	Hepatitis B Surface Antigen (qualitative)[1] Hepatitis B Surface Antibody (qualitative) [1] Hepatitis B Core Antibodies total (qualitative) [1] Hepatitis B Virus DNA (quantitative) [1, 2]Hepatitis C Antibodies (qualitative)[1] HIV-1, and HIV-2 Antibody (qualitative)[1,2] QuantiFERON®-TB[3] (if appricable)

[1] Hepatitis B, hepatitis C and HIV testing will be performed at screening and FU2/EOO Visit.
[2] If Hepatitis B Surface Antigen is negative but Hepatitis B Core Antibodies total is positive and/or Hepatitis B Surface Antibody is positive, Hepatitis B Virus DNA will be quantified. If HBV DNA level is undetectable (<20 IU/mL) at screening, the patient can participate in this trial. However, HBV DNA level will be monitored at least every 6 months.
[3] TB testing will be performed at screening and FU2/EOO Visit. QuantiFERON®, T-SPOT® or PPD skin test may be performed. T-SPOT® and PPD skin test will be performed at local laboratory.

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. 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 and the repeat used for analysis. Additional ECGs may be collected for safety reasons. Clinically relevant, abnormal findings will be reported as AEs.
Information about the details of ECG collection and the parameters assessed will be provided in the ISF.

ECGs will be read and evaluated by a central vendor. The study site will be informed about the results of the assessment of the ECG obtained at screening and if there are findings which would exclude the patient from study participation according to exclusion criterion in Section 3.3.3.

The electronic version of the ECG is regarded as source data.

5.3.5 Other safety parameters

Local tolerability at the administration site of the subcutaneous injection will be assessed by the investigator according to “swelling”, “induration”, “heat”, “redness”, “pain”, or “other findings” at the specified visits as noted in the Flow Chart. This assessment should be done pre-dose.

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 AE 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 authorisation include off-label use, overdose, misuse, abuse, and medication errors.

Serious adverse event
A serious adverse event (SAE) 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.

The following events will be handled as "deemed serious for any other reason".
An AE which possibly leads to disability will be reported as an SAE.

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, BI 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 EDC-system. These events should always be reported as SAEs as given above.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g., the potential for AEs based on knowledge from other compounds in the same class. 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 ISF.

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

Intensity of AEs

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by OMERACT (R13-3515). Refer to 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 AE. An adverse reaction, in contrast to an AE, 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 etiologies that could explain the event (e.g., preexisting 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 week 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.

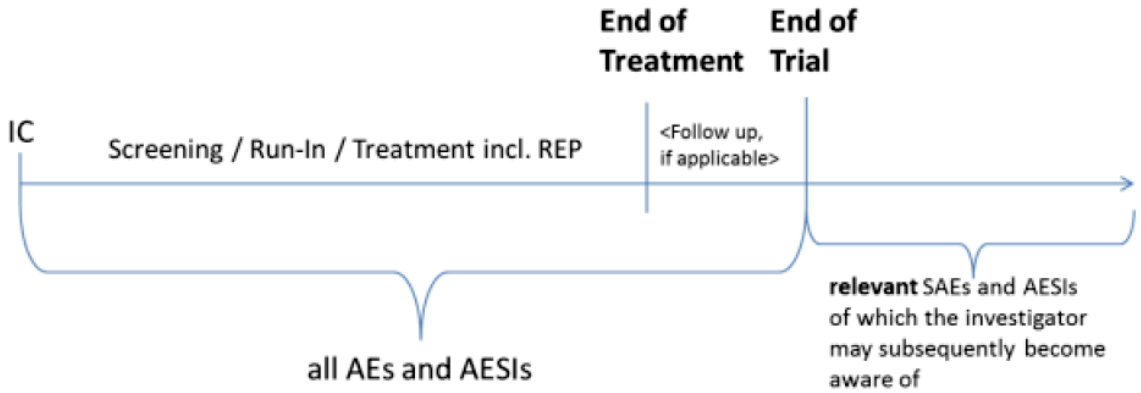
5.3.6.2 Adverse event collection and reporting

AE Collection
The Investigator shall maintain and keep detailed records of all AEs in their patient files.
The following must be collected and documented on the appropriate CRF 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.

  However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e., if further visits including telephone visits, or vital status assessments are planned) from then on and until the individual patient's end of the trial the investigator must report related SAEs and related 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 the investigator may become aware of.



The REP is defined as 15 weeks after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment please see Section 7.3.4. Events which occurred after the REP will be considered as post treatment events.

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.

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

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

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.

The following should also be recorded as an (S)AE in the eCRF 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 the rare case 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 (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 as an SAE form must be completed in addition.

Adverse event(s) due to Medical device failure of trial medication
The investigator must report "Medical device failure" that leads to AEs or is judged as a potential cause for leading SAEs by the investigator, on the Product/Device Complaints Form to the sponsor, see the instruction in ISF. "Medical device failure" that lead to SAEs and/or AESIs or is judged as a potential cause for leading SAE must be reported to the sponsor's Pharmacovigilance Department immediately.

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

BI 655066 concentrations will be reported descriptively. No PK parameters will be calculated. PK data will be incorporated into a larger pharmacometric analysis with other trials of BI 655066 project. The relationship between PK and selected efficacy endpoints, biomarkers, and AEs may be assessed. PK and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation in accordance with sponsor's standard procedures.
Detailed information on timing for dosing, PK and ADA sampling is provided in the Flow Chart. Date and exact clock time of drug administration and PK and ADA sampling will be recorded on eCRFs. These actual administration and sampling times will be used for determination of PK parameters. On visits with study medication dosing, PK and ADA sampling should occur prior to the drug administration.

5.4.2 Methods of sample collection

5.4.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of analyte plasma concentrations, approximately 3 mL of blood will be taken at the time points listed in the Flow Chart under PK sampling. For details on sample handling and logistics refer to the ISF (Laboratory Manual).
After completion of the study, plasma samples may be used for further methodological investigations, e.g., stability testing. However, only data related to the analyte will be generated by these additional investigations.

5.4.2.2 Plasma sampling for ADA

For ADA assessment, approximately 3 mL of blood will be taken at the time points listed in the Flow Chart under ADA sampling. For details on sample handling and logistics refer to the ISF (Laboratory Manual). Following the finalisation of the ADA bioanalytical report, selected ADA aliquots may be transferred to long term storage for possible additional ADA characterisation in the future.

5.4.3 Analytical determinations

BI 655066 concentrations will be determined by a validated Enzyme Linked Immunosorbent Assay (ELISA).
The presence of ADA to BI 655066 will be assessed via a tiered approach using a validated electrochemiluminescence assay (screening, confirmatory, and titration analysis as appropriate). Samples that are confirmed positive may be further characterised in a validated neutralising antibody assay.

5.4.4 Pharmacokinetic – Pharmacodynamic Relationship

Refer to Section 7.3.6.

5.5 ASSESSMENT OF BIOMARKERS

5.5.1 Assessment of soluble protein biomarkers

Serum will be collected to assess changes in protein levels of disease specific markers such as but not limited to β-defensin 2, neutrophil gelatinase associated lipocalin-2 (NGAL), S-100 A8 protein and adiponectin over time. In addition, changes in levels of biomarkers related to metabolic syndrome such as leptin, resistin, TNFa, IL-6 and VEGF will be explored.

5.5.1.1 Methods of sample collection

Approximately 8.5 ml of blood will be collected at time points indicated in the Flow Chart. Samples should be collected prior to administration of study drug at dosing visits. For details on sample handling and logistics refer to the ISF (Laboratory Manual).

5.5.1.2 Analytical determinations

These biomarkers are considered exploratory and respective assays will need to be qualified to meet the required performance criteria.

5.5.2 Biomarker sample banking

After completion of the study any unused serum samples collected for biomarker sampling as listed in Section 5.5.1 may be used for further investigations (e.g., additional biomarkers for immunological & inflammatory diseases), if participation and the informed consent for biomarker sample banking is agreed upon by the patient. Declination to allow storage and use of these samples will not preclude participation in this study. The study samples will be stored for a maximum period of 15 years (under consideration of local legislation and if consented by the patient) upon archiving of the final study report after study completion.

5.5.3 DNA Banking

Participation in the DNA banking sampling is voluntary and not a prerequisite for participation in the trial. The patient must provide informed consent for participation in this optional testing prior to any blood sampling used for DNA banking. The DNA banking sample will be stored in accordance with local ethical and regulatory requirements.

5.5.3.1 Methods of sample collection

One blood sample for DNA banking will be taken at Visit 2. A maximum of 8.5 mL blood will be collected per PaxGene DNA blood sampling tube. For details on sample handling and logistics refer to the ISF (Laboratory Manual).

5.5.3.2 Analytical determinations

The DNA banking sample, derived from the original blood sample, will be stored at BI and/or AbbVie. The stored DNA may be retrospectively analysed, e.g., to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements in psoriasis treatment trials and will be performed in order to monitor safety aspects or assess treatment response in an appropriate way.

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and the respective protocol sections. Refer to Section 5 for explanations of procedures. Additional details on procedures at selected visits are provided below.
Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits.
Patient reported outcome (PRO)s should be completed by the patient on his/her own in the pre-specified order (as programmed on the electronic device) in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team.

The order of completion for PROs is as follows, as applicable for each PRO at relevant visits according to the Flow Chart:

(1) PSS
(2) DLQI
(3) HAQ-DI (for PsA assessments)
(4) Pain visual analog scale (VAS) (for PsA assessments)
(5) Patient global assessment VAS (for PsA assessments)

6.2.1 Screening period

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 number should be recorded on the enrolment log and registered in IRT as a screened patient.

Screening (Visit 1) should normally take place no more than 42 days before Visit 2 and be completed no less than 14 days prior to Visit 2. Screening procedures may be extended to more than one physical visit, if needed.

Re-screening will not be permitted. Patients who fail screening following Visit 1 assessments should be registered as a screen failure in IRT.

Infection screening
Refer to exclusion criteria Section 3.3.3 with study participation directive for patients with a positive QuantiFERON®, T-SPOT®, or PPD skin test for TB.

Demographics
Informed consent date, sex, ethnicity and race will be collected and reported in the eCRF.

Medical History
Cardiovascular (CV) History and CV risk factors will be collected and reported in the Medical History eCRF page.

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

Psoriatic Arthritis Diagnosis Assessment
At Visit 1, all patients with a positive medical history of psoriatic arthritis will be further evaluated for psoriatic arthritis (PsA) diagnosis based on CASPAR (ClASsification of Psoriatic Arthritis) criteria (R15-1001). See Appendix 10.3 for further details

IRT
All patients who are screened must be registered with IRT. If the patient results in a screen failure, IRT should be notified as soon as possible and within the 42-day screening period. Details of IRT procedures can be found in the IRT manual located in the ISF.

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

The treatment period is from Visit 2 to EOT Visit.

Visits 2, 4, 6, 8, EOT, and FU2/EOO will be performed in fasted state (8 hours no food and only water). If a patient comes in non-fasted where a fasting condition is required, the visit should be performed, the non-fasted condition documented on the laboratory requisition, and the patient reminded about the expected conditions.

Urine pregnancy testing for all woman of child-bearing potential will be conducted on-site prior to every dosing and must be negative to further treat the patient. A positive urine test must be confirmed with a serum pregnancy test.

Randomisation via IRT and administration of study medication should be the last activity at Visit 2.

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

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 eCRFs.

6.2.3.1 Early treatment and trial termination

If study medication is discontinued prior to the planned Flow Chart EOT visit, every effort should be made to have the patient continue in the trial and complete all of the remaining Treatment Period Visits, as well as Follow-Up 1 and Follow-Up 2 Visits. Trial termination should be completed at Follow-Up 2 Visit and Follow-Up 3 Visit should not be completed.

If a patient cannot or will not continue in the trial, the patient should complete EOT visit procedures instead of the planned treatment period visit and return to the clinic for Follow-Up 3/End of Observation (FU3/EOO) Visit 16 weeks after last dose of study medication.

Patients who discontinue treatment early should be registered as withdrawn/discontinued in IRT will not have the option to participate in the extension trial.

6.2.3.2 Trial completion

Patients who finish the randomised treatment period will return to the clinic for Follow-Up 1 Visit (FU1) and Follow-Up 2 Visit (FU2). Completion is defined as a patient having reached the FU2 visit within the specified window per the Flow Chart. Patients who complete the randomised treatment period without early treatment discontinuation will have the option to participate in the extension trial.

After FU1 Visit, the Flow Chart visit schedule is dependent on extension participation:

- Patient who will not participate in the extension trial will return to the clinic for FU2/EOO Visit and FU3/EOO Visit. Trial termination will be completed at FU3/EOO. The decision not to enter the extension trial will be registered in IRT at FU2/EOO Visit.
- Patients who participate in the extension trial will complete FU2/EOO as the final 1311.38 study visit. Trial termination will be completed at FU2/EOO and registered in IRT.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a confirmatory, multicentre, randomised, double-blind, double-dummy, placebo controlled study evaluating the efficacy and safety of two different dose regiments of BI 655066 in patients with moderate to severe chronic plaque psoriasis. The primary objective of this trial is to assess the safety and efficacy of two different dose regiments of BI 655066 in comparison to placebo in patients with moderate to severe chronic plaque psoriasis.

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 is calculated by % PASI reduction from baseline = ((PASI at baseline - PASI at Visit X)/PASI at baseline) * 100, at all follow-up visits. Achieving an X% or larger reduction from baseline PASI score is denoted as PASI X.

Randomisation will be stratified by concomitant disease of PsA at baseline (Yes versus No) and body weight (≤ 90 kg versus >90 kg). Based upon these design considerations and the binary nature of the primary endpoint of PASI 90, they will be analysed using the Cochran-Mantel-Haenszel risk difference estimate stratified by the randomisation factors mentioned previously.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary hypotheses is that either BI 655066 150 mg or BI 655066 75 mg is superior to placebo in achieving ≥90% reduction from baseline in the PASI score (PASI 90) at Week 16 in participants with moderate to severe chronic plaque psoriasis.

In order to maintain the full significant level of 5%, the following null hypotheses will be tested using fixed-sequence method in the following order, with two-sided alpha level of 0.05.

1. BI 655066 150 mg is not different from placebo with respect to PASI 90 response at Week 16
2. BI 655066 75 mg is not different from placebo with respect to PASI 90 response at Week 16

7.3 PLANNED ANALYSES

The efficacy analyses will be based on the intent-to-treat principle, comprising all participants who were randomised. Efficacy analyses will be based on the planned treatment (i.e., the treatment assigned at randomisation); this set of patients is called the Intent-to-treat Population (ITT Population). Safety analyses will be performed on a Safety Population, comprising all randomized participants who received at least one dose of study drug. The

safety analysis will be performed based on the actual treatment received at the randomisation visit.

To evaluate the impact of protocol deviations on the primary endpoint, additional analyses will be performed on a Per-protocol (PP) Population. The PP Population will include those who were most compliant with the protocol in ways that could impact the primary endpoint. Final results and the criteria for exclusion of subjects will be finalized prior to the blind break.
The PP Population is defined as all subjects from the ITT Population who meet all the following criteria:

- Subjects must receive at least 75% of planned study drug injections during the first 16 Week.
- Subjects must have a PASI assessment post-baseline.
- Inclusion Criterion 2: Subjects must have stable moderate to severe chronic plaque psoriasis at baseline:
  - Have an BSA ≥ 10% and
  - Have a PASI ≥ 12 and
  - Have an sPGA ≥ 3.

PP Populations will be analyzed by treatment group as randomized.

7.3.1 Primary endpoint analyses

The achievement of PASI 90 at Week 16 is the primary endpoint and is a binary variable with values of 0 or 1. The difference in proportion responding between the BI 655066 arm and placebo arm will be estimated and tested using the Cochran-Mantel-Haenszel risk difference estimate stratified by the randomisation factors of concomitant disease of PsA at baseline (Yes versus No) and body weight (≤90 kg versus >90 kg) with weights proposed by Greenland & Robins, which is calculated as follows:

$$\hat{\delta}_{MH} = \frac{\sum_{i=1}^{u} w_i \cdot \hat{\delta}_i}{\sum_{i=1}^{u} w_i}, where$$

$$\hat{\delta}_i = \frac{x_i}{n_i} - \frac{y_i}{m_i} \ denotes\ the\ risk\ difference\ in\ stratum\ i, i = 1, \cdots, u$$

$$w_i = \frac{n_i \cdot m_i}{n_i + m_i} \ denotes\ the\ weight\ of\ stratum\ i, i = 1, \cdots, u$$

x_i denotes the number of patients with event in $treatment_1$ in stratum $i, i = 1, \cdots, u$
y_i denotes the number of patients with event in $treatment_2$ in stratum $i, i = 1, \cdots, u$
n_i denotes the number of patients on $treatment_1$ in stratum $i, i = 1, \cdots, u$
m_i denotes the number of patients on $treatment_2$ in stratum $i, i = 1, \cdots, u$

The estimated variance $\hat{\delta}_{MH}$ is calculated as:

$$\widehat{var}(\hat{\delta}_{MH}) = \frac{\sum_{i=1}^{u} L_i}{(\sum_{i=1}^{u} w_i)^2}$$

$$where\ L_i = \frac{x_i(n_i - x_i)\ m_i^3 + y_i(m_i - y_i)\ n_i^3}{n_i \cdot m_i \cdot (n_i + m_i)^2}\ , i = 1, \cdots, u$$

Assuming a normal distribution of $\hat{\delta}_{MH}$, an approximate 95 % CI is given as follows, where $z_{0.975}$ is the 97.5% quantile of the standard normal distribution:

$$CI = \left[\hat{\delta}_{MH} \pm z_{0.975} \cdot \sqrt{\widehat{var}\left(\hat{\delta}_{MH}\right)}\right]$$

Also, the approximate p-value can be calculated using the following:

$$pvalue = 2 \cdot Pr\left[Z > \left|\frac{\hat{\delta}_{MH}}{\sqrt{\widehat{var}\left(\hat{\delta}_{MH}\right)}}\right|\right], where\ Z \sim N(0,1)$$

If there is a stratum for a treatment group that has 0 patients in it, the 0 count will be replaced by 0.1 in order to prevent dividing by 0 in the above equations, as suggested in Greenland & Robins. Treatment versus placebo comparisons will include both a p-value and 95% confidence interval.

7.3.2 Secondary endpoint analyses

The same methods as discussed for the primary analyses will be used to analyse all binary secondary endpoint at Week 16.

Secondary endpoints for Week 52 will be summarised descriptively.

7.3.3 Further endpoint analyses

Change from baseline in PSS at Week 16 will be analysed by the van Elteren test between the BI 655066 arm and placebo arm. The other further endpoints will be summarised descriptively, with number and proportion of responders for dichotomous endpoints and mean, median, SD and IQR presented for continuous variables.

Time to onset of *Endpoint*, the time to event will be calculated as:

- Time to first onset (with observed event) = [date of first onset] – [date of first active treatment] + 1
- If a patient never attains Endpoint (e.g., PASI75 or PASI90), then that patient's time to first onset will be censored at the last visit where the Endpoint was measured (e.g., PASI).

Time to Loss of *Endpoint* (from time of randomisation), defined using the following algorithm:

a) Never attains *Endpoint* (Failure at time 0)
b) After achieving *Endpoint*, patient will be a failure if they subsequently do not achieve *Endpoint* and either discontinue from the study or switch therapy

while still not achieving *Endpoint*. Time to failure will be calculated using date of first failure to achieve *Endpoint*.

c) Patients randomised to placebo will have Week 16 (i.e. when they begin taking BI 655066) as Day 0 for determining Time to Loss of response.
d) Patients who maintain Endpoint throughout the study will be censored at their last measurement

Time to Loss of *Endpoint* (from time of achieving Endpoint or from specific point in time) will be defined as above but only for those patients that have achieved *Endpoint*.

All Time to Event endpoints will be presented using Kaplan-Meier curves.

As sensitivity analysis, the primary and secondary endpoints will be analysed in the same way based on PP Population.

7.3.4 Safety analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard AbbVie summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the REP, a period of 15 weeks after the last dose of trial medication, will be assigned to the treatment period for evaluation.

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

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment and end of the REP will be considered ‘treatment-emergent’. The residual effect period is defined as 15 weeks after the last trial medication application. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the 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.

7.3.5 Pharmacokinetic analyses

Descriptive statistics of BI 655066 concentration measurements by treatment group and visit will be provided.

PK data will be analysed using population PK approaches. For this purpose, data may also be combined with data from other trials and the results will be reported separately from the clinical trial report (CTR). Detail of the population PK analysis plan will be specified separately.

7.3.6 Pharmacodynamic analyses

No formal analysis of pharmacokinetic-pharmacodynamic relationships is planned. As the data from previous trials with BI 655066 suggest a PK- PD relationship for efficacy endpoints such as PASI, population PK-PD analyses will be performed. For this purpose, data may also be combined with data from other trials. Model based analyses will be planned and documented separately according to internal and external guidelines and SOPs. Other exploratory analyses of drug concentration, biomarker, or safety data may be performed using data obtained as part of this trial.

7.3.7 Biomarker analyses

Changes in serum protein biomarker levels over time will be described by treatment group.

7.4 INTERIM ANALYSES

Before the submission to regulatory agencies with the long-term data, an interim report will be prepared for the submissions. An analysis will be conducted when the last patient completes the Week 28 visit. Primary endpoint (PASI 90 score at Week 16) for all patients will be included in the Week 28 analyses; hence no alpha adjustment is required at the Week 28 analysis. For this analysis all efficacy endpoints and safety as well as PK and immunogenicity data will be analysed. As endpoints for Week 28, same analyses will be performed for the Week 52 endpoints defined in Section 5.

An independent team will be unblinded to perform this analysis. Unblinded treatment assignments will not be disseminated to the sites, investigators, or patients until the end of final database lock.

7.5 HANDLING OF MISSING DATA

Every effort should be made to collect complete data at all visits.
The following rules will be used to impute for missing data:

- For all non-binary endpoints, LOCF (Last Observation Carried Forward) will be used to impute missing values
- For all binary endpoints (i.e., endpoints that are either 1 (patient responded) or 0 (patient did not respond)):
  - If no data after that visit, then impute as failure (No Response Imputation [NRI])

- If data at visits before and after, only impute as success if both visits are successes;

else impute as failure

Missing items from the PROs will be handled according to the respective measure instructions (cf. Appendix 10.3). If there is no data for a particular visit, then it will be imputed following the same rules as described above.
Sensitivity analyses to assess the robustness of the hypothesis testing results will include:

- LOCF (for binary endpoints)
- Logistic regression
- MMRM (for continuous endpoints)
- Multiple imputation (for binary endpoints)

7.6 RANDOMISATION

Patients will be randomised in blocks to double-blind treatment, stratified by concomitant disease of PsA at baseline (Yes versus No) and body weight (≤90 kg versus >90 kg). Patients will be randomised to 4 sequences in a ratio of 1:1:2:2 within each level of stratification.

Sequence 1: Weeks 0-16: Placebo, Weeks 16-52: BI 655066 75 mg
Sequence 2: Weeks 0-16: Placebo, Weeks 16-52: BI 655066 150 mg
Sequence 3: Weeks 0-16: BI 655066 75 mg, Weeks 16-52: BI 655066 75 mg
Sequence 4: Weeks 0-16: BI 655066 150 mg, Weeks 16-52: BI 655066 150 mg

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation lists 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 sizes will be documented in the CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

The study is powered to show a benefit of BI 655066 over placebo in terms of PASI 90 response at Week 16. Based on the outcome from the trial 1311.2, the PASI 90 response rate at Week 16 is assumed to be at least 65% in the BI 655066 arm. There is only minimal data available on placebo response in the BI 655066 program but the phase 3 results from ustekinumab and secukinumab indicate a response rate for PASI 90 of approximately 5% in the placebo arm. With 2-sided significance level 5%, based on these assumptions (65% vs 5% PASI 90 response rates), 17 patients in the BI 655066 arm and 17 in the placebo arm will provide 95% power for each comparison and an overall power of at least 90%.

For the Japanese submission, the safety data of at least 100 Japanese patients exposed to BI 655066 at the registered dose(s) for 1 year or more is necessary for long team safety assessment as a result of the PMDA consultation meeting in 2015. This study will enrol a total of 168 patients, with 56 patients in each of the two BI 655066 arms and 56 patients in the placebo arm. It is expected that at least 68 patients exposed to BI 655066 75 mg and 68

patients exposed to BI 655066 150 mg will reach at least 1 year exposure to BI 655066 in this clinical trial or in the following extension study. Other global phase III trials where Japanese patients are to be enrolled will make up for the remaining safety data requirements.

8. 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 Harmonised Tripartite Guideline for GCP, relevant BI Standard Operating Procedures (SOPs), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains 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, of ICH GCP, or the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997).

The BI 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 contract with trial site. As a rule, no trial results should be published prior to finalisation of the CTR.
The rights of the Investigator/trial site and of the sponsor with regard to publication of the results of this trial are described in the Investigator contract/trial site's contract. As a general rule, no trial results should be published prior to finalisation of the CTR.

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

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 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 Japan. 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 must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free

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

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, by IRB 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 patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the 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) 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 eCRF, data must be derived from source documents, for example:
- Patient identification: gender, date or year of birth

- 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 (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 review and regulatory inspections. Direct access must be provided to the eCRF 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., PMDA). The CRA and auditor may review all eCRFs 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, ICH GCP, and Japanese GCP.

8.3.3 Storage period of records

Trial sites:
The trial sites must retain the source and essential documents (including ISF) according to the national or Japanese 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. 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 and the regulatory authorities.

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

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of GCP as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by BI are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment pf 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.

When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

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

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

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

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10. APPENDICES

10.1 PASI DEFINITIONS AND USE

The PASI score is an established measure of clinical efficacy for psoriasis medications (R96-3541).
The PASI is a tool which provides a numeric scoring for patients overall psoriasis disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected and the severity of erythema, infiltration, and desquamation over four body regions.

The endpoints used are based on the percent reduction from baseline, generally summarised as a dichotomous outcome based on achieving over an X% reduction (or PASI X), where X is 50, 75, 90 and 100.

To calculate the PASI score, the four main body areas are assessed: **head (h), trunk (t), upper extremities (u) and lower extremities (l)**. These correspond to 10, 30, 20 and 40% of the total body area respectively.
The area of psoriatic involvement of these four areas (Ah, At, Au, and Al) is given a numerical value: 0 = no involvement, 1 = <10%, 2 = 10 to <30%, 3 = 30 to <50%, 4 = 50 to <70%, 5 = 70 to <90%, and 6 = 90 to 100% involvement.
The **signs of severity, erythema (E), infiltration (I) and desquamation (D)** of lesions are assessed using a numeric scale 0-4 where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores are made independently for each of the areas, h, t, u and l and represents a composite score for each area. An illustration of judging erythema follows: 0 = no erythema, 1 = slight erythema, 2 = moderate erythema, 3 = striking erythema, and 4 = exceptionally striking erythema.
The PASI score is calculated according to the following formula:
PASI = 0.1(Eh+Ih+Dh)Ah + 0.3(Et+It+Dt)At + 0.2(Eu+Iu+Du)Au + 0.4(El+Il+Dl)Al

10.2 STATIC PHYSICIAN GLOBAL ASSESSMENT (SPGA)

This sPGA is a 5 point score ranging from 0 to 4, based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions (Table 10.2: 1) (R15-5200). The assessment is considered "static" which refers to the patients disease state at the time of the assessments, without comparison to any of the patient's previous disease states, whether at Baseline or at a previous visit.

A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

The investigator (or qualified site personnel) scores the erythema, induration and scaling of all psoriatic lesions from 0 - 4 based on the following descriptors:

Erythema
0 Normal (post-inflammatory hyper/hypopigmentation may be present)
1 Faint, diffuse pink or slight red coloration
2 Mild (light red coloration)

3 Definite red coloration (Dull to bright red)
4 Bright to Deep red coloration of lesions

Induration (plaque elevation)
0 None
1 Just detectable (possible slight elevation above normal skin)
2 Mild thickening (slight but definite elevation, typically edges are indistinct or sloped)
3 Clearly distinguishable to moderate thickening (marked definite elevation with rough or sloped edges)
4 Severe thickening with hard edges (marked elevation typically with hard or sharp edges)

Scaling
0 No scaling
1 Minimal focal scaling (surface dryness with some desquamation)
2 Predominately fine scaling (fine scale partially or mostly covering lesions)
3 Moderate scaling (coarser scale covering most or all of the lesions)
4 Severe/coarse scaling covering almost all or all lesions (coarse, non-tenacious scale predominates)

Scoring
A composite score is generated from the above data and the final sPGA is determined from this composite score as follows:

Clear	0 = 0 for all three
Almost clear	1 = mean >0, <1.5
Mild	2 = mean >=1.5, <2.5
Moderate	3 = mean >=2.5, <3.5
Severe	4 = mean >=3.5

Table 10.2: 1 sPGA rating scale for overall psoriatic disease

Score	Short description	Detailed description
0	**clear**	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present
1	**Almost clear**	Normal to pink coloration; Just detectable (possible slight elevation above normal skin) No to minimal focal scaling
2	**mild**	Pink to light red coloration Mild thickening (slight but definite elevation, typically edges are indistinct or sloped) Predominantly fine scaling
3	**moderate**	Dull to bright red coloration Clearly distinguishable to moderate thickening Moderate scaling
4	**severe**	Bright to deep dark red coloration; Severe thickening with hard edges Severe coarse scaling covering almost all or all lesions

10.3 DIAGNOSIS AND ASSESSMENTS FOR PATIENTS WITH PSORIATIC ARTHRITIS

10.3.1 psoriatic arthritis diagnosis at Screening

At Visit 1 at selected study site, patients with a positive history of PsA or suspected to have PsA will be further evaluated for PsA diagnosis based on CASPAR criteria (R15-1001). To be classified has having PsA, a patient must have inflammatory articular disease (joint, spine, or entheseal) with at least 3 points total from the 5 categories in Table 10.3.1: 1. All trial participants will have 2 points assigned due to evidence of current psoriasis per trial entry criteria and require at least one additional point for diagnosis of PsA.

Table 10.3.1: 1 CASPAR criteria

Category	Point assignment
Evidence of current psoriasis, a personal history of psoriasis, or a family history of psoriasis	2 points
Typical psoriatic nail dystrophy, including onycholysis, pitting, or hyperkaratosis observed on current physical examination	1 point
A negative test result for rheumatoid factor by any method except latex	1 point
Either current dactylitis, defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist	1 point
Radiographic evidence of juxta-articular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot	1 point

10.3.2 Psoriatic arthritis assessment

Visit 2
If a diagnosis of PsA is confirmed and the patient meets all study entry criteria for participation, the following will be performed at Visit 2:

- HAQ-DI (refer to Appendix 10.4.3)
- Patient's assessment of pain VAS (refer to Appendix 10.4.4)
- Patient global assessment VAS (refer to Appendix 10.4.5)
- Tender and Swollen Joint Counts as listed in Table 10.3.2: 1
- Physician's global assessment of disease activity (VAS)

Visit 6, Visit 8, EOT, and FU2/EOO
For patients with swollen or tender joint count ≥3 at Visit 2, the following will be performed at Visit 6, 8, EOT, and FU2/EOO Visit:

- HAQ-DI (refer to Appendix 10.4.3)
- Patient's assessment of pain VAS (refer to Appendix 10.4.4)
- Patient global assessment VAS (refer to Appendix 10.4.5)
- Tender and Swollen Joint Counts as listed in Table 10.3.2: 1
- Physician's global assessment of disease activity (VAS)

Table 10.3.2 : 1 Tender and Swollen Joint Counts

Joint	Left		Right	
	Tender	Swollen	Tender	Swollen
Temporomandibular				
Acromioclavicular				
Sternoclavicular				
Shoulder				
Elbow				
Wrist				
MCP1				
MCP2				
MCP3				
MCP4				
MCP5				
IP of the thumb				
PIP of fingers 2				
PIP of fingers 3				
PIP of fingers 4				
PIP of fingers 5				
DIP of fingers 2				
DIP of fingers 3				
DIP of fingers 4				
DIP of fingers 5				
Hip*				
Knee				
Ankle				
Mid-Tarsal				

Table 10.3.2 : 1 (continued) Tender and Swollen Joint Counts

Joint	Left		Right	
	Tender	Swollen	Tender	Swollen
MTP1				
MTP2				
MTP3				
MTP4				
MTP5				
IP of great toe				
PIP of toes 2				
PIP of toes 3				
PIP of toes 4				
PIP of toes 5				

* Hip will only be assessed for TJC (tender joint counts), not for SJC (swollen joint count).

Joint counts will be performed by assessor(s) who must be well trained and part of the site personnel. Whenever possible, the same evaluator should perform these assessments at all visits.

Number of tender joints:
The 68 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hips, 2 knees, 2 ankles2 mid-tarsal, 10 metatarsophalangeal, and 10 proximal interphalangeal joints of the feet.
Joints are be scored as either tender (1) or not tender (0)
Number of swollen joints:
The 66 joints to be examined for swelling are the same as those examined for tenderness, however excluding both hip joints.
Joints are to be scored as either swollen (1) or not swollen (0).
Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for swollen joint count. Dactylitis of a digit in the hand or the foot counts as one tender and swollen joint.
Data will be recorded for tender and swollen joints (right or left side), i.e., a box (no, yes or not applicable) needs to be ticked for all joints.

10.3.3 ACR Response Criteria

ACR 20 (R96-2379)**:**
- At least 20% improvement in SJC* compared to baseline **AND**
- At least 20% improvement in TJC* compared to baseline **AND**
- At least 20% improvement in at least 3 out of the following 5 variables

1. Patient's assessment of pain on VAS
2. Patient's global assessment of the disease on VAS
3. Physician's global assessment of the disease on VAS
4. Patient's assessment of disability on HAQ
5. Acute phase reactants (serum CRP)

* SJC and TJC are evaluated according to the complete joint count (see Appendix 10.3.2).

Physician's global assessment of disease activity
The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question "Considering all the ways the Subjects psoriatic arthritis affects them, how would you rate the way they felt over the past week? Place a vertical mark (|) on the line to indicate how they felt". To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his own assessment on that subject.

10.4 PATIENT REPORTED OUTCOMES

10.4.1 Psoriasis Symptom Scale (PSS)

The PSS will be self-administered by the patient at visits indicated in the Flow Chart.

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

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

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

10.4.2 Dermatology Life Quality Index (DLQI)

The DLQI will be self-administered by the patient at visits indicated in the Flow Chart.

The DLQI is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment (R05-2548). The DLQI has a one-week recall period. Item scores range from 0 (not relevant) and 1 (not at all) to 3 (very much). Question 7 is a "yes"/"no" question where "yes" is scored as 3.

DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0-1 = no effect on patient's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on patient's life. The higher the score, the more the quality of life is impaired. A 5-point change from baseline is considered a clinically important difference.

The DLQI has been extensively used in clinical trials and has a large evidence base supporting reliability and validity (R15-3845).

DERMATOLOGY LIFE QUALITY INDEX

DLQI

Hospital No: Date:
Name: Score:
Address: Diagnosis:

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

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

Please check you have answered EVERY question. Thank you.

10.4.3 Health Assessment Questionnaire Disability Index (HAQ-DI)

The HAQ-DI will be self-administered by the patient at visits indicated in the Flow Chart.
The HAQ-DI is a twenty-item patient reported outcome instrument that assesses current physical function/disability. The HAQ-DI covers eight categories (dressing and grooming, hygiene, arising, reach, eating, grip, walking and common daily activities). There are four response options, ranging from 0 (no difficulty) to 3 (unable to do). HAQ-DI score is reported as a mean score between 0 and 3 by dividing the total score by the number of items answered (R15-3849).
The HAQ-DI has been the most-widely used instrument to assess physical function clinical trials of treatments for rheumatoid and psoriatic arthritis and has extensive evidence of its validity and other psychometric properties in this context (R15-3846).
The HAQ-DI will be self-administered by the patient at visits indicated in the Flow Chart.

HEALTH ASSESSMENT QUESTIONNAIRE

PATKEY#_____
QUESTDAT_____

Name_____ **Date**_____

In this section we are interested in learning how your illness affects your ability to function in daily life. Please feel free to add any comments on the back of this page.

HAQADMIN_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

QUESTYPE_____

PMSVIS_____
RASTUDY_____
QUESTNUM_____

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
DRESSING & GROOMING					
Are you able to:					
- Dress yourself, including tying shoelaces and doing buttons?	____	____	____	____	
- Shampoo your hair?	____	____	____	____	DRESSNEW_____
ARISING					
Are you able to:					
- Stand up from a straight chair?	____	____	____	____	
- Get in and out of bed?	____	____	____	____	RISENEW_____
EATING					
Are you able to:					
- Cut your meat?	____	____	____	____	
- Lift a full cup or glass to your mouth?	____	____	____	____	
- Open a new milk carton?	____	____	____	____	EATNEW_____
WALKING					
Are you able to:					
- Walk outdoors on flat ground?	____	____	____	____	
- Climb up five steps?	____	____	____	____	WALKNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

____ Cane
____ Walker
____ Crutches
____ Wheelchair
____ Devices used for dressing (button hook, zipper pull, long-handled shoe horn, etc.)
____ Built up or special utensils
____ Special or built up chair
____ Other (Specify:_____)

DRSGASST_____
RISEASST_____

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

____ Dressing and Grooming
____ Arising
____ Eating
____ Walking

EATASST_____
WALKASST_____

Please check the response which best describes your usual abilities OVER THE PAST WEEK:

	Without ANY Difficulty	With SOME Difficulty	With MUCH Difficulty	UNABLE To Do	
HYGIENE					
Are you able to:					
- Wash and dry your body?	____	____	____	____	
- Take a tub bath?	____	____	____	____	
- Get on and off the toilet?	____	____	____	____	HYGNNEW_____
REACH					
Are you able to:					
- Reach and get down a 5 pound object (such as a bag of sugar) from just above your head?	____	____	____	____	
- Bend down to pick up clothing from the floor?	____	____	____	____	REACHNEW_____
GRIP					
Are you able to:					
- Open car doors?	____	____	____	____	
- Open jars which have been previously opened?	____	____	____	____	
- Turn faucets on and off?	____	____	____	____	GRIPNEW_____
ACTIVITIES					
Are you able to:					
- Run errands and shop?	____	____	____	____	
- Get in and out of a car?	____	____	____	____	
- Do chores such as vacuuming or yardwork?	____	____	____	____	ACTIVNEW_____

Please check any AIDS OR DEVICES that you usually use for any of these activities:

____ Raised toilet seat
____ Bathtub seat
____ Jar opener (for jars previously opened)
____ Bathtub bar
____ Long-handled appliances for reach
____ Long-handled appliances in bathroom
____ Other (Specify: _____)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

____ Hygiene
____ Reach
____ Gripping and opening things
____ Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

10.4.4 pain VAS

The pain-VAS will be self-administered by the patient at visits indicated in the Flow Chart. The patient's assessment of pain will be performed using a horizontal 100 mm VAS, ranging from 0 (no pain) to 100 (severe pain) after the question:
"Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your psoriatic arthritis in the past week".

10.4.5 Patient's global assessment VAS

The patient global assessment VAS will be self-administered by the patient at visits indicated in the Chart.
The patient's global assessment of disease activity will be performed using a horizontal 100 mm VAS, ranging from 0 (very well) to 100 (very poor) after the question:
"Considering all the ways psoriatic arthritis affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing in the past week".

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1.0
Date of CTP revision		08 Jun 2017
BI Trial number		1311.38
BI Investigational Product(s)		risankizumab, BI 655066
Title of protocol		A phase II/III, randomised, double-blind study to evaluate efficacy and safety of two different dose regimens of BI 655066 (risankizumab) and placebo and maintenance of response of BI 655066 (risankizumab) administered subcutaneously in Japanese patients with moderate to severe chronic plaque type psoriasis.
To be implemented only after approval of the IRB / IEC / Competent Authorities		☒
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		☐
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		Protocol synopsis
Description of change		Changed multiple testing procedure
Rationale for change		To decrease type II error and newly planned procedure also controls family-wise type I error of less than 5%.
Section to be changed		Flowchart
Description of change		Added “X” for sPGA at Visit 1
Rationale for change		sPGA entry criteria collected on the electronic device was added to Flow Chart as a clarification
Section to be changed		Section 2.3
Description of change		Changed a item number
Rationale for change		To correct typo error
Section to be changed		Section 3.1.1
Description of change		Added text to specify Data Manage will be done by

		BI and Statistical Evaluation will be done by AbbVie according to each SOPs.
Rationale for change		In February 2016, AbbVie entered into a license agreement with BI related to risankizumab, and in October 2016, the US IND for risankizumab transitioned from BI to AbbVie. To modify study conduct responsibilities as a result of that license agreement.
Section to be changed		Section 3.3.4.2
Description of change		Updated text to "BI/AbbVie reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons".
Rationale for change		In February 2016, AbbVie entered into a license agreement with BI related to risankizumab, and in October 2016, the US IND for risankizumab transitioned from BI to AbbVie. To modify study conduct responsibilities as a result of that license agreement.
Section to be changed		Table 4.2.2.1: 1
Description of change		Changed a lank of topical steroid from "mild" to "medium"
Rationale for change		To correct description
Section to be changed		Section 5.5.3.2
Description of change		Specified DNA banking sample storage
Rationale for change		In February 2016, AbbVie entered into a license agreement with BI related to risankizumab, and in October 2016, the US IND for risankizumab transitioned from BI to AbbVie. To modify study conduct responsibilities as a result of that license agreement.
Section to be changed		Section 7.2
Description of change		Changed multiple testing procedure
Rationale for change		To decrease type II error and newly planned procedure also controls family-wise type I error of less than 5%.
Section to be changed		Section 7.3
Description of change		Changed analysis populations : FAS to ITT Population SAF to Safety Population PPS to PP Population
Rationale for change		All changes were made under blinding prior Data

		base lock. FAS to ITT Population: ITT analysis is more conservative approach. SAF to Safety Population: Terminology changes PPS to PP Population: New definition is based on more concrete definition.
Section to be changed		Section 7.3.1
Description of change		Changed confidence interval
Rationale for change		It corresponds to changes in 7.2.
Section to be changed		Section 7.3.3
Description of change		Corrected typo Changed Definition of Loss of Endpoint
Rationale for change		To correspond to changes in 7.3 and it was based on ITT principle.
Section to be changed		Section 7.3.4
Description of change		Changed text to specify that AbbVie summary tables and listings will be produced and analyses based on AbbVie standards
Rationale for change		In February 2016, AbbVie entered into a license agreement with BI related to risankizumab, and in October 2016, the US IND for risankizumab transitioned from BI to AbbVie. To modify study conduct responsibilities as a result of that license agreement.
Section to be changed		Section 7.5
Description of change		Changed missing data handling
Rationale for change		To correspond to changes in 7.3 and it was based on ITT principle.
Section to be changed		Section 7.7
Description of change		Changed of comparison-wise significance level and assumption for statistical powers
Rationale for change		To correspond to changes in 7.2.
Section to be changed		Section 10.3.3
Description of change		Add the description of Physician's global assessment of disease activity.
Rationale for change		To clarify a procedure for the assessment.
Section to be changed		Section 10.4.4
Description of change		Changed text from "today" to "in the past week"
Rationale for change		To clarify a period for the assessment.

Section to be changed		Section 10.4.5
Description of change		Changed text from “today” to “in the past week”
Rationale for change		To clarify a period for the assessment.

APPROVAL / SIGNATURE PAGE

Document Number: c08943535 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: A phase II/III, randomised, double-blind study to evaluate efficacy and safety of two different dose regimens of BI 655066 (risankizumab) and placebo and maintenance of response of BI 655066 (risankizumab) administered subcutaneously in Japanese patients with moderate to severe chronic plaque type psoriasis.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
	[redacted]	09 Jun 2017 07:43 CEST
		12 Jun 2017 03:32 CEST
		12 Jun 2017 04:02 CEST
		12 Jun 2017 10:32 CEST
		16 Jun 2017 22:19 CEST
		19 Jun 2017 04:42 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed