Boehringer Ingelheim

CLINICAL TRIAL PROTOCOL

	Document Number:	**c03557743-03**
EudraCT No.:	2015-003622-13	
BI Trial No.:	1311.28	
BI Investigational Product(s):	BI 655066	
Title:	BI 655066/ABBV-066 (risankizumab) versus Ustekinumab and placebo comparators in a randomized double blind trIal for Maintenance use in Moderate to severe plaque type psoriasis-2 (UltIMMa-2)	
Brief Title:	BI 655066/ABBV-066 (risankizumab) compared to placebo and active comparator (ustekinumab) in patients with moderate to severe chronic plaque psoriasis	
Clinical Phase:	Phase III	
Trial Clinical Monitor:	[redacted]	
Coordinating Investigator:		
Status:	Revised Protocol based on global amendment 2	
Version and Date:	**Version: 3.0**	**Date: 12 Oct 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 655066	
Protocol date: 02 Nov 2015	**Trial number:** 1311.28		**Revision date:** 12 Oct 2016

Title of trial:	BI 655066/ABBV-066 (risankizumab) versus **U**stekinumab and **p**lacebo comparators in a randomized double blind **tr**I**a**l for **M**aintenance use in **M**oderate to severe plaque type psori**a**sis-2 (UltIMMa-2)
Coordinating Investigator:	[redacted] M.D. [redacted]
Trial site(s):	Multi-centre trial
Clinical phase:	III
Objective(s):	The main objective of this study is to assess the efficacy and safety of BI 655066 compared to ustekinumab and placebo in patients with moderate to severe chronic plaque psoriasis.
Methodology:	Placebo and Active-controlled, double-blind, double dummy, randomized, parallel design comparison of BI 655066 and ustekinumab and placebo over 52 weeks
No. of patients:	
total entered:	Approximately 500
each treatment:	300 BI 655066, 100 ustekinumab and 100 placebo
Diagnosis :	Moderate to severe chronic plaque psoriasis
Main criteria for inclusion:	Male or female patients with age ≥ 18 years at screening Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Have stable moderate to severe chronic plaque psoriasis with or

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	without psoriatic arthritis at both Screening and Baseline (Randomisation): - Have a BSA ≥ 10% and, - Have a PASI score ≥ 12 and, - Have a sPGA score of ≥ 3. Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator Must be a candidate for treatment with Stelara® (ustekinumab) according to local label.
Test product(s):	BI 655066
dose:	150mg (2 syringes, 75mg each) at week 0, 4 and every 12 weeks
mode of administration:	subcutaneous
Comparator products:	Placebo at week 0 and 4 Ustekinumab at week 0, 4 and every 12 weeks
dose:	Placebo: NA - ustekinumab: 45 or 90mg
mode of administration:	subcutaneous
Duration of treatment:	40 weeks
Endpoints	Primary Endpoints: - Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16, - Achievement of a sPGA score of clear or almost clear at Week 16, Key Secondary Endpoints - Achievement of ≥ 75% reduction from baseline PASI score (PASI 75) at Week 12, - Achievement of a sPGA score of clear or almost clear at week 12, - Achievement of 100% reduction from baseline PASI score (PASI

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	100) at Week 16, - Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 52, - Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 52, - Change from baseline in psoriasis symptoms evaluated using the total score on the Psoriasis Symptoms Scale (PSS) at Week 16, - Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16, - Achievement of total score on the PSS of 0 at Week 16.
Safety criteria:	Physical examination, vital signs, 12-Lead ECG, Laboratory tests, Adverse events, serious adverse event, and local tolerability
Statistical methods:	Co-primary analysis: The achievement of PASI 90 and sPGA of clear or almost clear at Week 16 are the co-primary endpoints and are binary variables 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 weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1) with weights proposed by Greenland & Robins. Secondary analysis: The same methods for the primary analyses will be used to analyse all binary secondary. Change from baseline in PSS at Week 16 will be analysed by the van Elteren test between the BI 655066 arm and placebo arm. All hypotheses will be tested in a hierarchical order using two-sided tests with a type I error of 0.05

FLOW CHART

Trial Periods	Screening	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 -7	1	28	56	84	112	154	196	238	280	322	364	392
Visit window (days)	na	0	±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												
Psoriasis arthritis history	X												
CASPAR[1]	X												
In-/exclusion criteria	X	X											
% BSA involvement	X	X											
Height	X												
Body weight and 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[4]	X[4]	X	X	X	X	X	X	X	X	X	X
AEs/Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection screening	X											X	
Pregnancy testing (prior each dosing)[5]	X	X	X			X		X		X	X	X	X
Safety laboratory tests[6]	X	X		X		X		X		X		X	
12 lead-ECG	X	X	X			X		X		X		X	
Blood sampling for PK[7]		X	X		X	X		X	X	X		X	
ADA sampling[7]		X	X			X		X		X		X	
Biomarkers sampling[8]		X	X			X		X		X		X	
Local tolerability			X	X	X	X	X	X	X	X			
PASI / sPGA	X	X	X	X	X	X	X	X	X	X	X	X	
NAPSI / PPASI / PSSI		X				X						X	
PSS daily take home[9,10]		X	X	X	X	X							
PSS during clinic visit[9,10]							X	X	X	X	X	X	
DLQI / EQ-5D-5L / HADs[10]		X			X	X						X	
ePRO device training		X											
HAQ-DI / pain VAS / pat. global assessment VAS[10, 11]		X				X		X				X	
Joint Count / DAS 28[11]		X				X		X				X	
Optional DNA banking		X											
Optional skin Photographs[12]		X	X	X	X	X						X	
Randomization via IRT		X											
Contact IRT	X	X	X			X		X		X		X	
Study drug administration		X	X			X		X		X			
Termination of trial med.[13]										X			
Trial completion[14]												X	X
Open label extension[15]												X	
Vital status[16]													X

Footnotes:

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 10.6.
2. Refer to Section 5.3.1 for weight and waist circumference procedure.
3. Physical examination: C=complete, T=targeted. Refer to Section 5.3.1.
4. Measurement of 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 and 60 minutes post-dose at Visit 2 and Visit 3. Monitor for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered at Visit 2 and 1 hour following all other doses of study drug.
5. Serum pregnancy testing 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 each Follow-Up (FU) Visit.
6. 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.
7. On dosing visits, PK and ADA sampling should be taken approximately within 1 hour prior to administration of study drug.
8. Biomarker sampling should be done prior to administration of study drug at dosing visits. Refer to Section 5.5.
9. At Visit 2 patient must be trained on the take home electronic device to be used for daily completion of the PSS from Visit 2 through Visit 6. PSS will be completed by the patient during clinic visits from Visit 7 through FU2/EOO Visit.
10. Refer to Section 6.2 and Appendix 10.7 for instructions and further details on administering electronic PROs (patient reported outcomes).
11. At selected study sites, patients diagnosed with PsA by CASPAR criteria will perform PsA assessments as detailed in Appendix 10.6.
12. Optional psoriasis skin lesions photographs. Refer to the procedure in the ISF.
13. Patients that terminate trial medication (med.) early should remain in the trial if possible and complete all remaining Treatment Period, 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.
14. Patients who finish the randomized treatment period, will complete either of the follow-up visit schedules dependent on OLE (Open Label Extension) trial participation (refer to Section 6.2.3):
    - Not participating in OLE: FU1, FU2/EOO, FU3/EOO (final 1311.28 visit), or
    - Participating in OLE: FU1, FU2/EOO (final 1311.28 visit), enter OLE trial
15. Patients who have completed the study without early treatment discontinuation and who meet the eligibility criteria will be offered to participate in an OLE trial. Refer to Section 6.2.3 and ISF.
16. For randomized patients leaving the study before the planned EOO, their vital status should be collected at Week 56.

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ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area Under the Curve
BI	Boehringer Ingelheim
BSA	Body Surface Area
CA	Competent Autority
CASPAR	ClASsification of Psoriatic Arthritis
CI	Confidence Interval
Cmax	maximal Concentration
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CTCAE	Common Terminology Criteria for Adverse Events
CTMF	Clinical Trial Master File
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardivascular
DILI	Drug Induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
ECG	ElectroCardioGram
eCOA	electronic Clinic Outcome Assessments
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EOO	End Of Observation
EOT	End Of Treatment
EQ-5D-5L	EuroQoL 5 Dimensions 5 Level
ePRO	electronic Patient Reported Outcome
Eu	European Union
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire Disability Index
HOMA	Homeostatis Model Assessment
HPC	Human Pharmacology Centre
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IC	Inhibitory Concentration
ICH	International Conference on Harmonisation
IgG	Immunoglobulin G
IL	Interleukin

IP	Interphalangeal
IQR	Interquartile Range
IRB	Institutional Review Board
IRT	Interactive Response System
ISF	Investigator Site File
i.v.	Intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LOCF	Last Observation Carried Forward
mAb	monoclonal Antibody
MACE	Major Adverse Cardiovascular Event
MedDRA	Medical Dictionary for Drug Regulatory Activities
MST	Medical Subteam
NA	Not applicable
Nab	Neutralizing Antibody
NAPSI	Nail Psoriasis Severity Index
NOAEL	No Observed Adverse Effect Level
NRI	No Response Imputation
OLE	Open Label Extension
OPU	Operative Unit
PASI	Psoriasis Area and Severity Index
Pbo	Placebo
PD	Pharmacodynamic
PK	Pharmacokinetic
p.o.	per os (oral)
PoCC	Proof of Clinical Concept
PRO	Patient Reported Outcome
PPASI	Palmoplantar Psoriasis Area Severity Index
PPD	Purified Protein Derivative
PSA	Psoriatic Arthritis
PSD	Psoriasis Symptom Diary
PSS	Psoriasis Symptom Scale
PSSI	Psoriasis Scalp Severity Index
q.d.	quaque die (once a day)
RCTC	Rheumatology Common Toxicity Criteria
RDC	Remote Data Caprure
REP	Residual Effect Period
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAF	Safety Set
s.c.	Subcutaneous
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating procedure
sPGA	Static Physician Global Assessment
SUSAR	Suspected Unexpected Serious Adverse Reactions

TB	Tuberculosis
TMW	Trial Medical Writer
TNF	Tumor Necrosis Factor
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of Normal
UVA	Ultraviolet A
UVB	Ultraviolet B
VAS	Visual Analog Scale
Wk	Week

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 recognized 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 (etanercept, adalimumab) 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, (R11-1547) 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 IL12/23 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. BI 655066 is a humanized 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 at least 75% reduction in Psoriasis Area and Severity Index (PASI 75) with no safety concerns (c02434648).

A 48 week Phase II dose ranging trial of BI 655066 versus ustekinumab indicates a 37% greater improvement for BI 655066 (90 mg and 180 mg, pooled data) compared to ustekinumab in the proportion of patients achieving 90% reduction in PASI (PASI 90) at week 12. We propose the current trial to establish the safety and efficacy of BI 655066 in larger numbers of patients over a longer duration of treatment.

1.2 DRUG PROFILE

BI 655066 is a fully humanized monoclonal antibody (mAb) of the IgG1 subclass directed towards IL-23p19. The antibody has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity. BI 655066 binds with high affinity to human IL-23 and inhibits IL-23 stimulated IL-17 production at IC 50 concentrations below 10 pM, as compared with 167 pM for ustekinumab in the same system. BI 655066 does not affect IL-12

at a maximum tested concentration (33 nM) and it does not inhibit IL-12 stimulated IFN-γ production.

The toxicology data suggest BI 655066 can be safely administered to humans, as supported by chronic administration to monkeys for up to 26 weeks. The monkey was identified as the most relevant toxicology species with a NOAEL of 50 mg/kg/dose, corresponding to an exposure (combined sex) of 677 µg/mL for the C_{max} and 86,250 µg*h/mL for AUC0-168, respectively.

BI 655066 has been studied in approximately 200 patients with psoriasis without any unexpected adverse events or signal of a safety issue. Based on the efficacy and safety findings in the completed and ongoing studies, the risk benefit profile of BI 655066 is appropriate for initiation of Phase III studies. 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. The severity of AEs did not appear related to the dose of BI 655066. Injection site reactions were reported in 2/18 patients receiving BI 655066 i.v., in 1/6 patients receiving placebo i.v. and in none of the patients receiving BI 655066 or placebo s.c.

In patients receiving BI 655066 either i.v. (n=18) or s.c. (n=13), 87% achieved at least 75% reduction in Psoriasis Severity and Area Index (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.

After a single i.v. administration, BI 655066 geometric mean AUC0–inf ranged from 2.93–1650 day*µg/mL and Cmax from 0.311–110 µg/mL, with exposure increasing in a dose-proportional manner. Group mean clearance and terminal phase volume of distribution were 0.33 L/day and 10.8 L, respectively. PK parameter variability, expressed as gCV (%) was <50%. After a single s.c. administration of BI 655066, maximal exposures were reached between 5–13 days and subcutaneous bioavailability was 73% (expressed as the ratio of geometric mean dose normalized AUC0–inf after s.c. and i.v. administration).

For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB, c01569420-06) 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 affecting 2% of the world population with significant impact on patient quality of life and associated with significant systemic disease. IL-23 plays a key role in the pathophysiology of psoriasis through induction and maintenance of Th-17 type cells that secrete inflammatory cytokines. BI 655066 is a humanized monoclonal antibody that specifically neutralizes the IL-23axis. 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 at least 75% reduction in Psoriasis Area and Severity Index (PASI 75) with no safety concerns (1311.1, c02434648).

The current trial is being performed to assess the safety and efficacy of BI 655066 to support registration 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 BI 655066 compared to ustekinumab and 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 addition, 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 gene and protein expression levels and disease specific protein markers.

The signs and symptoms of psoriatic arthritis will be evaluated in a subset of patients to assess if there is improvement during the trial.

Lastly, the influence of study treatment on some metabolic risk factors will be evaluated.

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 adverse events reported in these trials were mild symptoms of the upper respiratory tract, including nasal stuffiness, sore throat, and influenza, and headache, that showed no dose dependency. These events were not considered to be related to drug treatment. Local reactions following subcutaneous administration of BI 655066 were uncommon, and limited to redness, swelling or induration at the injection site. No serious drug related adverse events were reported.

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 a positive QuantiFERON®-test or a positive PPD (purified protein derivative) skin test for tuberculosis must fulfill entry criteria as specified in Section 3.3.3, item 7. 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-IL12/23 mAb ustekinumab has not suggested significant risk for cancer/serious infection. Patients will be monitored for signs and symptoms of malignancy at each visit.

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. While the likelihood of increased MACE 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 a 20% (1 in 5) chance in being randomized to the placebo arm. Patients assigned to placebo will have a low rate of response. These patients will be crossed over to active BI 655066 treatment at Week 16 of study participation. 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 or introduce any risk. 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 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.

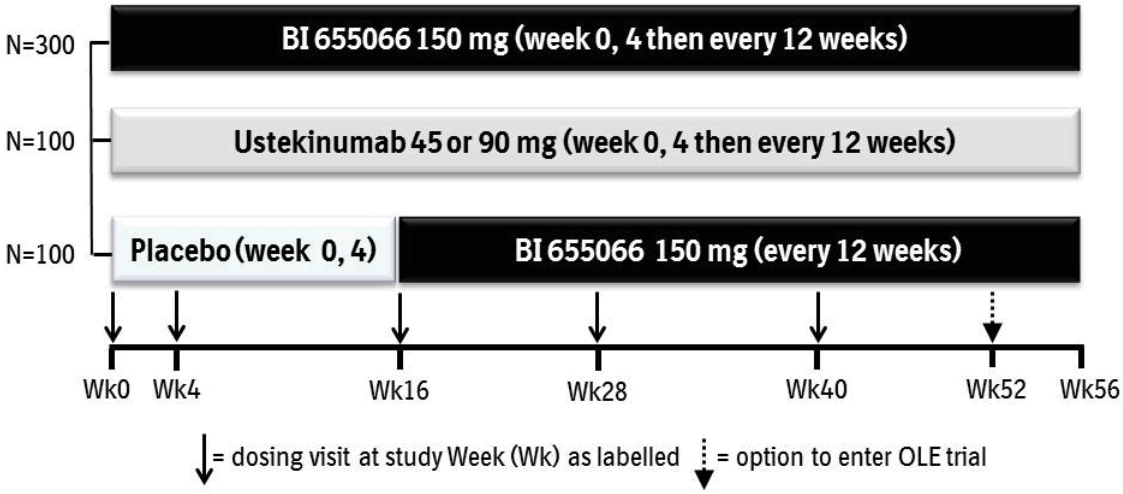
3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This confirmatory multi-national, randomized, double-blind, double dummy, placebo and active comparator controlled, parallel design study compares BI 655066 with ustekinumab and placebo. In total, approximately 500 patients with moderate to severe chronic plaque psoriasis will be randomized in this trial.

Patients are included in the study 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 randomized at a ratio of 3:1:1 to one of 3 treatment arms shown in Figure 3.1: 1. Randomization will be stratified 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. The end of the trial is defined as "last patient out", i.e. last scheduled visit completed by last patient.

Patients will be offered to roll over into an OLE trial, if they have completed the study and meet the inclusion criteria for OLE trial.

Patients who will not participate in the OLE 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 Abbvie in the USA and Boehringer Ingelheim (BI) ex-US. Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the material as needed for the trial, and,
- 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 centers participating in this multicenter 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 clinic outcome assessments (eCOA) and IRT (interactive response technology) will be used in this trial. Details will be provided in the applicable manuals available in the ISF.

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

A list of responsible persons and relevant local information (as protocol reference, if applicable) can be found in the ISF.

3.1.2 Data Monitoring Committee (DMC)

A data monitoring committee (DMC), independent of the Sponsor will be established to assess the progress of the clinical trial, including unblinded safety assessments 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

An independent adjudication committee will be used to adjudicate all observed cardio- and cerebro-vascular and thrombotic events reported during the conduct of the study to assure consistent assessment of Major Adverse Cardiovascular Events (MACE).This review will be blinded to treatment allocation; the events that are to be 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 randomized, double blind, double dummy, placebo and active comparator controlled, parallel design study. This trial design is appropriate for assessing the safety and efficacy of BI 655066 compared to placebo and ustekinumab 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 (see Section 2.3). In order to facilitate patient participation, the trial design will allow patients initially assigned to placebo to receive active treatment. Thus, only adverse events reported during the first 16 weeks of the trial can be directly compared to placebo. In this trial, patients who are considered to be BI 655066 or ustekinumab responders will be followed for a total of 56 weeks or, if participating in the OLE trial, 52 weeks in order to assess the safety and maintenance of efficacy of BI 655066 compared to ustekinumab.

The active comparator, ustekinumab, is commonly accepted as an efficacious psoriasis treatment with an acceptable safety profile and has approval in many countries.

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 500 patients will be randomized in the current trial. A sufficient number of patients will be screened to meet this randomized goal. Patients will be recruited at multiple investigative sites in multiple countries. Recruitment will be competitive.

A log of all patients enrolled into the trial (i.e. signed informed consent) will be maintained in the ISF at the investigational sites whether these patients 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, defined as ≥ 10% BSA involvement, PASI score ≥ 12 and sPGA score ≥ 3.

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

3.3.2 Inclusion criteria

1. 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 sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

2. Age ≥ 18 years at screening,
3. 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,
4. Have stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis at both Screening and Baseline (Randomization):
    a. Have an involved BSA ≥ 10% and,
    b. Have a PASI score ≥ 12 and,
    c. Have a sPGA score of ≥ 3.
5. Must be candidate for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator,
6. Must be a candidate for treatment with Stelara® (ustekinumab) according to local label.
7. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local 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. Previous exposure to ustekinumab (Stelara®),
5. 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,
6. Major surgery performed within 12 weeks prior to randomization or planned within 12 months after screening (e.g. hip replacement, aneurysm removal, stomach ligation),
7. Known chronic or relevant acute infections including active tuberculosis, HIV or viral hepatitis; QuantiFERON® TB test or PPD skin test will be performed according to local labelling for comparator products. If the result is positive, patients may participate in the study if further work up (according to local practice/guidelines)

establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is established, then treatment should have been initiated and maintained according to local country guidelines,

8. 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,
9. 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,
10. History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients,
11. Women who is pregnant, nursing, or who plans to become pregnant while in the trial,
12. 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 non-compliance, 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 study treatment or study 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, adverse events, other diseases, or pregnancy),
- Development of a toxicity or adverse event which warrants BI 655066 discontinuation including but not limited to SAEs or SUSARs
- If prohibited treatment is used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment,
- If a 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.

Of note: Discontinuation of study medication should not necessarily 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 5.3.7 for instructions on treatment termination.

Patients who discontinue the trial after receiving the first dose of study medication at Visit 2 will not be replaced.

For randomized patients leaving the study before the planned EOO, their vital status should be collected at Week 56.

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

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site,
2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial, or any other administrative reasons, i.e. problems with availability of the study medication, discontinuation of development of BI 655066,
3. Violation of 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 TREATMENTS TO BE ADMINISTERED

Multiple doses of BI 655066, placebo to match BI 655066, ustekinumab, and/or placebo to match ustekinumab will be administered subcutaneously. All products will be supplied by Boehringer Ingelheim.

4.1.1 Identity of BI investigational products and comparator 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 prefilled with 0.87 mL. Dispensed volume is 0.83 mL.
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Not applicable

Table 4.1.1: 2 Description of test product placebo to BI 655066 (Cont.)

Molecular weight	Not applicable
Unit Strength:	Not applicable
Route of administration:	Subcutaneous injection
Posology:	Week 0 and Week 4 for placebo arm or Week 0, Week 4, then every 12 weeks for ustekinumab group
Duration of use:	4 weeks for placebo arm or 40 weeks for ustekinumab group

Table 4.1.1: 3 Description of test product ustekinumab

Substance:	Ustekinumab (Brand name: Stelara®)
Pharmaceutical form:	Water for injection, sucrose, L-histidine, L-histidine monohydrochloride monohydrate, polysorbate 80, presented in a 0.5 mL or 1 mL pre-filled syringe. Dispensed volume is 0.5 mL or 1 mL.
Source:	Janssen-Cilag
Chemical form:	Anti-human IL-12/23 mAb
Molecular weight	148 to 149 kDa
Unit Strength:	45 mg or 90 mg ustekinumab 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: 4 Description of test product placebo to ustekinumab

Substance:	Placebo to match Ustekinumab
Pharmaceutical form:	0.9% sodium chloride solution presented in a 0.5 mL or 1 mL pre-filled syringe. Dispensed volume is 0.5 mL or 1 mL.
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Not applicable
Molecular weight	Not applicable

Table 4.1.1: 4 Description of test product placebo to ustekinumab (Cont.)

Unit Strength:	Not applicable
Route of administration:	Subcutaneous injection
Posology:	1 dose at Week 0, Week 4, then every 12 weeks
Duration of use:	40 weeks

4.1.2 Method of assigning patients to treatment groups

Through the utilization of IRT, patients will be randomized to receive BI 655066, ustekinumab or placebo in a ratio of 3:1:1.

After the eligibility criteria are confirmed, the investigator or designee will randomize 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.

4.1.3 Selection of doses in the trial

The dose selection strategy for phase III involved analyses of data from the completed phase I study (Trial 1311.1, c02434648) the ongoing phase II study (Trial 1311.2, c03272682) and PK-PD modelling of all available data from phase I and II.

The phase I and phase II data demonstrated an exposure-response relationship for BI 655066 where doses less than 0.25 mg/kg (intravenously or subcutaneously) were associated with lower clinical efficacy (assessed as decrease from baseline in the PASI score) while doses greater than 1.0 mg/kg achieved near maximal efficacy.

This exposure-response relationship was confirmed in the Phase II study where the 18 mg single injection of BI 655066 (approximately equivalent to 0.25 mg/kg in a 90 kg patient) had the lowest efficacy, while the 90 mg dose (approximately equivalent to 1 mg/kg) given at 0, 4 and 16 weeks had considerably higher efficacy (90% reduction in PASI achieved in 73.2% versus 32.6%, $p < 0.01$). Thus the dose-response (range) from 0.25 to 1.0 mg/kg identified in the phase I trial was roughly replicated in the phase II trial.

Furthermore, the 180 mg dose of BI 655066 was associated with a numerically higher proportion of patients achieving PASI 90, compared to the 90 mg dose (81.0% versus 73.2%). Although not statistically significant, this improved efficacy was noted in every endpoint (PASI 90, PASI 100 and sPGA) at each time point and was not associated with a safety issue.

PK-PD Modelling to Support Dose Selection:

A semi-mechanistic, indirect response PK-PD model was developed using available PK and PASI data across all currently available 1311.1 and 1311.2 PASI time course data. Similar PK-PD models for efficacy have been utilized across many development programs in

psoriasis A model-based assessment of exposure versus safety response was not currently feasible, as no dose-dependent AEs have been observed currently.

The current PK-PD modelling results indicate BI 655066 pharmacokinetics are linear with respect to time and dose, and are comparable to other IgG monoclonal antibodies binding soluble targets. PASI pharmacodynamics reflect endogenous psoriatic plaque formation rate similar to the reported literature values. The half-maximal inhibition (IC_{50}) concentration in the range of 1 ng/mL confirms the high (in vivo) potency of BI 655066.

The PK-PD modelling confirmed the conclusions of the clinical data that 180 mg provided optimal efficacy, defined at least 70% of patients achieving PASI 90. Doses above 180 mg were also modelled and these results indicated minimal improvements (<5%) in the proportion of patients achieving PASI 90. For example a dose of 300 mg was predicted to yield a PASI 90 at Week 12 of 71% (63 – 78%) compared to 68% (61 -76%) for 180 mg. The modelling also predicted that inclusion of the additional dose at Week 4 ("loading dose") would provide higher PASI 90 response rates at earlier time points e.g. Week 12 and Week 16 compared to regimens without this additional dose.

The model was also used to examine alternative dosing regimens, both longer (i.e. every 16 weeks) or shorter (i.e. every 8-week) dosing intervals. Compared to every 12 weeks dosing, decreases in efficacy were predicted when the 16 week dosing interval was examined, while increasing the dosing frequency to every 8 weeks provided only minor improvement in efficacy, i.e. 3-5% increase in the proportion of patients achieving PASI 90. Finally, the modelling predicts that at a dose of 180 mg administered at Weeks 0, 4 and 16 the effect of body weight on PASI response rates was minimal, when this covariate was included as part of the PK model.

In addition to the observed clinical data (safety and efficacy) and PK-PD modelling, the final dose selection for Phase III was influenced by formulation and patient acceptability factors. The highest concentration of BI 655066 that can be formulated in 1 mL (and thus administered with a single injection) is 150 mg. Given that administration involving more than one injection on an ongoing basis could limit patient acceptability, modelling was used to predict PASI responses for a 150 mg dose administered at Weeks 0, 4 and every 12 weeks thereafter.

PK-PD analyses indicated no relevant reduction in efficacy when the dose was changed from 180 mg to 150 mg (based on interpolation). In summary, taking into consideration expert advisor recommendation and prescriber preferences, the proposed dosing for BI 650666 in the upcoming phase III trials is 150 mg at weeks 0 and 4, followed by every 12 weeks. This regimen is anticipated to provide a favorable risk-benefit profile with a dosing schedule that is consistent with standard clinical practice.

In this trial the 150 mg dose will be administered as two prefilled syringes of 75 mg active drug each, as the 150 mg/mL formulation of BI 655066 is still being developed.

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. At visits where study medication is to be administered, study sites will be required to complete the medication resupply module in the IRT. These visits are specified in the Flow Chart.

At randomization 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/dummy fashion with each patient receiving 2 injections of BI 655066 or matching placebo and 1 injection of ustekinumab or matching placebo for a total of 3 injections at each dosing visit. The dose of ustekinumab is weight dependent and will be administered at the dose recommended in the prescribing information. Syringes will be administered per Flow Chart schedule as assigned by IRT.

The injections at each visit, including dummy injections of placebo necessary in order to assure blinding are presented in 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. Injections should be at least 2 cm 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 3 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 Arm	Ustekinumab Arm	Placebo Arm
Day 1 (Visit 2)	active BI 655066 placebo ustekinumab	placebo BI 655066 active ustekinumab	placebo BI 655066 placebo ustekinumab
Week 4 (Visit 3)	active BI 655066 placebo ustekinumab	placebo BI 655066 active ustekinumab	placebo BI 655066 placebo ustekinumab
Week 16 (Visit 6)	active BI 655066 placebo ustekinumab	placebo BI 655066 active ustekinumab	active BI 655066 placebo ustekinumab
Week 28 (Visit 8)	active BI 655066 placebo ustekinumab	placebo BI 655066 active ustekinumab	active BI 655066 placebo ustekinumab
Week 40 (EOT Visit)	active BI 655066 placebo ustekinumab	placebo BI 655066 active ustekinumab	active BI 655066 placebo ustekinumab

[1] Each patient will receive a total of 3 injections per dosing visit.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

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 randomized treatment assignments until after database lock.

The randomization code will be kept confidential by Clinical Trial Support up to database lock.

The randomization codes will be provided to bioanalytics prior to last patient out to allow for the exclusion from the analyses of pharmacokinetic (PK) samples taken from placebo patients. Bioanalytics will not disclose the randomization 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.

Due to the requirements to report SUSARs, it may be necessary for a representative from BI's drug safety group to access the randomization code for individual patients during study conduct via the IRT system. In such cases, access to the code will only be permitted by authorized drug safety representatives.

Refer to Section 4.1.5.2 for rules of breaking the blinding code for an individual or for all patients in emergency situations.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the investigator / pharmacist / investigational drug storage manager 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. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.

4.1.6 Packaging, labelling, and re-supply

BI 655066 and ustekinumab and placebo supplies will be provided by Boehringer Ingelheim Pharma GmbH & Co KG, Biberach, Germany (see Section 4.1.1 for more details). Pre-filled syringes of study medication will be provided in individual boxes identified with the trial number, batch and medication number. Supply of study medication will be managed by the IRT.

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 authorized personnel as documented in the trial staff list.

4.1.8 Drug accountability

Drug supplies will be provided by the sponsor.

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

- Approval of the trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the curriculum vitae of the principal investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the principal investigator,
- Availability of Form 1572 (only for US sites).

All unused medication must be returned to the sponsor. Receipt, usage, and return must be documented. Account must be given for any discrepancy. Used medication will be destroyed per local guidelines.

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

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

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 adverse events 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 neither before nor during trial participation
briakinumab, secukinumab (Cosentyx®),	6 months prior to randomization
brodalumab, ixekizumab	4 months prior to randomization
adalimumab (Humira®), infliximab (Remicade®) investigational products for psoriasis (non biologics)	12 weeks prior to randomization
etanercept (Enbrel®) live virus vaccinations	6 weeks prior to randomization
any investigational device or product (excludes psoriasis products) other systemic immunomodulating treatments (e.g. methotrexate, cyclosporine A, corticosteroids[1], cyclophosphamide) , tofacitinib (Xeljanz®), apremilast (Otezla®) other systemic psoriasis treatments (e.g. retinoids, fumarates, any other drug known to possibly benefit psoriasis) photochemotherapy (e.g., PUVA).	30 days prior to randomization
phototherapy (e.g., UVA, UVB) topical treatment for psoriasis or any other skin condition (e.g. corticosteroids[2], vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, andanthralin, α-hydroxy, fruit acids)	14 days prior to randomization

[1] No restriction on corticosteroids with only a topical effect (e.g. inhalative corticosteroids to treat asthma or corticosteroid drops used in the eye or ear).
[2] Exception: Topical steroids of US class 6 (mild, such as desonide) or US class 7 (least potent, such as hydrocortisone) for use on the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to trial visit in which 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 authorized study personnel (e.g. study nurse). The measured plasma concentrations will provide additional information about compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

None of the primary and secondary endpoints are considered safety issues.

5.1.1 Primary Endpoints

There are co-primary endpoints to assess the efficacy of BI 655066 for the treatment of moderate to severe chronic plaque psoriasis. These are as follows:

- Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16
- Achievement of an sPGA score of clear or almost clear at Week 16

At the trial level, the co-primary endpoints will be the proportion of patients achieving PASI 90 and a sPGA score of clear or almost clear at Week 16 in each of the treatment groups.

5.1.2 Secondary Endpoints

Key Secondary Endpoints:

The key secondary endpoints are as follows:

- Achievement of ≥ 75% reduction from baseline PASI score (PASI 75) at Week 12,
- Achievement of a sPGA score of clear or almost clear at week 12,
- Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16,
- Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 52,
- Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 52,
- Change from baseline in psoriasis symptoms evaluated using the total score on the PSS at Week 16,
- Achievement of a DLQI score of 0 or 1 at Week 16,
- Achievement of total score on the PSS of 0 at Week 16.

Other Secondary Endpoints:

The secondary endpoints are as follows:

- Achievement of ≥ 75% reduction from baseline PASI score (PASI 75) at Week 16,
- Achievement of a sPGA score of clear or almost clear at Week 52,
- Achievement of PASI 75 at Week 52.

5.1.3 Further Endpoint(s)

The further endpoints are as follows:

- Achievement of PASI 50 at all visits collected,
- Achievement of PASI 75 at all visits collected,
- Achievement of PASI 90 at all visits collected,
- Achievement of PASI 100 at all visits collected,
- 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 and percent change from baseline in PASI at all visits collected,
- Absolute PASI of < 3 at all visit collected,
- Achievement of a sPGA score of clear or almost clear at all visits collected,
- Achievement of a sPGA score of clear at all visits collected,
- Change from baseline in total score of the PSS at all visits collected,
- Achievement of PSS total score of 0 at all visits collected,
- Change from baseline in DLQI at all visits collected,
- Achievement of a DLQI score of 0 or 1 at all visits collected,
- Achievement of a reduction of 5 or more points from baseline in DLQI score at all visits collected,
- Change from baseline in HADs at all visits collected,
- Change from baseline in HAQ-DI at all visits collected, in patients selected for PsA assessment,
- Change from baseline in swollen or tender joint count (28 joints) at all visits collected, in patients selected for PsA assessment,
- DAS (Disease Activity Score) 28 at all visits where HAQ-DI and swollen or tender joint count collected, in patients selected for PsA assessment,
- Change and percent change from baseline in Nail Psoriasis Severity Index (NAPSI) at all visits collected,
- Change and percent change from baseline in Palmoplantar Psoriasis Severity Index (PPASI) at all visits collected,
- Change and percent change from baseline in Psoriasis Scalp Severity Index (PSSI) at all visits collected,
- Change of metabolic risk factors from baseline (waist circumference, body weight, HOMA-index).

5.2 ASSESSMENT OF EFFICACY

The skin condition will be assessed by using the PASI, sPGA, and other relevant scores as described in Section 5.1.1 and the ISF.

Symptoms, quality of life and physical function will be assessed by PSS, DLQI and, if selected for PsA assessments, HAQ-DI.

Details of the efficacy assessments are listed in the Appendix 10.

5.3 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events,
- Serious adverse events,
- Clinical laboratory values (hematology, clinical chemistry and urinalysis),
- Intensity of adverse events will be assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to ISF for details).

5.3.1 Physical examination

Complete and target physical examinations will be performed at visits as described in the Flow Chart. Complete physical examination will include vital sign assessment and general appearance as well as evaluation of all relevant organ systems. Targeted physical examination will include vital sign assessment and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

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

5.3.1.1 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 temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least five minutes. 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 (5minutes after last injection) and 60 minutes post-dose.

Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at Visit 2 and and approximately 1 hour after the last injection at all other visits 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 at 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 normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria (R13-3515).

Table 5.3.3:1 Laboratory tests

Category	Test name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hbc (HbA1c) Red Blood Cell Count/ Erythrocytes Reticulocyte Count White Blood Cells / Leukocytes Platelet Count/ Thrombocytes
Diff. 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)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen

Table 5.3.3:1 Laboratory tests (Cont.)

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) Lipase Amylase
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 HOMA-IR (only at Visit 2,Visit 6, and EOT Visit)
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 T3 and T4 in case of abnormal TSH)
Autoantibodies (only at screening)	Rheumatoid Factor
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

Table 5.3.3:1 Laboratory tests (Cont.)

Urine	Albumin (quantitative) Creatinine Albumin/creatinine ratio
Infections screening	Hepatitis B Surface Antigen (qualitative)[1] Hepatitis C Antibodies (qualitative)[1] HIV-1, and HIV-2 Antibody (qualitative)[1] QuantiFERON®-TB[2]

[1] Hepatitis B, hepatitis C and HIV testing will only be performed at FU2/EOO Visit.
[2] TB testing will only be performed at screening and FU2/EOO Visit. QuantiFERON® or PPD skin test may be performed. PPD test is site option that will not be provided or performed at central lab.

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 that 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 patient 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.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which:

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- 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 jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context 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.

AEs considered "Always Serious"

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

The latest list of "Always Serious AEs" can be found in the RDC. These events should always be reported as SAEs.

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, see Section 5.3.7.

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 $\geq$3 fold ULN combined with an elevation of total bilirubin $\geq$2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations $\geq$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 and the RDC-system.

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 the ISF for intensity/severity classification. Intensity options are:

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

Causal relationship of AEs

Medical 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.

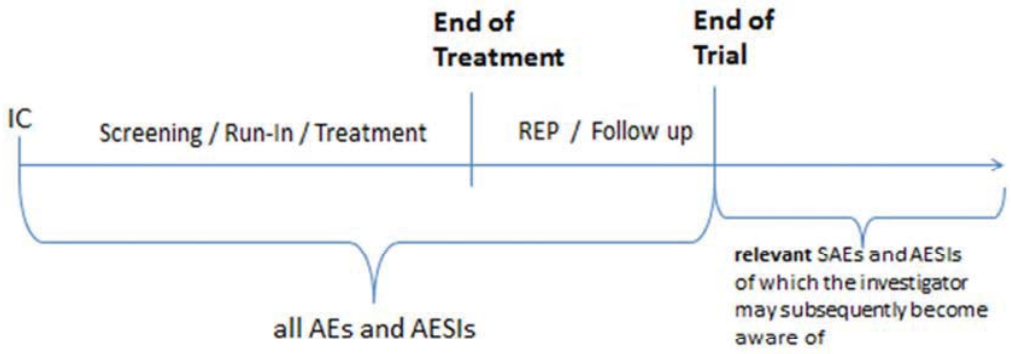
Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.

5.3.7 Adverse event collection and reporting

AE Collection

The following must be collected and documented on the eCRF by the investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP), until the end of a patient's trial participation, all AEs (serious and non-serious) and all AESIs.
- After the end of an individual patient's trial participation the investigator dos 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.



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.

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 (e)CRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The investigator should determine the causal relationship to the trial medication.

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

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

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

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

Screening failures:

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

Pregnancy:

In the rare case that a female subject participating in this clinical trial becomes pregnant after having taken trial medication, the investigator must report immediately (within 24 hours) the drug exposure during pregnancy (DEDP) to the Sponsor's unique entry point (country-specific contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

If a patient becomes pregnant during a trial, the study medication needs to be discontinued, and the patient will complete end of treatment as well as follow-up procedures. The patient will be followed up until birth or otherwise termination of the pregnancy.

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

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 will 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 2.5 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 2.5 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).

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 characterized in a validated neutralizing antibody (NAb) assay.

5.4.4 Pharmacokinetic - pharmacodynamic relationship

Refer to Section 7.3.6.

5.5 ASSESSMENTS OF EXPLORATORY 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-2) and S-100 A8 protein over time by treatment group. In addition, changes in levels of biomarkers related to metabolic syndrome such as leptin, resistin, TNFα, IL-6 and VEGF will be explored.

5.5.1.1 Methods of sample collection

Approximately 12.5 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 informed consent for biomarker sample banking is agreed upon by the patient.

Declination to allow collection, 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

Approximately 8.5 mL of blood will be taken at Visit 2. 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 AbbVie or a third party delegate (e.g. Boehringer Ingelheim Pharma GmbH & Co. KG; Birkendorfer Str. 65, 88397 Biberach, Germany. 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

5.6.1 Questionnaires

Patients will complete the EQ-5D-5L (refer to Appendix 10.7.7) at the time points indicated in the flow chart. These data will be analyzed separately and will not form part of the clinical trial report.

5.6.2 Photography of skin lesions

At selected sites, participation is voluntary and not a prerequisite for participation in the trial. Photography of skin lesions will be performed optionally for additional documentation. Front

and back trunk as well as target lesions photographs will be taken preferably as the time-points specified in the flow chart per instructions in the ISF.

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

5.7 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.

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule 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.

PROs 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 PSS will be completed daily on a take home electronic device for Visit 2 through Visit 6. For Visits 7 through FU2/EOO Visit the PSS will be completed during each clinic visit.

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

(1) PSS for in clinic completion (Visit 7 through FU2/EOO)
(2) DLQI
(3) HAQ-DI [if selected for PsA assessments]
(4) Pain VAS [if selected for PsA assessments]
(5) Patient global assessment VAS [if selected for PsA assessments]
(6) HADs
(7) EQ-5D-5L

Timing for downloading the data of PROs will be available in the ISF.

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 have started screening. The patient should be recorded on the enrolment log and be registered in IRT as a screened patient.

Screening (Visit 1) should normally take place no more than 42 days before Visit 2 and be completed no less than 7 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® or PPD skin test for TB.

Demographics
Informed consent date, HIPAA status (US patients only), sex, ethnicity and race (if allowed by local law) 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 labs, and any condition requiring therapy (excluding psoriasis) will be reported on the Baseline Condition eCRF page.

History for Psoriatic Arthritis
At Visit 1, all patients at all sites will be evaluated for history of psoriatic arthritis.

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

For all 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.

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

Psoriasis skin lesions photographs will be taken at Visit 2, 3, 4, 5, 6 and Visit FU1/EOO. For indications, refer to ISF.

Venepuncture (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 randomized 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, Fup1 and Fup Visits. Trial termination should be completed at Fup 2 Visit; Fup 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 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 OLE trial.

6.2.3.2 Trial completion:

Patients who finish the randomised treatment period will return to the clinic for Follow-up 1 (FU1) and FU2 Visits. Trial completion is defined as patients 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 OLE trial.

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

- Patient who will not participate in the OLE study will return to the clinic for FU2/EOO and FU3/EOO Visits. Trial termination will be completed at FU3/EOO. The decision not to enter the OLE will be registered in IRT at FU2/EOO Visit.
- Patients who participate in the OLE will complete FU2/EOO as the final 1311.28 study visit. Trial termination will be completed at FU2/EOO and these registered in IRT.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a confirmatory, multicentre, randomized, double-blind, placebo and active comparator controlled study evaluating the efficacy and safety 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 BI 655066 in comparison to both placebo and ustekinumab in patients with moderate to severe chronic plaque psoriasis.

Baseline refers to the measurement recorded at randomization (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 weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1). Based upon these design considerations and the binary nature of the co-primary endpoints of PASI 90 and sPGA 0 or 1, 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 BI 655066 is superior to placebo in achieving ≥ 90% reduction from baseline in the PASI score (PASI 90) and sPGA score of clear(0) or almost clear(1) at Week 16 in participants with moderate to severe chronic plaque psoriasis. For the primary analyses, this study has 3 treatment arms (BI 655066, ustekinumab, and placebo [see Figure 3.1: 1]).

The following null hypotheses will be tested in a hierarchical order using two-sided tests with a type I error of 0.05. The two co-primary endpoints need to be significant simultaneously, therefore no alpha adjustment is necessary.

1. BI 655066 arm is not different from placebo with respect to PASI 90 or sPGA score of clear(0) or almost clear(1) responses at Week 16
2. BI 655066 arm is not different from ustekinumab with respect to PASI 90 response at Week 16
3. BI 655066 arm is not different from ustekinumab with respect to achieving a sPGA score of clear(0) or almost clear(1) response at Week 16
4. BI 655066 arm is not different from ustekinumab with respect to PASI 75 response at Week 12
5. BI 655066 arm is not different from ustekinumab with respect to achieving a sPGA score of clear(0) or almost clear(1) response at Week 12

6. BI 655066 arm is not different from ustekinumab with respect to PASI 100 response at Week 16
7. BI 655066 arm is not different from ustekinumab with respect to PASI 90 response at Week 52
8. BI 655066 arm is not different from ustekinumab with respect to PASI 100 response at Week 52
9. BI 655066 arm is not different from placebo with respect to mean change from baseline in PSS total score at Week 16
10. BI 655066 arm is not different from placebo with respect to achieving a DLQI score of 0 or 1 at Week 16
11. BI 655066 arm is not different from placebo with respect to achieving a PSS score of 0 at Week 16
12. BI 655066 arm is not different from ustekinumab with respect to achieving a DLQI score of 0 or 1 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 and received at least one dose during the trial; this set of patients is called the Full Analysis Set (FAS). Efficacy analyses will be based on the planned treatment (i.e., the treatment assigned at randomisation). Safety analyses will be based on the actual treatment received at the randomisation visit; this set of patients is called the Safety Set (SAF). All efficacy analyses will be conducted on the FAS. All safety analyses will be conducted on the SAF.

Important violations of the protocol will include key inclusion and exclusion violations, incorrect medications taken, compliance with study medication, concomitant use of restricted medications, and any other violations of the protocol deemed important by the study team. All decisions concerning important protocol violations will be made prior to unblinding of the database. A per-protocol set (PPS) will be defined excluding patients with violations that affect Week 16 efficacy.

The hypothesis tests as described in Section 7.2 will be repeated on the PPS populations.

7.3.1 Primary endpoint analyses

The achievement of PASI 90 at Week 16 is the first co-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 weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1) 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 of $\hat{\delta}_{MH}$ is calculated as:

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

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:

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

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. Pairwise comparisons will include both a p-value and 95% confidence interval.

The achievement of a sPGA score of clear or almost clear at Week 16 is the second co-primary endpoint and is a binary variable with values of 0 or 1. The analysis of the sPGA co-primary endpoint will be identical to that of the PASI 90 co-primary endpoint detailed above.

7.3.2 Secondary endpoint analyses

The same methods as discussed for the primary analyses will be used to analyse all binary secondary. Change from baseline in PSS at Week 16 will be analysed by the van Elteren test between the BI 655066 arm and placebo arm.

7.3.3 Further endpoint analyses

Further endpoints will be summarized 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 that take prohibited meds to treat Psoriasis will be counted as failures at the time when they add the prohibited med.
d) Patients randomized to placebo will have Week 16 (i.e. when they begin taking BI 655066) as Day 0 for determining Time to Loss of response.
e) 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.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard AbbVie summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (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 adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period 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 adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

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.

More information about safety analysis will be provided in the TSAP.

7.3.5 Pharmacokinetic analyses

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

Pharmacokinetic data will be analysed using population pharmacokinetic approaches. For this purpose, data may also be combined with data from other trials.

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 pharmacokinetic (PK)-pharmacodynamic (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, tissue protein and RNA biomarker levels over time will be described by treatment group. The details of these analyses will be included in the TSAP.

7.4 INTERIM ANALYSES

No interim analysis is planned for this study

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 (NRI [No Response Imputation])

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

* Patients that take prohibited medications to treat Psoriasis will be treated the same as those that discontinued from the trial – i.e. subsequent visits following start of prohibited medication will be considered as failure for binary endpoints.

Missing items from the PROs will be handled according to the respective measure instructions (see Section 10). 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 weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1). Patients will be randomised to BI 655066:ustekinumab:placebo in a ratio of 3:1:1 within each level of stratification. 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 ustekinumab in terms of PASI 90 response and achievement of sPGA clear or almost clear at Week 16. Based on the outcome from the trials 1311.1 and 1311.2, the PASI 90 response rate at Week 16 is assumed to be at least 65% in the BI 655066 arm and at most 45% in the ustekinumab arm. Using a 3:1 randomisation scheme (BI 655066:ustekinumab), 300 patients in the BI 655066 arm and 100 in the ustekinumab arm will provide 94% power. See Table 7.7: 1 for more sample size calculations to have at least 90% power.

Table 7.7: 1 Sample sizes for 90% power for testing against an active comparator using PASI 90

Response Rate at Week 16			**Randomisation ratio BI 6550066: Ustekinumab= Total N**
BI 6550066	**Ustekinumab**	**Delta**	**3:1**
65%	45%	20%	255:85 = 340
70%	50%	20%	246:82 = 328
65%	40%	25%	162:54 = 216
70%	45%	25%	159:53 = 212
75%	50%	25%	150:50 = 200
70%	40%	30%	111:37 = 148
75%	45%	30%	105:35 = 140
80%	50%	30%	99:33 = 132

Calculated using ADDPLAN Version 6.0.4

Based on the outcome from the trials 1311.1 and 1311.2, the achievement of sPGA clear or almost clear rate at Week 16 is assumed to be at least 85% in the BI 655066 arm and at most 67.5% in the ustekinumab arm. Using a 3:1 randomisation scheme (BI 655066: ustekinumab 237 patients in the BI 150mg arm and 79 in the ustekinumab arm will provide 90% power. Using the PASI 90 required sample sizes, 300 patients in the BI 655066 arm and 100 patients in the ustekinumab arm will provide at least 95% power for the sPGA endpoint. The lower limit of the overall power for testing the co-primary endpoints is 0.94*0.95 =0.893, however as PASI 90 and sPGA are highly correlated this is an underestimate of the actual power of rejecting both hypotheses. See Table 7.7:2 for more sample size calculations to have at least 90% power.

Table 7.7: 2 Sample sizes for 90% power for testing against an active comparator using sPGA clear or almost clear

Response Rate at Week 16			Randomisation ratio BI 6550066: Ustekinumab= Total N
BI 6550066	**Ustekinumab**	**Delta**	**3:1**
85%	70%	15%	312:104 = 416
85%	67.5%	17.5%	237:79 = 316
87.5%	70%	17.5%	216:72 = 288
85%	65%	20%	186:62 = 248
87.5%	67.5%	20%	171:57 = 228
87.5%	65%	22.5%	141:47 = 188

Calculated using ADDPLAN Version 6.0.4

Thus, the total sample size for this trial is 500 patients (300 in BI 655066, 100 in ustekinumab, and 100 in placebo). Assuming a 5% response rate in the placebo group for both PASI 90 and sPGA clear or almost clear, this trial will have >99% power for comparing the BI 655066 arm to placebo on both of these endpoints. The assumptions used for sample size calculations are based on the current knowledge from the phase I study 1311.1, phase II study 1311.2, and phase III studies of ustekinumab for moderate to severe chronic plaque psoriasis (R11-1519, R13-3519, R13-3513, c03272682).

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs), and 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 patients against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The rights of the investigator and of the Sponsor with regard to publication of the results of this trial are described in the Investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

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

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

Electronic Case Report Forms (e)CRF 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

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

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

An adaptive approach to clinical trial monitoring will be utilized. This is initiated by an assessment of the risk associated with the trial combined with identification of critical data and processes. An Integrated Quality and Risk Management Plan documents the strategies involved with the implementation of onsite, offsite and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to subject safety and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any monitoring adaptations.

8.3.3 Storage period of records

Trial sites:

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

Sponsor:

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

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided.

For the study drug BI 655066 this is the current version of the Investigator's Brochure (c01569420-06). For ustekinumab this is the EU SmPC (R15-5190).

The current versions of these reference documents are provided in the ISF. No AEs are classified as listed for matching placebo, trial design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IEC / IRB

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSAR) to health authorities and IEC / IRB, will be done according to local regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers. Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the Sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.6 END OF TRIAL

The end of the trial is defined as described in Section 6.2.3.

The Last Patient Visit Primary Endpoint is defined as last patient in the trial to complete Visit 6, Week 16 assessments.

The IEC / competent authority in each participating EU member state will be notified about the end or early termination of the trial.

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10. APPENDICES

10.1 PASI SCORE DEFINITION 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 summarized 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 subject'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 (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 NAPSI : NAIL PSORIASIS SEVERITY INDEX

The NAPSI assesses how much of the fingernail is affected with psoriasis with scores ranging from 0 to 80.

If a patient has nail psoriasis, the physician will assess the nail psoriasis at each protocol defined time point. Fingers (5) on each hand will be individually examined for two distinct assessments and are graded as follows:

- Nail Matrix Assessment:
  0 = None
  1 = present in 1 quadrant of nail
  2 = present in 2 quadrants of nail
  3 = present in 3 quadrants of nail
  4 = present in 4 quadrants of nail

- Nail Bed Assessment:
  0 = None
  1 = present in 1 quadrant of nail
  2 = present in 2 quadrants of nail
  3 = present in 3 quadrants of nail
  4 = present in 4 quadrants of nail

The sum of the scores will be added resulting a range of 0 to 80. If an individual finger assessment is missing (not done), the average of the remaining measured digits will be imputed and added to the sum. If < 50% of the finger assessments are missing the imputation will be performed. If more than 50% of the assessments are missing then the sum of the scores will be left as missing.

10.4 PPASI : PALMOPLANTAR PSORIASIS SEVERITY INDEX

The PPASI provides a numeric scoring for psoriasis affecting the hands and feet with scores ranging from 0 to 72. It is a linear combination of percent of surface area of hands and feet that are affected and the severity of erythema, induration, and desquamation.

If a patient has palmoplantar psoriasis, the physician will assess the psoriasis at each protocol defined time point. Both palms and soles on each hand and foot will be individually assessed for erythema, induration, desquamation and percentage of area affected as follows:

- Erythema, Induration and Desquamation:

  0 = None
  1 = Slight
  2 = Moderate
  3 = Severe
  4 = Very Severe

- Percent of Palm and Sole Area Covered:

  0 = Clear
  1 = <10%
  2 = 10-29%
  3 = 30-49%
  4 = 50-69%
  5= 70-89%
  6= 90-100%

The PPASI is a composite score and will be computed for each palm and sole, left and right and is derived from the sum of the scores for erythema (E), induration (I) and desquamation (D) multiplied by the score recorded for the extent of palm and sole area involved.

PPASI is calculated as follows: (sum of scored for E+I+D)*Area *0.2(location:right palm) + (sum of scored for E+I+D)*Area *0.2(location:left palm) + (sum of scored for E+I+D)*Area*0.3(location:right sole) +(sum of scores for E+I+D)*Area *0.3(location:left sole). The range is 0 to 72.

10.5 PSORIASIS SCALP SEVERITY INDEX (PSSI)

If a patient has scalp psoriasis, the physician will assess the erythema (redness), induration (hardness), desquamation (shedding of skin) and percent of scalp covered at each protocol defined time point.

- Erythema, Induration and Desquamation:

  0 = None
  1 = Slight
  2 = Moderate
  3 = Severe
  4 = Very Severe

- Percent of Scalp Covered:

  1 = <10%
  2 = 10-29%
  3 = 30-49%
  4 = 50-69%
  5 = 70-89%
  6 = 90-100%

The PSSI is a composite score derived from the sum of the scores for erythema, induration and desquamation multiplied by the score recorded for the extent of scalp area involved. The range is 0 to 72.

10.6 DIAGNOSIS AND ASSESSMENTS FOR PATIENTS WITH PSORIATIC ARTHRITIS

10.6.1 Visit 1 psoriatic arthritis diagnosis

At Visit 1 at selected study sites, patients with a positive history of PsA or suspected to have PsA will be further evaluated for PsA diagnosis based on CASPAR (ClASsification of Psoriatic Arthritis) 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 10.6.1: 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 10.6.1:1 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

10.6.2 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 10.7.3)
- Pain VAS (refer to Appendix 10.7.4)
- Patient global assessment VAS (refer to Appendix 10.7.5)
- Swollen or tender joint count (28 joints) as listed in Table 10.6.2: 1
- Entry of data for calculation of DAS28 on electronic device (Refer to Appendix 10.6.3)

Visit 6, 8, and FU2/EOO
For patients with swollen or tender joint count (28 joints) ≥ 3 at Visit 2, the following will be performed at Visit 6, Visit 8, and FU2/EOO Visit:

- HAQ-DI, pain VAS, patient global assessment VAS
- Swollen or tender joint count (28 joints)
- Entry of data for calculation of DAS28 on electronic device

Table 10.6.2: 1 Swollen or tender joint count (28 joints)

Joint	Right		Left	
	Tender	Swollen	Tender	Swollen
Shoulder				
Elbow				
Wrist				
MCP1				
MCP2				
MCP3				
MCP4				
MCP5				
IP of the thumb				
PIP of finger 2				
PIP of finger 3				
PIP of finger 4				
PIP of finger 5				
Knee				

Metacarpal-phalangeal (MCP) joints, Interphalangeal (IP) joints, Proximal interphalangeal (PIP) joints Tenderness/swelling will be evaluated as "0" absent or "1" present

10.6.3 DAS 28

DAS 28 will be calculated using the following formula by the electronic device:

- DAS28=0.56*√(tender joint count) + 0.28*√(swollen joint count) + 0.36*Ln(CRP+1) + 0.014*(patient global assessment VAS) + 0.96

For the DAS 28 calculation, the CRP value from laboratory report of current visit will be entered on the electronic device. Data from swollen and tender joint count (28 joints) and patient global assessment VAS will have already been recorded on the electronic device.

10.7 PATIENTS REPORTED OUTCOMES

10.7.1 Psoriasis Symptom Scale (PSS)

The PSS will be self-administered by the patient as a daily diary from Visit 2 through Visit 6 and will be completed by the patient during clinic visits from Visit 7 through FU2/EOO Visit.

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 (PSI) and the Psoriasis Symptom Diary (PSD). 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

10.7.2 Dermatology Life Quality Index (DLQI)

The DLQI is a subject-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 subject's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on subject'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).

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

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.

10.7.3 Health Assessment Questionnaire Index (HAQ-DI)

The HAQ-DI will be self-administered by the patient (for PsA patients at selected sites) 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).

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_____

STANFORD-RA (MAY99 - Phase 31) – English, USA -1- ©Stanford University

HAQ-DI - United States/English
f:\institut\cultadap\project\5008\study5008\questionnaire\original\forproject\haq-di_au1.0-eng-usori.doc-10/12/2008-co

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_____

10.7.4 Pain VAS

The Pain VAS will be self-administered by the patient (for PsA patients at selected sites) at visits indicated in the Flow Chart.

The patient's assessment of pain will be performed using a horizontal 10 cm visual analog scale (VAS), ranging from 0 (no pain) to 100 (severe pain) after the question:

> "How much pain have you had because of your psoriatic arthritis in the past week? Place a vertical (|) mark on the line to indicate the severity of the pain."

10.7.5 Patient Global assessment VAS

The patient global assessment VAS will be self-administered by the patient (for PsA patients at selected sites) at visits indicated in the Flow Chart.

The patient's global assessment of disease activity will be performed using a horizontal 10 cm VAS, ranging from 0 (very well) to 100 (very poor) after the question:

> "Considering all the ways your psoriatic arthritis affects you, how would you rate the way you felt over the past week? Place a vertical (|) mark on the line to indicate how you felt."

10.7.6 EuroQoL 5-Dimension 5-Levels (EQ-5D-5L)

The EQ-5D-5L is a generic measure of health status, which is used for clinical and economic appraisal (R07-1314, R12-1920). The instrument consists of 2 sections - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises the following 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondent is asked to indicate his/her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

The EQ-5D-5L will be self-administered by the patient at visits indicated in the flowchart.

EQ-5D-5L

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

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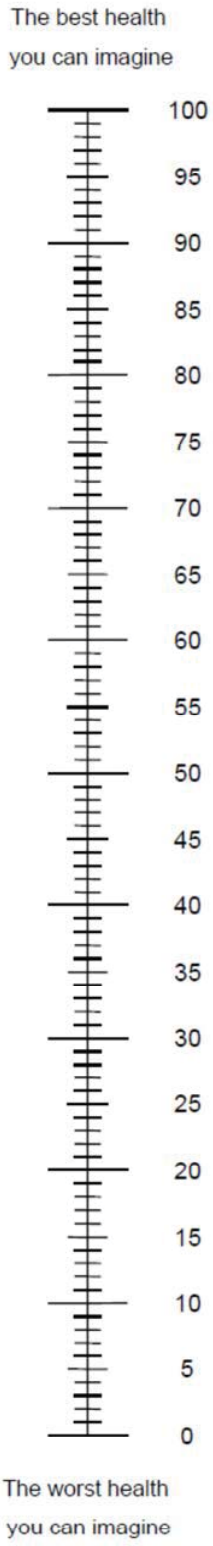
- We would like to know how good or bad your health is

  TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



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10.7.7 Hospital Anxiety and Depression scale (HADs)

The HADs is a self-assessment scale which detects the presence and severity of anxiety and depression in the general population (R02-0127). It contains 14 items and is comprised of anxiety (7 items) and depression (7 items) subscales, which are scored separately and summed to give a total score. Item scores range from 0 (best) to 3 (worst) and total scores are categorized as normal (0-7), borderline abnormal (8-10) and abnormal (11-21). The HADs has been widely used in clinical trials in a variety of disease areas and has extensive evidence to support its acceptability, reliability and validity (R07-1226, R15-3850).

The HADS will be self-administered by the patient at visits indicated in the flowchart.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1.0
Date of CTP revision		24 May 2016
EudraCT number		2015-003622-13
BI Trial number		1311.28
BI Investigational Product(s)		BI 655066
Title of protocol		BI 655066 (risankizumab) versus **U**stekinumab and p**l**acebo comparators in a randomized double blind t**rI**al for **M**aintenance use in **M**oderate to severe plaque type psoriasis-2 (UltIMMa-2)
To be implemented only after approval of the IRB / IEC / Competent Authorities	X	
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		Title Page, synopsis
Description of change		Added risankizumab after BI 655066
Rationale for change		New name added for completeness
Section to be changed		Flow Chart
Description of change		1. ADA sampling added to Week 4, 2. Line item “biologic therapy history” changed to “psoriasis therapy history”, 3. % BSA involvement added as line item, 4. Remove IRT call from Fup 3 Visit, 5. Patient with a positive history of PsA or suspected PsA will be evaluated via CASPAR, 6. Added “approximately” to vital signs time points 7. Replaced criteria for eligibility in the OLE study of “without having missed more than one study treatment” with “without early treatment discontinuation”.

Rationale for change		1. Request from Health Authorities, 2. Clarification, 3. % BSA entry criteria collected on the electronic device was added to Flow Chart as a clarification, 4. Correction to original CTP, 5. Correction to original CTP, 6. Clarification, 7. Correction to original CTP.
Section to be changed		Section 2.3 Benefit-Risk Assessment
Description of change		Removed “prior to receiving BI 655066”
Rationale for change		Clarification to be aligned with entry criteria
Section to be changed		Section 3.1.2 Data Monitoring
Description of change		Clarification on how efficacy data will be used upon submission to the DMC as well as additional information on unblinding
Rationale for change		Clarification
Section to be changed		Section 3.1.3 MACE Adjudication Committee
Description of change		Added “thrombotic events”
Rationale for change		Clarification
Section to be changed		Section 3.3.4.1 Removal of Individual Patients
Description of change		Patients that discontinue study medication should complete all study visits and procedures as initially planned
Rationale for change		Update to original CTP
Section to be changed		Section 4.1.4 Drug assignment and administration
Description of change		Added regions and instructions for subcutaneous injection
Rationale for change		Update to original CTP
Section to be changed		Table 4.2.2.1:1 Restricted Medications
Description of change		1. Added tofacitinib (Xeljanz®) and apremilast (Otezla®), 2. Removed efalizumab (Raptiva) .
Rationale for change		1. Additional medications requiring washout 2. Medication not available
Section to be changed		Section 5.1.3 Further Endpoints
Description of change		Added “absolute PASI of <3 at all visits collected

Rationale for change		Update to CTP
Section to be changed		Section 5.3.2 Vital Signs
Description of change		Added “approximately” to vital signs time points
Rationale for change		Clarification and instructions for subcutaneous injection added
Section to be changed		Table 5.3.3:1 Laboratory tests
Description of change		1 HOMA-IR Visit 6 not at visit 7, 2 Added “test done in clinic” for urine pregnancy test, 3 Added absolute count to the differential manual, 4 Added “Activated” to partial thromboplastin time, 5 Added albumin/creatinine ration to urine section, 6 Specified PPD skin test is not provided or performed by central laboratory.
Rationale for change		1 To be consistent with the flow chart, 2 to 6 Clarification to table text.
Section to be changed		Section 6.2 Details of Trial Procedures at Selected Visits
Description of change		Removed “At visit 2 these questionnaires should be obtained after having the patient randomised”
Rationale for change		To match order of assessments on the electronic device to perform patient reported outcomes first from Visit 2 onwards.
Section to be changed		Section 6.2.1 Screening period
Description of change		1 Removed maximum of 2 visits for screening, 2 Removed “or local tolerability”.
Rationale for change		1 Patients may require more than 2 visits to the clinic during screening, 2 Correction to original CTP.
Section to be changed		Section 6.2.3 Follow-up Period and Trial Completion
Description of change		1. Replaced criteria for eligibility in the OLE study of “without having missed more than one study treatment” with “without early treatment discontinuation”, 2. Patients discontinuing treatment early should continue in the study, 3. Removal of IRT call at FU3 Visit.

Rationale for change		Corrections to original CTP
Section to be changed		Section 7.3 Planned Analysis
Description of change		1. Clarifying the definition of analysis sets, 2. Added definition of iPV and PPS, 3. Added "The hypothesis tests as described in Section 7.2 will be repeated on the PPS populations", 4. Added definition for time to onset of endpoint.
Rationale for change		In response to questions from Health Authorities
Section to be changed		Section 7.3.3 Further endpoint analyses
Description of change		Add the definition of time to event
Rationale for change		Clarification
Section to be changed		Section 7.4 Interim analysis
Description of change		Removed redundant DMC information provided in Section 3 and added "No interim analysis is planned for this study".
Rationale for change		Clarification that no interim analysis is planned.
Section to be changed		Section 7.5 Handling of Missing data
Description of change		Removed sentence that additional information may be included in TSAP and added information on sensitivities analyses.
Rationale for change		Provide additional information concerning primary and secondary endpoints to be pre-defined in the protocol.
Section to be changed		Appendix 10.6
Description of change		Order of PsA assessments changed at Visit 2
Rationale for change		To match order of assessments on the electronic device and due to requirement to perform joint counts last
Section to be changed		Section 1.2, Drug Profile, Listedness Section 8.4.1, and Unpublished Reference Section 9.2
Description of change		Document ID for the new version of the Investigator Brochure has changed to "c01569420-06"
Rationale for change		Updated document ID

Number of global amendment		2.0
Date of CTP revision		12 October 2016
EudraCT number		2015-003622-13
BI Trial number		1311.28
BI Investigational Product(s)		BI 655066
Title of protocol		BI 655066/ABB-066 (risankizumab) versus **U**stekinumab and p**l**acebo comparators in a randomized double blind **trI**al for **M**aintenance use in **M**oderate to severe plaque type psoriasis-2 (UltIMMa-2)
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	X	
Section to be changed	1	Title page, Synopsis
Description of change		Changed BI drug or BI investigational product or BI 655066 to refer to either names for this compound: BI 655066/ ABBV-066/risankizumab.
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. This protocol change reflects that AbbVie will now be the Sponsor of this study in the US, as well as the modifications to certain study conduct responsibilities as a result of that license agreement are listed as separate changes below.
Section to be changed	2	Section 3.1.1 Administrative structure of the trial
Description of change		1. Changed sponsor from Boehringer Ingelheim (BI) to AbbVie in the US and BI for all other participating countries. 2. Changed text to specify Statistical Evaluation will be done by AbbVie according to their SOPs.
Rationale for change		Refer to rational for first change listed

Section to be changed	3	Section 3.3.4.2
Description of change		Updated text to "AbbVie/Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons".
Rationale for change		Refer to rational for first change listed
Section to be changed	4	Section 5.5.4.2 Analytical determinations
Description of change		Changed DNA banking sample storage from Boehringer Ingelheim to AbbVie or a third party delegate (e.g. Boehringer Ingelheim Pharma GmbH & Co. KG; Birkendorfer Str. 65, 88397 Biberach, Germany).
Rationale for change		Refer to rational for first change listed
Section to be changed	5	Section 7.3.4 Safety Analyses
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		Refer to rational for first change listed

Boehringer Ingelheim

APPROVAL / SIGNATURE PAGE

Document Number: c03557743 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol

Title: BI 655066/ABBV-066 (rizankizumab) versus Ustekinumab and placebo comparators in a randomized double blind trIal for Maintenance use in Moderate to severe plaque type psoriasis-2 (UltIMMa-2)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-Therapeutic Area Head	[redacted]	14 Oct 2016 11:23 CEST
Author-Trial Statistician		14 Oct 2016 16:05 CEST
Approval-Clinical Program Leaders		14 Oct 2016 18:09 CEST
Approval-Trial Clinical Monitor		17 Oct 2016 12:05 CEST
Verification-Paper Signature Completion		19 Oct 2016 10:05 CEST

(Continued) Signatures (obtained electronically)

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