CLINICAL TRIAL PROTOCOL

	Document Number	**c03416278-02**
EudraCT No.:	2015-003625-34	
BI Trial No.:	1311.5	
Investigational Product:	BI 655066/ABBV-066/risankizumab	
Title:	A randomised, double-blind, placebo-controlled, proof-of-concept, dose-ranging study of BI 655066/ABBV-066/risankizumab in patients with active psoriatic arthritis	
Brief Title:	BI 655066/ABBV-066/risankizumab compared to placebo in patients with active psoriatic arthritis	
Clinical Phase:	II	
Trial Clinical Monitor:	[redacted]	
Coordinating Investigator:	[redacted]	
Status:	Final Protocol (Revised Protocol (based on global amendment 1)	
Version and Date:	**Version: 2.0**	**Date: 12 Oct 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim (Sponsor for countries outside the United States)**	**AbbVie, Inc. (Sponsor United States Only)**
Name of finished product:		Not applicable	
Name of active ingredient:		BI 655066/ABBV-066/risankizumab	
Protocol date: 15 Dec 2015	**Trial number:** 1311.5		**Revision date:** **12 Oct 2016**

Title of trial:	A randomised, double-blind, placebo-controlled, proof-of-concept dose-ranging study of BI 655066/ABBV-066/risankizumab in patients with active psoriatic arthritis
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre, multi-national
Clinical phase:	II
Objectives:	To provide proof-of-concept and dose-ranging data of BI 655066/ABBV-066/risankizumab in patients with active psoriatic arthritis
Methodology:	Randomised, parallel-design, dose-ranging, multiple-doses, placebo-controlled, double-blind
No. of patients:	
total entered:	Approximately 180
each treatment:	40 each arm (150 mg BI 655066/ABBV-066/risankizumab Arms 1, 2 and 3), 40 (placebo Arm 5), and 20 (75 mg BI 655066/ABBV-066/risankizumab Arm 4)

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Protocol date: 15 Dec 2015	**Trial number:** 1311.5		**Revision date:** **12 Oct 2016**

Diagnosis :	Active psoriatic arthritis
Main criteria for inclusion:	1. Age ≥ 18 years at screening, males or females 2. Have psoriatic arthritis (PsA) symptoms for ≥ 6 months prior to screening, as assessed by the investigator 3. Have PsA on the basis of the Classification Criteria for Psoriatic Arthritis (CASPAR) with peripheral symptoms at screening visit, as assessed by the investigator 4. Have ≥5 tender joints and ≥5 swollen joints at screening and randomisation visits, as assessed by the investigator 5. At least one psoriasis (PsO) lesion or a documented personal history of PsO at screening, as assessed by the investigator
Test product:	BI 655066
dose:	Arm 1: 150 mg BI 655066/ABBV-066/risankizumab (2 syringes, 75 mg each) at Weeks 0, 4, 8, 12 and 16 Arm 2: 150 mg BI 655066/ABBV-066/risankizumab (2 syringes, 75 mg each) at Weeks 0, 4 and 16 Arm 3: 150 mg BI 655066/ABBV-066/risankizumab (2 syringes, 75 mg each) at Weeks 0 and 12 Arm 4: 75 mg BI 655066/ABBV-066/risankizumab (1 syringe, 75 mg) at Week 0
mode of administration:	Subcutaneous injection
Comparator products:	Placebo
dose:	Arm 5: Placebo at Weeks 0, 4, 8, 12 and 16 Arms 2, 3, 4 as needed for blinding

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mode of administration:	Subcutaneous injection
Duration of treatment:	16 weeks
Endpoints	Primary endpoint: Proportion of subjects achieving American College of Rheumatology (ACR) 20 response at Week 16
Safety criteria:	Physical examination, vital signs, 12-Lead ECG, laboratory tests, adverse events, serious adverse events, and local tolerability
Statistical methods:	The primary analyses will be based on the intent-to-treat principle, comprising all participants who were randomised and received at least one dose of assigned therapy during the trial. Safety analyses will be based on actual treatment received. Sample size was determined on the basis of a one-sided comparison between the average ACR 20 response at Week 16 of Arm 1 and Arm 2 versus placebo. With the assumed Week 16 ACR 20 response rate of 38% in the combined arms (Arm 1 and Arm 2) and of 15% in the placebo arm, 40 participants each for Arm 1, Arm 2 and placebo will provide 85% power to detect a 23% difference in proportion (combination of Arm 1 and Arm 2 versus placebo) using a one-sided test of 0.05 significance. Randomisation is stratified based on prior TNF inhibitor experience (naïve or experienced) and concurrent methotrexate use (yes or no) as determined at baseline. The difference in proportion of participants achieving ACR 20 at Week 16 between the combined arms of Arm 1 and Arm 2 of BI 655066/ABBV-066/risankizumab and the placebo arm will be estimated and tested using the stratified Cochran-Mantel-Haenszel risk difference estimate. Pairwise comparisons of the BI 655066/ABBV-066/risankizumab dose groups will be conducted using the same Cochran-Mantel-Haenszel methods. There will be no adjustments for multiplicity in

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	these analyses and nominal p-values of these comparisons will be provided.		

FLOW CHART

Trial period	Screening	Treatment						Follow-up			
Visit	V1	V2	V3	V4	V5	V6	V7 (EOT)/ Early EOT[1]	V8	V9[2]	V10[2]	EOS[3]
Week	-6 to -1	0	2	4	8	12	16	20	24	28	32
Day	-42 to -7	1	15±2	29±3	57±3	85±3	113±4	141±4	169±4	197±4	225±7
Informed consent	x										
Demographics	x										
Medical history	x										
Smoking, alcohol history	x										
TNFi therapy history	x										
Infection screening	x										
Physical examination (c= complete, t=targeted)[4]	xc	xt	xt	xt	xt	xt	xt	xt	xc	xt	xt
Vital signs[5]	x	x	x	x	x	x	x	x	x	x	x
Inclusion/exclusion criteria	x	x									
Randomisation		x									
Contact IRT	x	x		x	x	x	x				
Study drug administration		x		x	x	x	x				
Termination of trial medication							x				
Background medication check[6]		x	x	x	x	x	x	x	x	x	x
Pregnancy testing[7]	x	x		x	x	x	x	x	x	x	x
12-lead ECG	x	x	x		x		x		x		x
Safety laboratory tests[8]	x	x	x	x	x	x	x	x	x	x	x
Blood sampling for serum protein biomarkers[9]		x		x		x			x		x
Blood sampling for cellular biomarkers[9]		x				x					
Blood sampling for RNA[9]		x				x			x		
Blood sampling for PK[10]		x		x	x	x	x	x	x	x	x
ADA sampling[10]		x			x	x	x		x		x
Optional sampling for DNA banking[11]		x									
AEs/Concomitant therapy	x	x	x	x	x	x	x	x	x	x	x
Local tolerability			x	x	x	x	x	x			

FLOW CHART (cont.)

Trial period	Screening	Treatment						Follow-up			
Visit	V1	V2	V3	V4	V5	V6	V7 (EOT)/ Early EOT[1]	V8	V9[2]	V10[2]	EOS[3]
Week	-6 to -1	0	2	4	8	12	16	20	24	28	32
Day	-42 to -7	1	15±2	29±3	57±3	85±3	113±4	141±4	169±4	197±4	225±7
Tender and Swollen Joint Counts (TJC 68, SJC 66)	x	x	x	x	x	x	x	x	x	x	x
Patient's assessment of pain (VAS)		x	x	x	x	x	x	x	x	x	x
Patient's global assessment of disease activity (VAS)		x	x	x	x	x	x	x	x	x	x
Physician's global assessment of disease activity (VAS)		x	x	x	x	x	x	x	x	x	x
HAQ-DI[12]		x	x	x	x	x	x	x	x	x	x
Leeds Dactylitis Index (LDI)[12]		x	x	x	x	x	x	x	x	x	x
Leeds Enthesitis Index (LEI)[12]		x	x	x	x	x	x	x	x	x	x
SPARCC[12]		x	x	x	x	x	x	x	x	x	x
PASI[12]		x	x	x	x	x	x	x	x	x	x
BSA[12]		x	x	x	x	x	x	x	x	x	x
sPGA[12]		x	x	x	x	x	x	x	x	x	x
mNAPSI[12]		x		x	x	x	x	x	x	x	x
BASDAI[12,13]		x					x		x		
SF-36 v2[12]		x		x			x		x		
FACIT-F[12]		x		x			x		x		
X-Ray[14]		x							x		
MRI (only if in MRI sub-study)[14]		x					x				
Conclusion of patient participation									x[2]	x[2]	x

Footnotes:
1. End of Treatment (EOT). For patients who discontinue treatment early, an early EOT visit is required at the first missed visit. Study drug must not be administered at early EOT. For procedures for patients who discontinue treatment prematurely cf. Section 3.3.4.1.
2. Subjects that enrol in the extension study, at Week 24 or Week 28 visit, do not need to attend any remaining visits in study 1311.5; however, the Trial Completion page and Visit date page at the EOS visit in the eCRF must be completed.
3. End of Study (EOS).
4. Physical examination: C=complete, T=targeted. Refer to Section 5.3.1.

5. Vital signs will be assessed before study drug administration. In addition at Visits 2, 4 and 6 vital signs will be assessed at 5 and 60 minutes after study drug administration. 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. Height and weight will be assessed at screening visit.
6. Background medications i.e. MTX, folic acid, systemic corticosteroids, NSAIDs and paracetamol/acetaminophen PRN medication will be recorded by patients in diaries provided and assessed by study staff.
7. Serum pregnancy testing for female patients of childbearing potential 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 visit.
8. 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.
9. Biomarker sampling should be done prior to administration of study drug at dosing visits. Refer to Section 5.5.
10. PK and ADA (Anti Drug Antibody) samples at dosing visits should be taken pre-dose.
11. Voluntary DNA banking sample will be stored after separate informed consent is given in accordance with local ethical and regulatory requirements (Section 5.5.3).
12. HAQ-DI (Health Assessment Questionnaire Disability Index), LDI (Leeds Dactylitis Index), LEI (Leeds Enthesitis Index), SPARCC (Spondyloarthritis Research Consortium of Canada) Enthesitis Index, PASI (Psoriasis Area and Severity Index), BSA (Body Surface Area), sPGA (Static Physician Global Assessment), mNAPSI (modified Nail Psoriasis Severity Index), BASDAI (Bath AS Disease Activity Index), SF-36 v2 (Medical Outcome Short Form Health Survey Version 2), FACIT-F (Functional Assessment of Chronic Illness Therapy-Fatigue),. For details cf. Appendices 10. PASI and sPGA are assessed in patients with ≥ 3% BSA of psoriatic plaques at baseline and/or at current visit.
13. Assessed only in patients with baseline inflammatory spondylitis based on investigator judgement.
14. If X-Ray and/or Magnetic Resonance Imaging (MRI) are performed at screening, it does not need to be repeated at Week 0 (cf. Section 5.6).
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ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Anti Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
Anti-CCP	Anti-Cyclic-Citrullinated Peptide
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BASDAI	Bath AS Disease Activity Index
BI	Boehringer Ingelheim
BSA	Body Surface Area
CA	Competent Authority
CASPAR	ClASsification criteria for Psoriatic Arthritis
C_{max}	Maximal Concentration
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CTP	Clinical Trial Protocol
DAS28	Disease Activity Score in 28 joints
DEDP	Drug Exposure During Pregnancy
DILI	Drug Induced Liver Injury
DIP	Distal Interphalangeal
DMARDs	Disease-Modifying Antirheumatic Drugs
DMC	Data Monitoring Committee
DN	Double Negative
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ELISA	Enzyme Linked Immunosorbent Assay
EOS	End Of Study
EOT	End Of Treatment
EudraCT	European Clinical Trials Database
EULAR	European League Against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FACS	Fluorescence-Activated Cell Sorting
FAS	Full Analysis Set
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
HAQ-DI	Health Assessment Questionnaire-Disability Index
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
IC_{50}	Half-maximal Inhibition

IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
ILCs	Innate Lymphoid Cells
IP	Interphalangeal
IRB	Institutional Review Board
IRT	Interactive Response System
ISF	Investigator Site File
ITT	Intention-To-Treat
i.v.	intravenous
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
mAb	monoclonal Antibody
MACE	Major Adverse Cardiovascular Event
MAR	Missing At Random
MCP	Metacarpalphalangeal
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed Model Repeated Measures Model
mNAPSI	Modified Nail Psoriasis Severity Index
MRI	Magnetic Resonance Imaging
mTSS	Modified Total Sharp Score
MTX	Methotrexate
NGAL	Neutrophil Gelatinase Associated Lipocalin-2
nM	Nanomolar
NOAEL	No Observed Adverse Effect Level
NRI	Non-Responder Imputation
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
OLE	Open-Label Extension
OMERACT	Outcome Measures in Rheumatology
OPU	Operation Unit
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic
PIP	Proximal Interpalangeal
PK	Pharmacokinetic
pM	Picomolar
PMN	Polymorphonuclear
PPD	Purified Protein Derivative
PRN	*(Pro re nata)* when necessary
PsA	Psoriatic Arthritis
PsAMRIS	Psoriatic Arthritis Magnetic Resonance Image Scoring System
PsARC	Psoriatic Arthritis Response Criteria
PsO	Psoriasis
PUVA	Psoralen and ultraviolet A
RCTC	Rheumatology Common Toxicity Criteria

RDC	Remote Data Capture
REML	Residual Maximum Likelihood Method
REP	Residual Effect Period
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SF-36	Short Form-36 Health Survey
SJC	Swollen Joint Count(s)
SOP	Standard Operating Procedure
SPARCC	Spondyloarthritis Research Consortium of Canada
sPGA	Static Physician Global Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TCM	Trial Clinical Monitor
t.i.d.	ter in die (3 times a day)
TJC	Tender Joint Count(s)
TNF	Tumor necrosis factor
TNFi	Tumor necrosis factor inhibitor(s)
TSAP	Trial Statistical Analysis Plan
UV(A/B)	Ultraviolet (A/B)
VAS	Visual Analog Scale
W	Week
WBC	White Blood Count

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Psoriatic Arthritis (PsA) is a chronic seronegative spondyloarthritis characterized by peripheral synovitis, enthesitis, dactylitis and spondylitis (R14-4870; R15-1089). PsA is mostly associated with Psoriasis (PsO) and nail involvement (R15-1020). Prevalence estimates for PsA among PsO patients vary across studies, ranging from 6 to 30% (R15-1003; R15-1002), with PsA affecting about 0.3 to 1% of the global population, equally men and women (R15-1020). The cause of PsA is not known, but hereditary factors, infection and physical trauma are frequently referred to as potential risk factors.

Although effective treatments for PsA are approved (traditional disease-modifying antirheumatic drugs (DMARDs) (methotrexate (MTX), leflunomide), apremilast, tumour necrosis factor inhibitors (TNFi) (certolizumab pegol, adalimumab, etanercept, infliximab, golimumab), and anti-IL-12/23p40 (ustekinumab)), the unmet medical need remains for safer therapy that works more effectively on measures of signs and symptoms of PsA, prevention of structural damage and PsO and that maintains the efficacy over time, preferably with a new mode of action to provide more treatment options to patients who have already failed the currently approved therapies.

BI 655066/ABBV-066/risankizumab (risankizumab) is a humanized monoclonal antibody (mAb) directed against human IL-23 that specifically neutralizes this cytokine and prevents binding and signalling through the IL-23 receptor, expressed on Th17 cells as well as subset of γδ T cells, NK cells, innate lymphoid cells (ILCs) and double negative (DN) entheseal-residing T cells. risankizumab has a potential for addressing some of the unmet needs in PsA.

PsO and PsA share common pathologies based on cellular pathways (T cells/ plasmacytoid dendritic cells), transcription factors (decreased AP-1), genetic susceptibility loci (CARD15/PSORAS1/NOD2, TNF gene polymorphism) and cytokines/ other mediators (TNF, type 1 interferon, amphiregulin) (R15-1030). Pro-inflammatory mediators that act as drivers of PsO and PsA are released by a variety of cell types, including innate immune cells, adaptive immune cells and resident immune cells (R11-1257). Plasmacytoid dendritic cells are found in psoriatic skin and psoriatic synovium and activated dendritic cells present antigens and produce interferon (IFN)-α and pro-inflammatory mediators, such as IL-12 and IL-23. Antigen presented by myeloid dendritic cells to T-cells results in proliferation and differentiation into type 1 and type 17 T helper cells, which increase secretion of inflammatory cytokines (R11-1257; R15-1033).

The role of the IL-23/IL-17 axis in PsA is well documented in the literature (R14-5175). IL-23 is expressed in the synovial tissue of patients with PsA (R15-1008).

Single nucleotide polymorphisms in this genetic pathway are related to genetic susceptibility to PsA (R15-1035; R15-0998). IL-23 has been shown to cause enthesitis (one of the key features of PsA) in a rodent model (R15-1070). The role of IL-23 (through its effect on Th17 cells) has been implied in bone erosion and dysregulated bone formation in PsA. IL-17 can cause cartilage degradation via effects on chondrocytes (R15-1066) In addition, IL-23 (independent of Th17) activates IL-23R+ entheseal resident lymphocyte cell population, which produces IL-22, and can promote entheseal and periosteal bone formation (R15-1070).

1.2 DRUG PROFILE

Risankizumab is a humanized monoclonal antibody (mAb) of the IgG1 subclass directed towards IL-23p19.

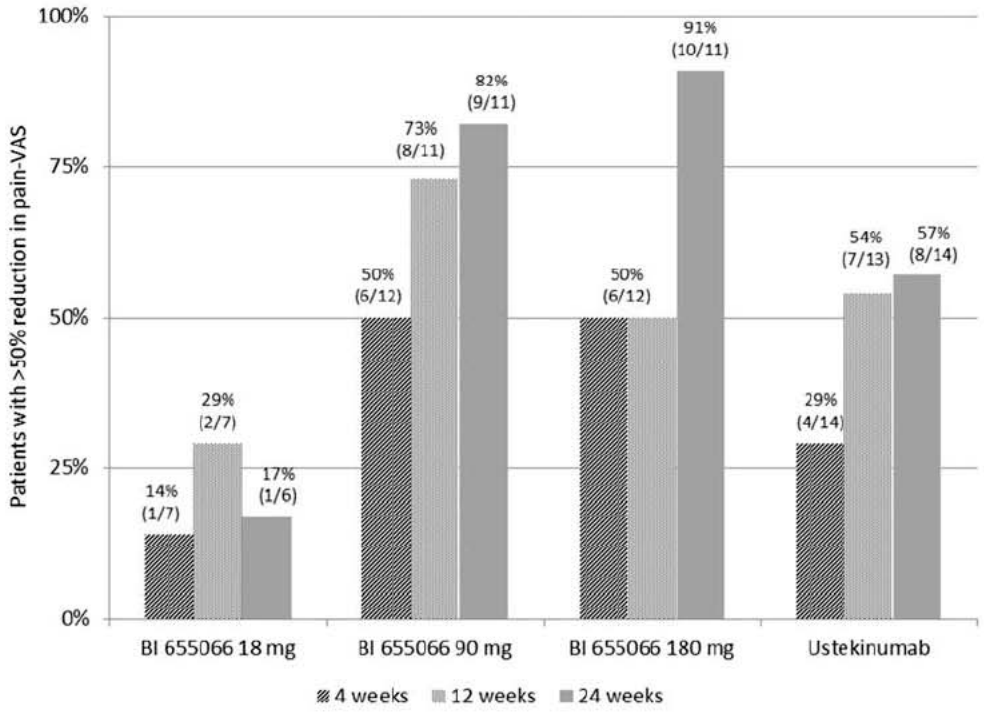
The toxicology data suggest risankizumab can be safely administered to humans, as supported by chronic administration to monkeys for up to [redacted] weeks. The monkey was identified as the most relevant toxicology species with a NOAEL (no observed adverse effect level) of [redacted] mg/kg/dose (highest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

Proof of clinical concept for risankizumab through IL-23/IL-17 pathway was demonstrated in a single rising dose Phase I trial in 39 patients with moderate to severe plaque PsO where 87% of patients achieved at least 75% reduction in Psoriasis Area and Severity Index (PASI 75) with no safety concerns (c02434648).

In a Phase II dose-ranging trial of risankizumab vs. ustekinumab, the primary endpoint of PASI 90 response at Week 12 was achieved by 32.6% (14/43), 73.2% (30/41), and 81.0% (34/42) of risankizumab patients in the 18 (single dose at Week 0), 90, and 180 mg (dosed at Weeks 0, 4 and 16) groups, respectively, and 40.0% (16/40) of ustekinumab patients (dosed at Weeks 0, 4 and 16, weight based). A two-sided Cochran-Mantel-Haenszel test of PASI 90 response at Week 12 between the 18, 90, and 180 mg groups ofrisankizumab, and ustekinumab, gave p-values of 0.4337, 0.0013, and <0.0001, respectively (c03272682). In addition, in this PsO trial, Pain Visual Analog Scale (pain-VAS [0-100 mm]) data over time was obtained from 46 patients who had concurrent diagnosed by rheumatologist or suspected PsA. The criterion of >50% decrease in pain-VAS (defined *post hoc*, as one of the potential domains contributing to ACR 50 response) at Week 24 was achieved in 16.7% (1/6), 81.8% (9/11), and 90.9% (10/11) of patients in risankizumab18, 90, and 180 mg dose groups, respectively, compared with 57.1%

(8/14) for ustekinumab. In the risankizumab 90 and 180 mg dose arms the reductions in pain-VAS score were observed as early as 4 weeks, and were highest at 24 weeks (Figure 1.2: 1), supporting the therapeutic rationale of risankizumab in PsA. Risankizumab was well tolerated in this Phase II study.

Figure 1.2: 1 Reduction in pain – rates of patients with >50% reduction in pain-VAS score from baseline at Weeks 4, 12, and 24



[redacted]

For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB, c02161217) which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

This trial is performed to provide proof-of-concept and dose-ranging data for risankizumab in patients with active PsA. The rationale for starting risankizumab development in PsA by performing this trial is based on the observed efficacy of risankizumab in PsO in Phase I and II trials (c02434648, c03272682) as well as pain-VAS data obtained from PsO patients with concurrent PsA in Phase II trial (c03272682), supporting a role of IL-23p19 as a therapeutic target in PsA and supplementing the pre-clinical pharmacologic rationale for IL-23 pathway in this indication. In addition, positive Phase III data from approved and investigational anti-IL-12/23p40 and anti-IL-17 mAbs on various PsA domains confirm the role of IL-23/IL-17 pathway inhibition in treatment of active PsA patients.

2.2 TRIAL OBJECTIVES

The objectives of this study are to provide proof-of-concept and dose-ranging data of risankizumab in patients with active PsA to support dose selection for the pivotal program in this indication. The proof-of-concept will be achieved through the primary endpoint comparison (ACR 20 rates at Week 16) from the pooling of the two highest exposure arms versus placebo. The short-term utility of an additional dose at Week 4 will be evaluated by comparison of 150 mg at Weeks 0 and 12 versus 150 mg at Weeks 0, 4, and 16. In addition, clinical efficacy (based on secondary and further endpoints) will be evaluated. Onset of response and assessment of duration of response will be assessed during treatment and through Week 32 follow-up, or until last visit prior to enrolling into the open label extension (OLE) study.

Safety of risankizumab will be evaluated during treatment and through Week 32 follow-up. The effect of emergence of anti-drug antibodies (ADA) on safety and efficacy will be explored.

In addition, risankizumab PK exposure will be assessed to provide data for subsequent PK-PD modelling. The risankizumab exposure-response profile will be characterised through a relatively wide exposure range achieved by 150 mg every 4 weeks to 75 mg single dosing.

Prevention of structural damage will be explored through X-ray endpoints at Week 24 and MRI endpoints at Week 16. Influence of risankizumab on pathway gene and protein expression levels as well as disease specific protein markers will be explored.

2.3 BENEFIT-RISK ASSESSMENT

Participation in this study may help generate future benefit for larger groups of patients with PsA if risankizumab proves to be successful in treating this disease to address an unmet medical need as described in Section 2.1. Risankizumab has been studied in 46 PsO patients who had concurrent diagnosed by rheumatologist or suspected by investigator PsA. The rates of patients with >50% reduction at Week 24 (from baseline) in pain-VAS in the 90 mg and 180 mg of risankizumab arms were comparable with ustekinumab arm and numerically better than in risankizumab18 mg single dose arm. In addition, 70-80% of patients with moderate to severe PsO receiving 90 mg and 180 mg of risankizumab achieved PASI 90 in their skin disease.

However, no direct benefit for individual participants in this study can be assumed, because efficacy of risankizumab has not been confirmed in PsA and because some patients will be randomised to the placebo arm. Measures are in place to minimize administration of potentially sub-optimal treatment long-term. In particular, at Week 16, after last study drug administration and regardless of treatment arm, patients with reduction in both tender and swollen joint count of <20%, will be able to change their concomitant PsA medication according to investigator's judgment and local standard of care, except addition of new biologic treatment (cf. Section 4.2.1). Starting from Week 24 patients that are not enrolling in the OLE study can receive rescue treatment (cf. Section 4.2.1), including biologic treatment, according to investigator's judgment and regardless of the degree of improvement in their symptoms. Patients will be continuing their follow-up procedures within this study regardless if they have started rescue treatment.

Risankizumab has been administered to approximately 350 patients with moderate to severe plaque PsO, ankylosing spondylitis and Crohn's disease in completed or ongoing studies. The most common adverse events (AEs) reported in these trials were mild symptoms of the upper respiratory tract, including nasal stuffiness, sore throat, 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 risankizumab were uncommon, and limited to redness, swelling or induration at the injection site. No serious drug related AEs were reported. As with any immune modulating agent, risankizumab may impair immune function resulting in a risk of infection. This will be monitored by collection of any AEs during the treatment and observation periods. There is not enough information at this time to rule out a risk of cancer with risankizumab, but this risk is considered small with this type of compound as experience with the anti-IL-12/23 mAb ustekinumab has not suggested significant risk for cancer/serious infection. 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 confirmed with longer observation times. 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.

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 this study.

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 is a multi-national, randomised, parallel-design, dose-ranging, multiple-doses, placebo-controlled, double-blind Phase II study. Approximately 180 eligible patients with active PsA will be randomised at 2:2:2:1:2 ratio, stratified based on prior TNFi use and concurrent MTX use into five treatment arms shown in Figure 3.1: 1. Patients with prior TNFi experience will be capped at approximately 70%.

Overall trial treatment duration is 16 weeks with additional 16 weeks follow-up. Patients who have completed all doses of study drug and the Week 24 visit will have the option to enrol into a separate OLE study. The OLE study will be sponsored by AbbVie as part of a collaboration of the risankizumab development program. Those patients rolling over to the OLE study, will not complete any remaining follow-up visits in this study and will follow the procedures in the OLE study protocol.

Patients will receive risankizumab/placebo as described in Figure 3.1: 1. The overall dosing schedule will be the same in all treatment arms in order to keep the blind; this is further described in Section 4.1.4.

If patients have reduction in both tender and swollen joint count of <20% relative to baseline at the Week 16 assessment, they may alter their concomitant PsA treatment or start additional treatment, except biologics, according to investigator's judgement and local standard of care, after receiving Week 16 study drug dose. After Week 24, patients that are not enrolling in the OLE study may start rescue treatment with local standard of care, including biologic treatment, if considered appropriate by the investigator, regardless of the joint count improvement. For details refer to Section 4.2.1.

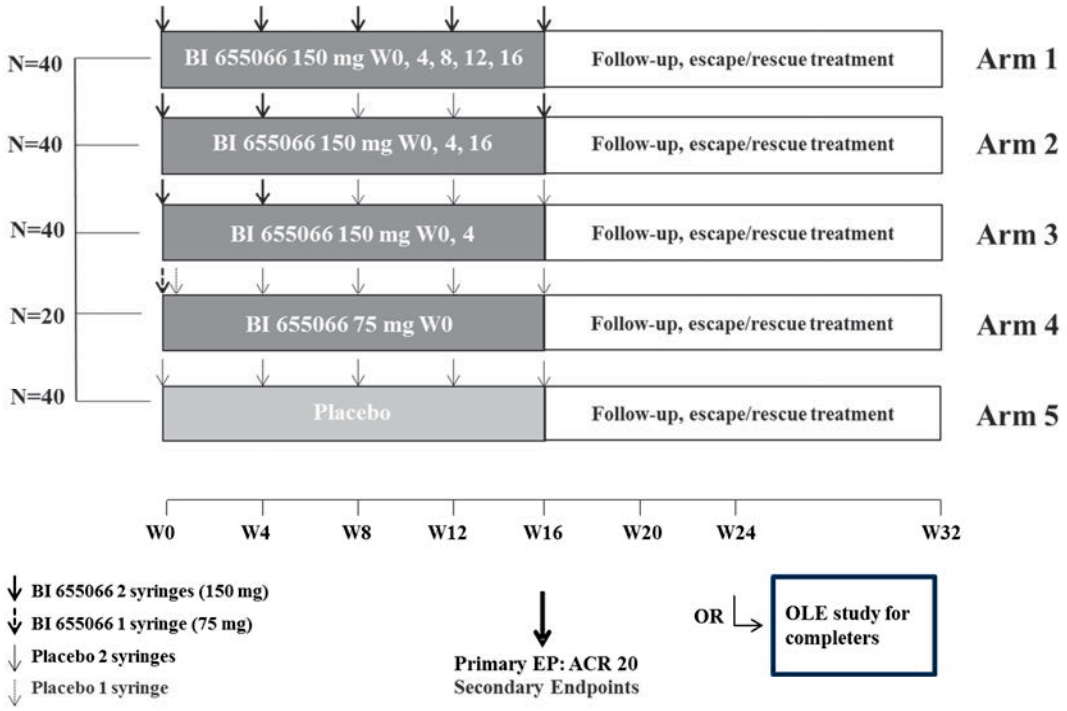
In addition to clinical endpoint assessments, patients will have X-rays performed at Weeks 0 and 24 for assessment of the modified total Sharp score (mTSS). Approximately 90 patients from selected sites with access to MRI will be included in the MRI sub-study, with MRI assessments performed at Weeks 0 and 16.

The analysis of the primary endpoint will be performed when the last patient completes the Week 16 visit, when the primary endpoint (ACR 20 at Week 16) is assessed. The trial will be unblinded to the sponsor for analysis, but patients and investigators will remain blinded until after the completion of the trial.

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.

Figure 3.1: 1 Trial design



3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim (BI) outside of the US and by AbbVie, Inc. in the US only. Boehringer Ingelheim will continue to manage the 1311.5 study in all countries.

Boehringer Ingelheim has appointed a Trial Clinical Monitor, responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs),
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- order the materials as needed for the trial; and

- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

A Coordinating Investigator will be responsible to coordinate activities of investigators at different centres participating in this multicentre 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 an IRT (interactive response technology) vendor will be used in this trial. In addition, a centralised review of collected X-rays and MRI will be conducted by selected vendors. Details will be provided in IRT Manual and Central Laboratory Manual and other documentation, available in ISF.

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

3.1.1.1 Data monitoring committee

A data monitoring committee (DMC), independent of the Sponsor will be established to assess the progress of the clinical trial, including an unblinded safety and efficacy assessment at specified intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial. Measures are in place to ensure blinding of the Sponsor and all other trial participants. The tasks and responsibilities of the DMC will be specified in the DMC Charter. The DMC will maintain written records of all its meetings.

3.1.1.2 MACE adjudication committee

An independent adjudication committee will be used to adjudicate all observed cardio- and cerebro-vascular 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 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 GROUP

This is a randomised double-blind, placebo-controlled, parallel-design study. This design is appropriate for providing proof-of-concept/dose-ranging and assessing the safety and efficacy of risankizumab compared to placebo in patients with active PsA.

While there is a low rate of response with placebo treatment, it is important to have a placebo control to address potential confounding factors, such as placebo effect, potential investigator bias in safety and efficacy assessment or regression to the mean in endpoint scoring. Escape criteria are defined at Week 16 to ensure adjustment of treatment for all patients who have reduction in both tender and swollen joint count <20% at Week 16. In addition from Week 24, patients not enrolling in the OLE study can start rescue treatment with local standard of care, including biological treatment, as needed (i.e., without the need to meet any predefined escape criteria). The start of an alternative biologic treatment is delayed until Week 24, to allow for at least 8 weeks washout after the last dose of risankizumab in treatment Arms 1 and 2 for safety considerations. In addition, this delay will keep Week 24 assessments less biased considering the known significant efficacy of biologic treatments in PsA. The expectation of structural damage within Weeks 0 to 24 period (within which biologic treatment with proven effect on structural damage is restricted) is low (R15-1020). All patients, regardless if they have started rescue treatment need to be followed up to through EOS visit, if possible, except for patients who enrol in OLE studyto ensure safety follow-up during Residual Effect Period (REP) as defined in Section 5.3.7. Those patients rolling over to the OLE study, will not complete the remaining follow-up visits in this study and will follow the procedures in the OLE study protocol.

Four active arms will be studied to provide a range of exposure. For primary analysis, primary endpoints from Arms 1 and 2 will be pooled for comparison with placebo with the aim of obtaining proof-of-concept in PsA patients at Week 16. Arm 2 will be compared to Arm 3 at Weeks 8 and 12 to assess the utility of the Week 4 dose in Arm 2. Arm 4 will provide what is expected to be a sub-optimal exposure for assessing a relatively wide exposure range that will be used in exposure-response profiling of risankizumab in PsA.

The reason for stratification based on prior TNFi experience is, that patients with prior TNFi experience may be more difficult to treat in comparison to others (R15-1091, R15-3527, R15-5899). The number of patients with TNFi experience is capped at 70%, to have at least 30% TNFi naïve patients to allow for exploratory analysis of risankizumab efficacy in both sub-populations. Stratification based on concomitant MTX use is performed, because efficacy of risankizumab may be

different between patients with and without concomitant MTX use (i.e. concomitant MTX may provide additional efficacy).

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 180 patients will be randomised in this trial. A sufficient number of patients will be screened to meet this randomised goal. Patients will be recruited at approximately 70 sites in multiple countries. The planned number of patients per site is 2 – 3. 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 with active PsA will be included. PsA will be diagnosed based on the Classification Criteria for Psoriatic Arthritis (CASPAR) that combine variable clinical patient characteristics and require inflammatory articular disease plus at least 3 points from different categories for a PsA diagnosis (Appendix 10.1). Active PsA will be defined by presence of ≥ 5 tender joints and ≥ 5 swollen joints.

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

3.3.2 Inclusion criteria

1. Age ≥ 18 years at screening, males or females
2. Have PsA symptoms for ≥ 6 months prior to screening, as assessed by the investigator
3. Have PsA on the basis of the Classification Criteria for Psoriatic Arthritis (CASPAR) with peripheral symptoms at screening visit, as assessed by the investigator
4. Have ≥ 5 tender joints and ≥ 5 swollen joints at screening and randomisation visits, as assessed by the investigator
5. At least one PsO lesion or a documented personal history of PsO at screening, as assessed by the investigator
6. If patients receive concurrent PsA treatments, these need to be on stable doses as below:

For subjects receiving MTX: subject has received treatment for ≥ 3 months, with stable dose and stable route of administration (not to exceed 25 mg MTX per week) for ≥ 4 weeks prior to randomisation to Week 24; subjects on MTX should be taking folic acid supplementation according to local standard of care before randomisation and during the trial to minimize the likelihood of MTX associated toxicity

For subjects receiving oral corticosteroids: the subject must be on a stable dose (not to exceed the equivalent of 10 mg of prednisone per day) for ≥ 2 weeks prior to randomisation to Week 24

For subjects receiving non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol/acetaminophen PRN: the subject must be on stable dose for ≥ 2 weeks prior to randomisation to Week 24

7. Active PsA that has been inadequately controlled by standard doses of NSAIDs administered for ≥ 4 weeks, or traditional DMARDs (including sulfasalazine) administered for ≥ 3 months, or TNFi agents, or subjects are intolerant to NSAIDs or DMARDs or TNFi agents, as assessed by the investigator

8. Signed and dated written informed consent prior to admission to the study in accordance with Good Clinical Practice (GCP) and local legislation

9. 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).

3.3.3 Exclusion criteria

1. Major chronic inflammatory or connective tissue disease other than PsA (e.g. rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, Lyme disease, gout) and fibromyalgia, as assessed by the investigator
2. Has received any therapeutic agent directly targeted to IL-12/23 (including ustekinumab), IL-23 or IL-17 (including secukinumab)

3. Prior use of more than two different TNFi agents
4. Use of the following treatments:

   - TNFi agents (including, infliximab, adalimumab, certolizumab pegol or golimumab) within 12 weeks prior to randomisation
   - Etanercept within 8 weeks prior to randomisation
   - Leflunomide without cholestyramine wash-out within 8 weeks prior to randomisation
   - Systemic non-biologic medications for PsA or PsO (including apremilast and leflunomide with cholestyramine wash-out) and photochemotherapy within 4 weeks prior to randomisation
   - Intraarticular injections (including steroids) and intramuscular or intravenous corticosteroid treatment within 4 weeks prior to randomisation
   - Topical PsO medications and phototherapy within 2 weeks prior to randomisation
   - Low and high potency opioid analgesics (e.g. methadone, hydromorphone, morphine) within 2 weeks prior to randomisation
5. Previous treatment with any cell-depleting therapies including but not limited to anti-CD20 (e.g. rituximab), investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)
6. Participation in another trial with an investigational drug or device within 4 weeks (if the trial is for PsA treatment, within 12 weeks) or 5 half-lives (whichever is greater) prior to randomisation
7. Use of any restricted medication as specified in Table 4.2.2.1: 1 or any drug considered likely to interfere with the safe conduct of the study, as assessed by the investigator
8. Plans for administration of live vaccines during the study period or within 6 weeks prior to randomisation.
9. History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients
10. Active systemic infections during the last 2 weeks (exception: common cold) prior to randomisation, as assessed by the investigator
11. Chronic or relevant acute infections including HIV (human immunodeficiency virus), viral hepatitis and (or) active tuberculosis. Patients with a positive QuantiFERON TB or PPD test 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 tuberculosis treatment may be deferred until completion of the trial according to clinical judgment of investigator and local country guidelines.

12. 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
13. Major surgery performed within 12 weeks prior to randomisation or planned within 32 weeks after randomisation (e.g. hip replacement, aneurysm removal, stomach ligation), as assessed by the investigator
14. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than PsA and PsO, surgical procedure (i.e., organ transplant), medical examination finding (including vital signs and electrocardiogram (ECG)), or laboratory value at the screening visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data.
15. Total white blood count (WBC) < 3,000/µL, or platelets < 100,000/µL or neutrophils < 1,500/µL, or hemoglobin <8.5 g/dL at screening
16. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2x the upper limit of normal, or serum direct bilirubin ≥ 1.5 mg/dL at screening
17. Positive rheumatoid factor or anti-cyclic-citrullinated peptide (anti-CCP) antibodies at screening
18. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
19. Patients with cochlear implants, cardiac pacemakers, metallic foreign bodies in their eye or who have an aneurysm clip in their brain, and/or ferromagnetic surgical implants in the body or claustrophobia (MRI-sub-study patients only)
20. Patients who are legally institutionalized

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

All patients have the right to discontinue the study treatment early and/or 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.

In order to minimize missing data in the evaluation of intention-to-treat "observed" data analysis, patients who discontinue study treatment early should complete early EOT visit as per Flow Chart at the first missed visit and continue to be followed for

all regularly scheduled follow-up visits (Visit 8, 9, 10 and EOS) for safety and efficacy assessments. These patients should be registered as early treatment discontinuations (treatment withdrawal) in IRT. If these patients do not agree to continue all scheduled visits, they need to be recommended to at least return to the clinic for EOS visit, 16 weeks after last dose of study medication for safety. Refer to Section 6.2.3. These patients are not eligible for the OLE study.

Early study treatment discontinuation is to be differentiated from study withdrawal. The only reasons for study withdrawal are patient withdrawal of consent to contribute additional outcome information (including after early study treatment discontinuation) and loss to follow-up.

Study medication should be discontinued 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 risankizumab discontinuation including but not limited to SAEs or SUSARs.
- If the subject received a live vaccine during the study.
- 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 study drug. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator.
- If the patient experiences an intolerable increase of PsA during the course of the trial treatment the patient will be discontinued from the trial treatment to receive rescue treatment as deemed appropriate by the investigator.

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 all patients the reason for early study treatment discontinuation and study withdrawal must be recorded in the electronic case report form (eCRF). These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for 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 ofrisankizumab, or
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 and placebo to match BI 655066 will be administered subcutaneously. All products will be supplied by Boehringer Ingelheim.

4.1.1 Identity of BI investigational 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 pre-filled syringe, concentration 90 mg/mL
Route of administration:	Subcutaneous injection
Posology:	Arm 1: 150 mg (two 75 mg syringes) at Week 0, 4, 8, 12 and 16 Arm 2: 150 mg (two 75 mg syringes) at Week 0, 4, 16 Arm 3: 150 mg (two 75 mg syringes) at Week 0 and 12 Arm 4: 75 mg (one 75 mg syringe) at Week 0
Duration of use:	16 weeks

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

Substance:	Placebo to BI 655066
Pharmaceutical form:	0.9% sodium chloride solution presented in a 1 mL syringe pre-filled with 0.87 mL. Dispensed volume is 0.83 mL.
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Not applicable
Molecular weight	Not applicable
Unit Strength:	Not applicable
Route of administration:	Subcutaneous injection
Posology:	Arm 5: Weeks 0, 4, 8, 12 and 16 Arms 2-4: cf. Table 4.1.4: 1
Duration of use:	16 weeks

4.1.2 Method of assigning patients to treatment groups

Through the utilisation of IRT, patients will be randomised to receive BI 655066 or placebo in a ratio of 2:2:2:1:2 stratified based on prior TNFi use (naïve or experienced) and concurrent MTX use (yes or no) in five treatment arms.

After the eligibility criteria are confirmed, the investigator or designee will randomise the patient on Day 1 (Visit 2) through IRT call or website entry.

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

There are four active dosing regimens in this Phase II trial as described previously in Figure 3.1: 1 and discussed below. The dose selection for this first BI 655066 trial in patients with PsA considers all available BI 655066 safety and efficacy clinical data available from trials in other indications (PsO, Crohn's disease and ankylosing spondylitis), as well as formulation and patient acceptability considerations.

Arm 2 regimen (150 mg at Weeks 0, 4 and then a dose at week 16) represents the initial three doses of the single regimen tested in the confirmatory studies in PsO indication with BI 655066. Considering that approximately 30% of patients with PsO are also diagnosed with PsA (R15-1002), this regimen will provide data on BI 655066 efficacy across both diseases and facilitate comparisons. Initial, albeit limited data (Figure 1.2: 1) suggests that subjects administered BI 655066 exhibit clinical improvements in PsA pain symptoms over the range of exposures also found to be effective in PsO. This finding appears consistent with other biologic agents that are approved in both PsA and PsO.

Additional dosing regimens have been selected to inform exposure response in PsA.

Dosing every 4 weeks (approximately every half-life of BI 655066) in Arm 1 may provide efficacy in a higher proportion of PsA patients with a hypothesis that higher exposures may yield an improvement in joints relative to skin. This may be particularly true for difficult to treat sub-populations (for example, TNFi experienced patients), heavier patients or for reducing the extent of structural damage. Efficacy data from Arms 1 and 2 will be pooled for proof-of-concept analysis.

Based on the assumption of similar pharmacokinetics in PsA and PsO, this increased dosing frequency may result in [redacted]

The safety data as of July 2015 from BI 655066 studies across all indications (approximately 330 subjects with PsO, ankylosing spondylitis and Crohn's disease) suggest that BI 655066 has an acceptable safety profile across all dosing regimens under evaluation. In particular, dosing frequency in the ankylosing spondylitis Phase II Trial 1311.8 was every 8 weeks dosing (n~40 patients for each of the 90 and 180 mg dose groups) and Crohn's disease Phase II Trial (1311.6) included 200 and 600 mg dose levels administered intravenously every 4 weeks for up to 12 weeks (with safety information available for approximately 30 patients for each dose) without any identified significant safety issues. Therefore, it is not anticipated that there would be additional safety concerns with the every 4 weeks dosing.

Arm 3 regimen (150 mg every 12 weeks) does not include dosing at Week 4 which will afford an assessment of the influence of the Week 4 dosing on clinical efficacy at Weeks 8 and 12 assessment time points. To provide efficacy information at lower exposures of BI 655066, a potentially sub-optimal 75 mg of BI 655066 as a single dose is also included with 20 patients in this treatment group. In addition to the statistical analyses outlined in Section 5, clinical efficacy and safety data from this trial will be analysed using PK-PD approaches to inform dosing regimens in subsequent trials.

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 to receive assigned medication numbers. Site personnel will enter the medication numbers in the eCRF. Dosing visits are specified in the Flow Chart.

BI 655066 and/or matching placebo will be administered subcutaneously in a double blind fashion and are presented in Table 4.1.4: 1. At each dosing visit, two subcutaneous injections will be given.

Table 4.1.4: 1 Dosing schedule

Week	0	4	8	12	16
Arm 1: 150 mg W 0, 4, 8, 12, 16	2 x 75 mg	2 x 75 mg	2 x 75 mg	2 x 75 mg	2 x 75 mg
Arm 2: 150 mg W 0, 4, 16	2 x 75 mg	2 x 75 mg	2 x placebo	2 x placebo	2 x 75 mg
Arm 3: 150 mg W 0, 12	2 x 75 mg	2 x placebo	2 x placebo	2 x 75 mg	2 x placebo
Arm 4: 75 mg single dose W 0	1 x 75 mg 1 x placebo	2 x placebo	2 x placebo	2 x placebo	2 x placebo
Arm 5: placebo	2 x placebo	2 x placebo	2 x placebo	2 x placebo	2 x placebo

Dose modifications or adjustments are not permitted. In exceptional cases of missed or delayed visits, study drug of the following visit should not be administered within 7 days of the prior dose. There should be at least 7 days between two consecutive study drug administrations. The information on technique of injection and injection materials (syringes, needles) is provided in the ISF. Study medication will be administered exclusively at the study site, by authorised study personnel (e.g. study nurse).

BI 655066 and/or matching placebo will be administered as a subcutaneous injection in the abdomen and thighs. 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.

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 randomised treatment assignments until after 16-week primary analysis database lock. In addition, patients and investigators will further remain blinded until after the final database lock. After the last patient completes the 16-week visit, the database will be locked for analysis of the primary endpoint and BI study and project teams will become unblinded to treatment and dose assignments.

The randomisation code will be kept secret by Clinical Trial Support up to the final database lock.

The randomisation 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 randomisation code or the results of their measurements until the trial is officially unblinded for primary

analysis. 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 Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's drug safety group to access the randomisation code for individual patients during study conduct via the IRT system. In such cases, access to the code will only be permitted by authorised 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.

An independent DMC will provide an unblinded safety and efficacy assessment at specified interval, please refer to Section 3.1.1.1.

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 eCRF 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 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 / pharmacist / 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 medications 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 and/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.

All concomitant, and/or rescue therapies will be recorded on the appropriate pages of the eCRF.

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to not exclude the patient from participation (cf. 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 case of adverse events in need of treatment symptomatic therapy according to investigator judgment will be permitted.

If patients receive optional concurrent PsA treatment, these need to be on stable doses prior to randomisation to Week 24, as specified in Inclusion Criterion 6.

Methotrexate

Subjects taking MTX (up to 25 mg/week) must be on a stable dose and stable route of administration for at least 4 weeks before randomisation and maintained stable until Week 24.

Folic acid

Subjects on MTX must be taking folic acid supplementation according to local standard of care before randomisation and during the trial to minimize the likelihood of MTX associated toxicity.

Corticosteroids

Treatment with systemic corticosteroids is permitted up to a maximum daily dosage of 10 mg prednisone equivalent and if the dose was stable within the 2 weeks preceding randomisation. The subject should remain on a stable dose until Week 24.

Intra-articular corticosteroids are not permitted within the 4 weeks preceding randomisation and up to Week 24.

Topical steroids of US class 6 (mild, such as desonide) or US class 7 (least potent, such as hydrocortisone) will be permitted for use limited to the face, axilla, and/or genitalia. These topical medications should not be used within approximately 24 hours prior to visits requiring PASI assessment.

Non-steroidal anti-inflammatory drugs (NSAIDs) or paracetamol/ acetaminophen PRN

Subjects on regular use of NSAIDs or paracetamol/acetaminophen PRN (PRN referring to the latter only) should be on stable dose for at least 2 weeks before randomisation to allow inclusion. They should remain on a stable dose in the study up to Week 24; however, they have to refrain from any intake during at least 24 hours before a visit with disease activity assessment.

Rescue treatment

If the patient experiences an intolerable increase in diseases activity of PsA during the course of the trial treatment the patient will be discontinued from the trial treatment to receive rescue treatment as deemed appropriate by the investigator. These patients will complete early EOT visit and continue to be followed for all regularly scheduled follow-up visits for safety and efficacy assessments, as detailed in Section 3.3.4.1.

If patients have reduction in both tender and swollen joint count of <20% at the Week 16 assessment (escape criteria), they can start rescue treatment with local standard of care, except biologics, after receiving Week 16 study drug dose. For that purpose they can change the doses of concurrent medication and/or start new non biologic medication. These patients will continue with all scheduled follow-up visits.

After Week 24, patients can start rescue treatment with local standard of care, including biologic treatment, if considered appropriate by the investigator, regardless of the joint count improvement. These patients too will continue with all scheduled follow-up visits.

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

Investigational products not otherwise described below	4 weeks (if the trial is for PsA treatment, 12 weeks) or 5 half-lives, whichever is greater prior randomisation and for the trial duration including the follow-up period
Investigational anti-IL-12/23, anti-IL-23, and anti-IL-17	Prior to the study and for the trial duration including the follow-up period
Cell-depleting therapies including but not limited to anti-CD20 (e.g. rituximab), investigational agents (e.g. CAMPATH, anti-CD4, anti-CD5, anti-CD3, anti-CD19)	Prior to the study and for the trial duration including the follow-up period
Ustekinumab and secukinumab	Prior to the study and within 24 weeks after randomisation
TNFi, except etanercept	12 weeks prior randomisation and within 24 weeks after randomisation
Etanercept	8 weeks prior randomisation and within 24 weeks after randomisation
Apremilast or other PsA non biologic systemic treatment, including leflunomide with wash-out with cholestyramine*	4 weeks prior randomisation and within 24 weeks after randomisation†
Leflunomide without wash-out with cholestyramine	8 weeks prior randomisation and within 24 weeks after randomisation†
Intraarticular injections (including steroids)	4 weeks prior randomisation and within 24 weeks after randomisation†
Intramuscular or intravenous corticosteroid treatment	4 weeks prior randomisation and within 24 weeks after randomisation†
Oral or injectable PsO medications (not biologicals) including retinoids and fumarates, or any other drugs known to possibly benefit PsO Photochemotherapy (e.g. PUVA) Any drug known to interfere with or to aggravate PsO including but not limited to lithium and interferons	4 weeks prior randomisation and within 24 weeks after randomisation
Phototherapy (e.g. UVA, UVB) Topical PsO treatments such as steroids or other topicals as retinoids, vitamin D analogs, vitamin A analogs and anthralin	2 weeks prior randomisation and within 24 weeks after randomisation (for exceptions cf. Section 4.2.1)
Low and high potency opioid analgesics (e.g. methadone, hydromorphone, morphine)	2 weeks prior randomisation and within 24 weeks after randomisation†
Live vaccines	6 weeks prior randomisation and for the trial duration including the follow-up period

* Stable doses of methotrexate, corticosteroids, NSAIDs, or paracetamol/acetaminophen PRN are allowed (cf. as specified in Inclusion Criterion 6 and Section 4.2.1)

† these treatments or their change are allowed from Week 16, if escape criteria are met (cf. Section 4.2.1, Rescue treatment)

Leflunomide wash-out with cholestyramine

In case of leflunomide treatment, a drug wash-out of 8 weeks has to be performed. However, another wash-out procedure might be considered. Cholestyramine could be given orally to wash-out the drug at a dose of 8 g t.i.d. Cholestyramine reduced plasma levels of the active leflunomide metabolite by approximately 40 % in 24 hours and by 49 % to 65 % in 48 hours in three healthy volunteers. Therefore, the administration of cholestyramine is recommended in subjects who require a drug elimination procedure. If a subject receives 8 g t.i.d. for 11 days he/she could be safely randomised 4 weeks after the beginning of the 11 days treatment period.

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.

In addition, both female patients of childbearing potential and male patients with female partners of childbearing potential, taking MTX as background medication, must follow the national regulatory guidelines regarding contraception while taking these medications.

4.3 TREATMENT COMPLIANCE

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

Any missed dose has to be documented and reported to the CML.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

5.1.1 Primary endpoint

- ACR 20 response at Week 16

5.1.2 Secondary endpoints

- ACR 50 response at Week 16
- ACR 70 response at Week 16
- Change in Tender Joint Count at Week 16 as compared to baseline
- Change in Swollen Joint Count at Week 16 as compared to baseline
- Change in HAQ-DI at Week 16 as compared to baseline
- Change in SF-36 at Week 16 as compared to baseline
- Change in Dactylitis count at Week 16 as compared to baseline (in patients with dactylitis at baseline)
- Change in SPARCC Enthesitis Index at Week 16 as compared to baseline (in patients with enthesitis at baseline)
- Change in mNAPSI at Week 16 as compared to baseline (in patients with nail psoriasis)
- $PASI_{90}$ response at Week 16 assessed in patients with a $\geq$ 3% baseline PsO BSA

5.1.3 Further endpoints

- ACR 20 and secondary measures at all other measured time points
- Change in Physician's Global (VAS) at all measured time points as compared to baseline
- Change in Patient's Pain (VAS) at all measured time points as compared to baseline
- Change in Patient's Global Activity (VAS) assessments at all measured time points as compared to baseline
- Change in C-Reactive Protein (CRP) at all measured time points as compared to baseline
- Change in minimal disease activity (MDA) at at all measured time points compared to baseline
- Change in DAS28-CRP at all measured time points as compared to baseline
- PsO endpoints assessed at all measured time points in patients with a $\geq$ 3% baseline PsO BSA:
  - $PASI_{75}$ response
  - Change in sPGA clear and almost clear

- EULAR (European League Against Rheumatism) response at all measured time points
- Change in PsARC (Psoriatic Arthritis Response Criteria) at all measured time points as compared to baseline
- Presence of dactylitis (yes/no) at all measured time points
- Change in LDI at all measured time points as compared to baseline (in patients with dactylitis at baseline)
- Change in LEI at all measured time points as compared to baseline (in patients with enthesitis at baseline)
- Change in FACIT-F at all measured time points as compared to baseline
- Change in BASDAI at Weeks 16 and 24 (in patient with baseline inflammatory spondylitis) as compared to baseline
- Change in mTSS at Week 24 as compared to baseline
- Change in PsAMRIS parameters at Week 16 as compared to baseline

5.2 ASSESSMENT OF EFFICACY

Table 5.2.1 presents clinical and patient reported efficacy endpoints assessed over the course of the study. Details of the efficacy assessments are listed in the Appendix (Section 10).

Assessments are completed in all patients as per Flow Chart except:

- PASI and sPGA are assessed only in patients with ≥3% BSA of psoriatic plaques at baseline and/or with ≥3% BSA psoriatic plaques at the current visit.
- BASDAI is assessed only in patients with baseline inflammatory spondylitis based on investigator judgement.

Table 5.2: 1 Efficacy endpoint assessments

Trial periods	**Treatment**						**Follow-up**			
Visit	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**EOS**
Week	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**
Tender Joint Count (68)	x	x	x	x	x	x	x	x	x	x
Swollen Joint Count (66)	x	x	x	x	x	x	x	x	x	x
Patient's assessment of pain (VAS)	x	x	x	x	x	x	x	x	x	x
Patient's global assessment of disease activity (VAS)	x	x	x	x	x	x	x	x	x	x
Physician's global assessment of disease activity (VAS)	x	x	x	x	x	x	x	x	x	x
HAQ-DI	x	x	x	x	x	x	x	x	x	x
CRP	x	x	x	x	x	x	x	x	x	x
Leeds Dactylitis Index, dactylitis count, dactylitis presence	x	x	x	x	x	x	x	x	x	x
Leeds Enthesitis Index (0-6)	x	x	x	x	x	x	x	x	x	x
SPARCC Enthesitis Index (0-16)	x	x	x	x	x	x	x	x	x	x
BSA	x	x	x	x	x	x	x	x	x	x
PASI, assessed in patients with ≥3% BSA of psoriatic plaques at baseline and/or at current visit	x	x	x	x	x	x	x	x	x	x
sPGA assessed in patients with ≥3% BSA of psoriatic plaques at baseline and/or at current visit	x	x	x	x	x	x	x	x	x	x
mNAPSI	x		x	x	x	x	x	x	x	x
SF-36 Version 2	x		x			x		x		
FACIT-F	x		x			x		x		
BASDAI, assessed only in patients with baseline inflammatory spondylitis based on investigator judgement	x					x		x		
DAS28-CRP (calculated)	x	x	x	x	x	x	x	x	x	x
EULAR response criteria (calculated)		x	x	x	x	x	x	x	x	x
ACR 20, 50, 70 (calculated)		x	x	x	x	x	x	x	x	x
PsARC (calculated)		x	x	x	x	x	x	x	x	x
MDA (calculated)	x	x	x	x	x	x	x	x	x	x

5.3 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events
- Serious adverse events (SAEs)
- Clinical laboratory values (haematology, 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)
- Physical examination
- Vital signs
- 12-lead ECG

- Local tolerability

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

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

5.3.2 Vital signs

Vital signs evaluations will be performed at visits as shown in the Flow Chart. This includes 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 Visits 2, 4 and 6 additional evaluations will be taken at 5 minutes post-dose and 60 minutes post-dose.

Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the first dose administered and 1 hour following all other doses of study drug. Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further injections might be considered and will be agreed on between investigator and BI clinical monitor.

Anaphylaxis is a serious allergic reaction that is rapid in onset and may cause death (R11-4890). To be able to prospectively define and assess any potential cases of anaphylaxis, the clinical criteria for diagnosis of anaphylaxis defined in Section 10.16 are to be considered.

5.3.3 Safety laboratory parameters

The laboratory tests listed in Table 5.3.3: 1 will be performed at the central laboratory service provider. 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 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) (only at screening) 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
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine eGFR (estimated by CKD-EPI formula) (only at screening) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin (Reflex, in case of elevated CK) Protein, Total Albumin C-Reactive Protein (CRP) (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol HDL-Cholesterol

Table 5.3.3:1 Laboratory tests (cont.)

Category	Test name
Urine Pregnancy test (only for female patients of childbearing potential)	Human Chorionic Gonadotropin in 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 free T4 in case of abnormal TSH result)
Autoantibodies (only at screening)	Rheumatoid Factor anti-CCP antibodies
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urine (only at screening)	Albumin (quantitative) Creatinine Albumin/creatinine ratio
Infections screening (only at screening)	Hepatitis B Surface Antigen (qualitative) Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON®-TB[1] PPD skin test[1]

[1] QuantiFERON®-TB or PPD (Purified Protein Derivative) skin test may be performed.

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.

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

5.3.5 Other safety parameters

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

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

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

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

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

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

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

or

- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

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

AEs considered "Always Serious"
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.

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

The latest list of "Always Serious AEs" can be found in the Remote Data Capture (RDC) system. These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)
The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, 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 ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" (Drug Induced Liver Injury) 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
The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced

- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications)
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome)
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

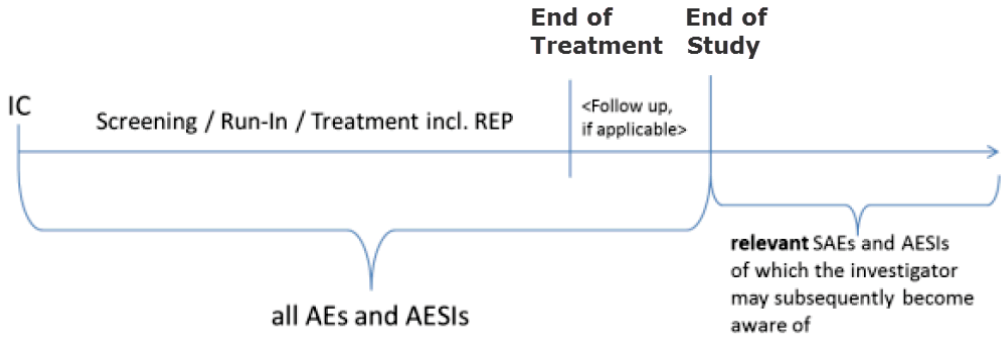
- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event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

For Japan only, the reason for the decision on causal relationship for unlisted AEs needs to be provided in the eCRF.

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 does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.



The REP is defined as 15 weeks after the last trial medication application. Therefore, EOS visit was selected to be at Week 32 (±7 days) (16 weeks of treatment plus 15 weeks of REP plus 1 week visit window). 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.

For Japan only, all SAEs and AESIs must be reported immediately to the head of the trial site.

Information required

For each AE, the Investigator should provide the information requested on the appropriate eCRF 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 eCRF and SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.

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

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

Pregnancy
In the rare case that a female patient participating in this clinical trial becomes pregnant after having taken trial medication, the Investigator must report immediately (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/AESI, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. If there is an SAE/AESI associated with the pregnancy then the SAE/AESI 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

Risankizumab concentrations will be tabulated and summary statistics will be provided by treatment group and visit and no PK parameters will be calculated. The concentration data generated in this will be incorporated into a pharmacometric analysis with other trials of risankizumab 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. ADA data will be reported as needed.

Detailed information on timing for dosing, PK and ADA sampling is provided in 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 (a nominal time of one hour pre-dose will be used). 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 assessment. For details on sample handling and logistics refer to ISF (Laboratory Manual).

5.4.3 Analytical determinations

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

The presence of ADA to risankizumab 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 assay.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKERS

This section refers to exploratory biomarkers.

5.5.1 Assessment of soluble and cellular blood biomarkers and RNA

Serum will be collected pre and post treatment. Samples may be used to to assess changes in protein levels of soluble biomarkers associated with inflammation (such as ß-defensin 2, neutrophil gelatinase associated lipocalin-2 (NGAL) and S-100 A8 protein), bone resorption (such as, MMP-3, cartilage oligomatrix protein, osteoprotegerin, RANKL) and bone formation (such as dickkopf 1, osteocalcin, bone morphogenetic protein 7, sclerostin). Samples for these assessments will be collected as per Flow Chart.

RNA (Ribonucleic Acid) will be isolated from whole blood to assess changes in expression levels pre and post treatment with risankizumab at time points indicated in the Flow Chart. Please note that messenger RNA expression levels are dynamic and not comparable to a "static" pharmacogenetic test as only the amount and not the composition of RNA will be tested.

For cellular biomarker assessment, blood will be collected to evaluate markers including but not limited to IL-23R expression on specific cell types (i.e. T cell and monocyte subsets) utilizing FACS (fluorescence-activated cell sorting) analysis at time points indicated in the Flow Chart.

Evaluations performed with the above samples may also include analysing biomarkers related to the pathway(s) targeted by the study drug, believed to be related to the disease, or in the development of new therapies.

5.5.1.1 Methods of sample collection

For the assessment of soluble proteins, approximately 8.5 mL of blood will be collected from a vein 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).

For the assessment of RNA expression from whole blood, approximately 2.5 mL of blood will be collected from a vein in PAXgene RNA tubes 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).

For FACS analysis, approximately 8.5 mL of blood will be collected from a vein at the time points indicated in the Flow Chart. 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, peripheral blood mononuclear cells (PBMCs), and RNA samples collected for biomarker sampling as listed in Section 5.5.1 and 5.5.2 may be used for further investigations (e.g. additional biomarkers for immunological and inflammatory diseases), if participation and informed consent for biomarker sample banking is agreed upon by the patient. The types of biomarkers to be analysed may include, but are not limited to: RNA proteins, lipids or metabolites.

Declining to allow storage and use of these samples will not preclude participation in this study. The study samples will be stored for a maximum period of 15 years (under consideration of local legislation and if consented by the patient) upon archiving of the final study report after study completion.

5.5.3 DNA banking

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

5.5.3.1 Method 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 Boehringer Ingelheim, AbbVie or a third party delegate. 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

X-ray assessments

The modified total Sharp score (mTSS) has been used to evaluate radiographic evidence of damage in rheumatoid arthritis and has been adapted to PsA, including distal interphalangeal joints (R15-1027). mTSS has been demonstrated to be sensitive enough to assess treatment effect over a short time (R15-1027). X-rays of hands, wrists and feet will be performed at the time points specified in the Flow Chart. Images will be read centrally for each patient at two time points (Weeks 0 and 24) in a random order and without knowledge of time point, patient identity, or treatment assignment. If a patient has to be rescued by a biologic treatment after Week 12 and prior to Week 24, X-ray images need to be obtained prior to the start of rescue biologic treatment. If the rescue treatment is initiated prior to Week 12, post-treatment X-rays are not required. The details of X-ray collection and evaluation are provided in ISF.

MRI assessments

The international "MRI in inflammatory arthritis" group of OMERACT (Outcome Measures in Rheumatology) has developed the OMERACT Psoriatic Arthritis Magnetic Resonance Image Scoring System (PsAMRIS) for evaluation of inflammatory and destructive changes in PsA hands and feet (R15-1026, R15-5992). Hand (or foot, if no swollen joint is available in hands at baseline) MRI will be performed as presented in the Flow Chart in the first approximately 90 patients from the sites selected for MRI sub-study. Images will be read centrally for each patient at two time points (Weeks 0 and 16) in a random order and without knowledge of patient identity or treatment assignment. If a patient has to be rescued by a biologic treatment after Week 4 and prior to Week 16, MRI images need to be obtained prior to the start of rescue biologic treatment. If the rescue treatment is initiated prior to Week 4, post-treatment MRIs are not required. The details of MRI scanning and evaluation are provided in ISF.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients are to adhere to the visit schedule as specified in the Flow Chart. Each visit date (with its window) is to be counted from Day 1. If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

Regarding instructions for drug administration at missed or delayed visits, please refer to Section 4.1.4.

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 and 10 (Appendix) for explanations of procedures. Additional details on procedures at selected visits are provided below.

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

Patient Reported Outcomes (PROs) should be completed by the patient on his/her own in a pre-specified order in a quiet area/room before any other visit assessments or treatments, and, if possible, before any interaction with the investigator or other members of the study team.

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

1) Patient's global assessment of disease activity (VAS)
2) Patient's assessment of pain (VAS)
3) HAQ-DI
4) BASDAI
5) SF-36
6) FACIT-F

All visits starting from Visit 2 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.

6.2.1 Screening and run-in period

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

Once consented, the patient is considered to be enrolled in the trial and has started screening. The patient 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. Visit 1 procedures may be completed over two physical visits, if needed.

The time window for Visit 1 may be extended at the discretion of the CML in conjunction with the TCM (Trial Clinical Monitor) on a case by case basis or re-screening is performed. Re-screening will be allowed once.

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

Patients who fail screening following Visit 1 assessments should be registered as a screen failure in IRT.

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

6.2.2 Treatment period

After eligibility is confirmed, randomisation via IRT will be performed at Visit 2. The treatment period is from Visit 2 (Week 0) to 7 (Week 16/EOT, End of Treatment).

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

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

6.2.3 Follow-up Period and Trial Completion

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

6.2.3.1 Early treatment termination

Patients who discontinue treatment prior to the planned Flow Chart visit schedule will complete early EOT procedures instead of the planned treatment period visit. These patients should be registered as withdrawn in IRT and return to the clinic for all follow-up visits (Visits 8, 9, 10 and EOS). These patients will not be eligible to participate in the OLE study.

6.2.3.2 Trial completion

Patients who finish the randomised treatment period will return to the clinic for follow-up visits (Visits 8, 9, 10 and EOS). Completion is defined as a patient having reached the EOS visit, except for patients who enrol in the OLE study where study completion is defined as the final visit, on or after completion of Visit 9 (Week 24).

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial is a proof-of-concept, multi-center, randomised double-blind, placebo-controlled, parallel-group Phase II dose-ranging study of risankizumab in patients with active PsA. The main objective of this trial is to show superior efficacy of treatment of risankizumab as compared to placebo for demonstration of proof-of-concept. All eligible patients will be randomised in a 2:2:2:1:2 ratio at Week 0 to receive one of the four active regimens of risankizumab or placebo. There are five treatment arms as shown in Figure 3.1: 1. Randomisation is stratified based on prior TNFi experience (naïve or experienced) and concurrent MTX (yes or no) use as determined at baseline.

The statistical model for the binary endpoint is a stratified Cochran-Mantel-Haenszel test with stratification factors of naïve or experienced to TNFi and concurrent MTX use (yes or no) as the stratification variables.

7.2 NULL AND ALTERNATIVE HYPOTHESIS

Null hypothesis: The proportion of participants who achieve ACR 20 at Week 16 is equal between the combined arms of Arm 1 and Arm 2 of risankizumab and placebo.

Alternative hypothesis: The proportion of participants who achieve ACR 20 at Week 16 in the combined arms of Arm 1 and Arm 2 of risankizumab is superior to placebo.

The overall level of significance is set to be alpha=0.05 (one-sided). The combination of Arm 1 and Arm 2 is simply for the primary inferential analyses, as these two arms represent the most intense regimens for the stated goal of achieving the proof-of-concept.

7.3 PLANNED ANALYSES

The primary analyses will be based on the intent-to-treat principle, comprising all participants who were randomised and received at least one dose of assigned therapy during the trial (full analysis set (FAS)). Safety analyses will be based on actual treatment received. Definitions of analysis sets will be specified in the TSAP.

The trial design incorporates multiple doses and dose frequencies; therefore, to obtain a proper evaluation of the effect of dose and dose frequency on ACR response, a systematic approach to the pairwise evaluation of treatment regimens must be undertaken. Although only the two most intense dose regimens (Arm 1 and

Arm 2) are considered for the evaluation of the pre-specified proof-of-concept at Week 16, Arm 3 and Arm 4 are expected to provide critical information on our dose selection objectives including the magnitude of maximum ACR response as well as the timing of maximum ACR response.

To address the dose response for the 75 mg dose, Arms 3 and 4 will be analysed at Weeks 8 and 12. Furthermore, to evaluate the effect of the loading dose, Arm 2 will be compared to Arm 3 at Weeks 8 and 12. If the loading dose shows response improvement (Arm 2 compared to Arm 3) then the examination of the possible need for a higher dose frequency can be evaluated by comparing Arm 1 against Arm 2 from Week 12 onwards. Lastly, the achieved response of all regimens will be evaluated at Week 24. The aforementioned analyses along with the evaluation of ACR 20, ACR 50, and ACR 70 over time will be instrumental not only in dose regimen selection but also in establishing the time point for the primary endpoint assessment for Phase III.

Pairwise comparison will be carried out between risankizumab dose groups and nominal p-values of these comparisons will be provided.

7.3.1 Primary endpoint analyses

The proportion of patients who achieve ACR 20 at Week 16 is the primary endpoint. The difference in proportion of participants that achieve ACR 20 between the combined groups of risankizumab (Arm 1 and Arm 2) and the placebo arm (Arm 5) will be estimated and tested using the stratified Cochran-Mantel-Haenszel risk difference estimate. Pairwise comparisons of the risankizumab dose groups will be conducted using the same stratified Cochran-Mantel-Haenszel methods. There will be no adjustments for multiplicity in these analyses.

The primary analysis will be performed when the last patient completes the Week 16 visit, when the primary endpoint (ACR 20 at Week 16) is assessed. The trial will be unblinded to the sponsor project and trial team to perform this analysis. Blinded treatment assignments will not be disseminated to the sites, investigators, and patients at this time. More details about the Week 16 analysis will be specified in the TSAP.

7.3.2 Secondary endpoint analyses

Binary endpoints will be analysed in a similar fashion as the primary endpoint.

Continuous endpoints will be analysed using a mixed model repeated measures model (MMRM) which is valid under the missing at random (MAR) assumption. Under the MMRM model, there's no explicit imputation of missing data, rather, the future statistical behavior of those participants who drop out given their past

measurements is assumed to be the same as those who remain with the same history.

Specifically, for continuous endpoints, such as HAQ-DI at Week 16, a MMRM which is valid under the missing at random (MAR) assumption will be implemented. In particular, between-treatment differences in the change in HAQ-DI at Week 16 (from baseline) will be evaluated using a MMRM with treatment regimen, clinical visit and stratification factors as fixed factors, and baseline HAQ-DI score as a fixed continuous covariate. In addition, participants will be included in the model as a random effect. Furthermore, the treatment by clinical visit interaction will be included in the model. An unstructured covariance structure will be used to model the within-patient measurements. Parameter estimation of the MMRM will be based on the residual maximum likelihood method (REML). If all post-baseline values are missing then the missing value will not be imputed and the data for the respective participant will be removed from the analysis, thus, the total number of participants providing data for analysis could be smaller than the total number of participants in the FAS. *If the analysis fails to converge, alternate covariance structures will be tested, details will be provided in the TSAP*.

7.3.3 Further endpoint analyses

Analyses at Week 24 will be conducted in a similar fashion as for Week 16 endpoints. Further efficacy endpoints will be summarized descriptively. Continuous endpoints will be summarized with the use of box plots, while proportions will be displayed by histograms as appropriate. Additional further endpoints may be defined in the trial statistical analysis plan (TSAP).

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 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 (REP) will be considered ‘treatment-emergent’. The REP is defined as 15 weeks after the last trial medication application and will include adverse events reported through EOS visit. 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 the safety analysis will be provided in the TSAP.

7.3.5 Pharmacokinetic analyses

Descriptive statistics of risankizumab concentration measurements by treatment group and visit will be provided in clinical trial report. Pharmacokinetic data will also be analysed using population pharmacokinetic approaches. For this purpose, data may also be combined with data from other trials and will be summarized as a stand-alone report.

7.3.6 Pharmacodynamic analyses

As the data from previous risankizumab trials, primarily in psoriasis, suggest a pharmacokinetic (PK)-pharmacodynamic (PD) relationship for efficacy endpoints, 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. Model-based PK-PD analyses (PMx) will be part of a stand-alone report(s) and not part of the clinical trial report. Trial specific PK-PD analyses based on observed data will be reported in the clinical trial report, as appropriate. Other exploratory analyses of drug concentration, biomarker or safety data may be performed using data obtained as part of this trial.

In total, data from 40 patients in Arms 1, 2, 3 and 5 and 20 patients in Arm 4 (for a total of 180 patients) are considered sufficient to explore the exposure-response relationship through modelling.

7.3.7 Biomarker analyses

Changes in cellular, serum, 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 handling of missing data for the primary endpoint and secondary endpoints for data up to Week 24 will be handled as follows.

Participants that use protocol-prohibited medications, a non-responder imputation (NRI) will be used to impute their binary endpoint. Missing data due to loss of follow-up or due to the withdrawal of consent will be addressed by considering the participant a non-responder for their binary endpoint. For all other cases, regardless of the type of the endpoint, the de facto estimand, ITT (Intention-To-Treat), will be used. Namely, analyses will be conducted using the observed response regardless of adherence to treatment or early discontinuation. Hence, it is critical to continue collecting data on participants even if they withdraw from the study, except for the cases for which informed consent is withdrawn.

Details on the algorithm to impute mTSS will be described in TSAP.

7.6 RANDOMISATION

Eligible patients will be randomised to five parallel groups, Arm 1 – Arm 5, in a 2:2:2:1:2 ratio, respectively. See Figure 3.1: 1 for a description of the study arms.

Randomisation will be stratified with respect to naïve or experienced to TNFi therapy and concurrent MTX (yes or no) use as determined at baseline.

The randomisation list will be generated using a validated system, which involves a pseudorandom number generator to guarantee the reproducibility of the assignments. This randomisation list will be checked by an independent statistician and used by a third-party. IRT system to assign randomisation numbers to eligible patients.

7.7 DETERMINATION OF SAMPLE SIZE

Sample size was determined on the basis of a one-sided comparison between the average in ACR 20 response at Week 16 of Arm 1 and Arm 2 versus placebo. With the assumed Week 16 ACR 20 response rate of 38% in the combined arms (Arm 1 and Arm 2) and of 15% in the placebo arm, 40 participants each for Arm 1, Arm 2 and placebo will provide 85% power to detect a 23% difference in proportion (combination of Arm 1 and Arm 2 versus placebo) using a one-sided test of 0.05 significance. Please see Table 7.7: 1 for the estimated power based on a range of possible placebo rates. Power analysis was conducted using the Chi-Square Test; the software used was ADDPLAN version 6.0.4.

Although not included in the hypothesis testing strategy, Arm 3 will have about 40 participants. In addition, we plan to enrol 20 participants into Arm 4 for pharmacokinetic modelling. The total sample size for this study is therefore 180 participants. Figure 3.1: 1 provides details on the study arms. This study is not powered to detect statistically significant differences between risankizumab treatment arms.

Table 7.7: 1 Power and sample size for the superiority test of ACR 20 at Week 16

	Risankizumab	Placebo	Difference	1-sided type I error	Total sample size	Drop-out rate	Power
ACR 20 rate at Week 16	38%	15%	23%	0.05	120	0%	85%
	40%	17%					84%
	42%	19%					83%
	44%	21%					82%
	46%	23%					81%
	48%	25%					80%
	38%	17%	21%				78%
	38%	19%	19%				69%

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), the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) 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.

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.

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

confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the Sponsor, Sponsor's designees, 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 (eCRF) 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 eCRF 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 (Food and Drug Administration)). 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.

8.3.3 Storage period of records

Trial sites:

The trial sites must retain the source and essential documents (including ISF) according to the national or 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 risankizumab this is the current version of the Investigator's Brochure (c02161217).

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 in Section 6.2.3.

The Last Patient Visit Primary Endpoint is defined as last patient in the trial to complete Visit 7, 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.

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

8.7 PROTOCOL VIOLATIONS

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

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

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

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10. APPENDICES

10.1 CASPAR

To meet the **CASPAR** (**C**l**AS**sification criteria for **P**soriatic **AR**thritis) criteria*, a patient must have inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following 5 categories (R15-1001):

1. Evidence of **current psoriasis, a personal history of psoriasis, or a family history of psoriasis**.
   - Current psoriasis is defined as psoriatic skin or scalp disease present today as judged by a rheumatologist or dermatologist.†
   - A personal history of psoriasis is defined as a history of psoriasis that may be obtained from a patient, family physician, dermatologist, rheumatologist, or other qualified health care provider.
   - A family history of psoriasis is defined as a history of psoriasis in a first- or second-degree relative according to patient report.
2. Typical **psoriatic nail dystrophy** including onycholysis, pitting, and hyperkeratosis observed on current physical examination.
3. A **negative test result for the presence of rheumatoid factor** by any method except latex but preferably by enzyme-linked immunosorbent assay or nephelometry, according to the local laboratory reference range.
4. Either current **dactylitis,** defined as swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist.
5. **Radiographic evidence of juxtaarticular new bone formation**, appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand or foot.

* The CASPAR criteria have specificity of 98.7% and sensitivity of 91.4%.
† Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.

10.2 JOINT ASSESSMENT

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

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

* Hip will only be assessed for TJC (Tender Joint Counts), not for SJC (Swollen Joint Count).

Joints which will also count for DAS28-CRP evaluation.

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

Number of tender joints:

The 68 joints assessed for tenderness include the 2 temporomandibular, 2 sternoclavicular, 2 acromioclavicular joints, 2 shoulders, 2 elbows, 2 wrists, 10 metacarpophalangeal, 10 proximal interphalangeal, 8 distal interphalangeal joints of the hands, the 2 hips, 2 knees, 2 ankles2 mid-tarsal, 10 metatarsophalangeal, and 10 proximal interphalangeal joints of the feet.

Joints are be scored as either tender (1) or not tender (0)

Number of swollen joints:

The 66 joints to be examined for swelling are the same as those examined for tenderness, however excluding both hip joints.

Joints are to be scored as either swollen (1) or not swollen (0).

Synovial fluid and/or soft tissue swelling but not bony overgrowth represents a positive result for swollen joint count.

Data will be recorded for tender and swollen joints (right or left side), i.e. a box (no, yes or not applicable) needs to be ticked for all joints. The total number of tender and swollen joints (right and left) will be automatically calculated in the eCRF.

10.3 ACR RESPONSE CRITERIA

ACR 20:

- At least 20% improvement in SJC* compared to baseline **AND**
- At least 20% improvement in TJC* compared to baseline **AND**
- At least 20% improvement in at least 3 out of the following 5 variables

ACR 50:

- At least 50% improvement in SJC* compared to baseline **AND**
- At least 50% improvement in TJC* compared to baseline **AND**
- At least 50% improvement in at least 3 out of the following 5 variables

ACR 70:

- At least 70% improvement in SJC* compared to baseline **AND**
- At least 70% improvement in TJC* compared to baseline **AND**
- At least 70% improvement in at least 3 out of the following 5 variables

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

* SJC and TJC are evaluated according to the complete joint count (see Appendix 10.2).

Reference: R96-2379

For Patient's assessment of PsA pain intensity c.f. Section 10.14.5

For Patient's global assessment of disease activity c.f. Section 10.14.6

Physician's global assessment of disease activity
The physician's global assessment of disease activity will be performed using 100 mm VAS ranging from no disease activity to maximal disease activity, after the question "Considering all the ways the disease affects your patient, draw a line on the scale for how well his or her condition is today". To enhance objectivity, the physician must not be aware of the specific patient's global assessment of disease activity, when performing his own assessment on that subject.

10.4 LEEDS DACTYLITIS INDEX (LDI)

The LDI basic measures the ratio of the circumference of the affected digit to the circumference of the digit on the opposite hand or foot, using a minimum difference of 10% to define a dactylitic digit. The ratio of circumference is multiplied by a tenderness score, using a modification of LDI which is a binary score (1 for tender, 0 for non-tender). If both sides are considered involved, or the circumference of the contralateral digit cannot be obtained, the number will be compared to data provided in the standard reference tables (Table 10.4.1 and 10.4.2). This modification is referred to as LDI basic and will be applied in this study. The LDI requires a finger circumference gauge or a tape measure to measure digital circumference.

Dactylitis count

The dactylitis count is the number of fingers and toes with dactylitis, with a range of 0-20.

Presence of dactylitis

If dactylitis is present with any finger or toe, the subject is counted as a subject with dactylitis.

Table 10.4.1. – Hands (in cm)

Digit	**Men**	**Women**
Thumb	7.0	5.8
Index	6.3	5.4
Middle	6.3	5.4
Ring	5.9	5.0
Little	5.2	4.4

Table 10.4.2. – Feet (in cm)

Digit	**Men**	**Women**
Central toe	8.2	7.2
Second	5.2	4.6
Middle	5.0	4.4
Fourth	5.0	4.4
Little	5.2	4.5

Reference: R15-4755

10.5 LEEDS ENTHESITIS INDEX (LEI)

LEI is a validated enthesitis index that uses 6 sites for evaluation of enthesitis: lateral epicondyle humerus left and right, Achilles tendon insertion left and right and medial condyle femur left and right. The LEI demonstrated substantial to excellent agreement with other scores in the indication of psoriatic arthritis.

Enthesitis count

Tenderness on examination is recorded as either present (1) or absent (0) for each of the 6 sites, for an overall score range of 0–6.

Presence of enthesitis

If enthesitis is present with any of the 6 sites (lateral epicondyle humerus left and right, Achilles tendon insertion left and right and medial condyle femur left and right), the subject is counted as a subject with enthesitis.

Reference: R15-1355

10.6 SPONDYLOARTHRITIS RESEARCH CONSORTIUM OF CANADA (SPARCC) ENTHESITIS INDEX

Enthesial sites examined include medial epicondyle (left and right), lateral epicondyle (left and right), supraspinatus insertion into greater tuberosity of humerus (left and right), greater trochanter (left and right), quadriceps insertion into superior border of patella (left and right), patellar ligament insertion into inferior pole of patella or tibial tubercle (left and right), Achilles tendon insertion into calcaneum (left and right), plantar fascia insertion into calcaneum (left and right).

Enthesitis count

Tenderness on examination is recorded as either present (1) or absent (0) for each of the 18 sites, for an overall score range of 0–16.

Reference: R15-4751

10.7 MINIMAL DISEASE ACTIVITY

The proportion of subjects achieving minimal disease activity (MDA) will be analysed. A patient is classified as achieving MDA when meeting 5 of the 7 following criteria are met:

- Tender joint count ≤ 1
- Swollen joint count ≤ 1
- PASI ≤ 1 or BSA ≤ 3 %
- Patient pain-VAS ≤ 15
- Patient global activity VAS ≤ 20
- HAQ-DI ≤ 0.5
- Tender entheseal points ≤ 1

Reference: R15-1218

10.8 DAS28 4V – CRP

Will be calculated taking the following variables into account:

- TJC (on 28 joints, see Appendix 10.2)
- SJC (on 28 joints, see Appendix 10.2)
- Patient's global assessment of the disease on VAS (0-100)
- Serum CRP level (mg/L)

The formula used for DAS28 4v - CRP is: DAS28=0.56*$\sqrt{}$(TJC) + 0.28*$\sqrt{}$(SJC) + 0.36 *Ln(CRP+1) + 0.014*VAS + 0.96

Reference: R00-0676

10.9 EULAR RESPONSE CRITERIA

DAS28 at endpoint	**Improvement in DAS28 from baseline:**		
	> 1.2	**> 0.6 and ≤ 1.2**	**≤ 0.6**
≤ 3.2	Good	Moderate	None
> 3.2 and ≤ 5.1			
> 5.1			

10.10 PSARC RESPONSE

A subject is defined as a PsARC responder if, and only if, they have an improvement in two of the following four factors (with at least one factor being a joint count) and no worsening in the remaining factors:

- Patient global assessment of disease activity (0-100 mm VAS scale, improvement defined as decrease of ≥ 20 mm)
- Physician global assessment of disease activity (0-100 mm VAS scale, improvement defined as decrease ≥ 20 mm)
- Tender 68-joint count (improvement defined as decrease of ≥ 30%)
- Swollen 66-joint count (improvement defined as decrease of ≥ 30%)

Reference: R06-0073

10.11 PASI SCORE DEFINITIONS AND USE

The PASI score is an established measure of clinical efficacy for psoriasis medications (R96-3541).

The PASI is a tool which provides a numeric scoring for patients overall psoriasis disease state, ranging from 0 to 72. It is a linear combination of percent of surface area of skin that is affected and the severity of erythema, infiltration, and desquamation over four body regions.

The endpoints used are based on the percent reduction from baseline, generally 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

10.12 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 10.12: 1) (R15-5200).
The assessment is considered "static" which refers to the patients disease state at the time of the assessments, without comparison to any of the patient's previous disease states, whether at Baseline or at a previous visit.

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

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

Erythema
0 Normal (post-inflammatory hyper/hypopigmentation may be present)
1 Faint, diffuse pink or slight red coloration
2 Mild (light red coloration)
3 Definite red coloration (Dull to bright red)
4 Bright to Deep red coloration of lesions

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

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

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

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

Table 10.12: 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

10.13 MNAPSI – MODIFIED NAIL PSORIASIS SEVERITY INDEX

Modified NAPSI Instructions

This tool will ask you to assess each abnormality for each of a subject's fingernails. If you question which grade to give, your answer should be the lower of the grades. Three features or groups of features (pitting, onycholysis and oil-drop dyschromia, and crumbling) of each fingernail will be graded on a scale from 0 to 3, according to the directions below. Four features (leukonychia, splinter hemorrhages, hyperkeratosis, and red spots in the lunula) will be graded as either present or absent for each fingernail.

1. Onycholysis: Separation of the nail plate from the nail bed. The separated part of the nail is opaque and can have white, yellow, or greenish tinge. If there is a piece of nail missing, estimate where the nail normally would have ended at the end of the nail bed, and count that missing part as involved in onycholysis.

Oil-drop (salmon patch) dyschromia: Reddish-brown discoloration under the nail plate.

Onycholysis and oil-drop dyschromia are considered together. When looking at the nail, combine the total percentage area of the nail that is affected by either and use that combined total to score the nail.

Score	**Percent of nail with onycholysis or oil-drop dyschromia present**
0	No onycholysis or oil drop dyschromia present
1	1-10% of the nail has onycholysis or oil-drop dyschromia
2	11-30% of the nail has onycholysis or oil-drop dyschromia
3	> 30% of the nail has onycholysis or oil-drop dyschromia

2. Pitting: Small, sharply defined depressions in the nail surface. Pits are discrete abnormalities ("ice-pick-like"). If there is nail plate crumbling that is confluent with pits, do not score for pits. If the pits are separate from crumbling, they may be scored regardless of whether crumbling is present or not.

Score	Number of pits
0	0
1	1-10
2	11-49
3	> 50

3. Nail plate crumbling: Crumbling or fragmentation of friable nail plate which may be associated with confluent pitting. Crumbling involves alteration of the nail plate surface. Horizontal ridging of the nail, "wave-like" appearance, and horizontal lines are all features of crumbling.

Score	Percent of nail with crumbling present
0	No crumbling
1	1-25% of the nail has crumbling
2	26-50% of the nail has crumbling
3	> 50% of the nail has crumbling

The next 4 abnormalities are scored only by their presence or absence. A score of 1 indicates present and a score of zero indicates not present.

1. Leukonychia: White spots in the nail plate due to psoriasis in the mid matrix. Leukonychia are just color changes. If it appears that there is depression or irregularity to the nail surface, this may be pitting or crumbling, not leukonychia. If the leukonychia is adjacent to, or confluent with crumbling or pits, it is counted as part of the crumbling or pitting and not as a separate abnormality.

2. Splinter hemorrhages: Small, longitudinal, linear, dark brown hemorrhage under the fingernail.

3. Nail bed hyperkeratosis: Thickened keratin in the nail bed.

4. Red spots in the lunula: Small pink or red macules in the lunula.

Reference: R15-5029

10.14 PATIENT REPORTED OUTCOMES

10.14.1 Health Assessment Questionnaire Disability Index (HAQ-DI)

The HAQ-DI is a twenty-item patient reported outcome instrument that assesses current physical function/ disability. The HAQ-DI covers eight categories (dressing and grooming, hygiene, arising, reach, eating, grip, walking and common daily activities). There are four response options, ranging from 0 (no difficulty) to 3 (unable to do). HAQ-DI score is reported as a mean score between 0 and 3 by dividing the total score by the number of items answered (R15-3849).

The HAQ-DI has been the most-widely used instrument to assess physical function clinical trials of treatments for rheumatoid and psoriatic arthritis and has extensive evidence of its validity and other psychometric properties in this context (R15-3846).

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

10.14.2 BASDAI (BATH AS DISEASE ACTIVITY INDEX)

Each question is answered on a 0 to 10 scale. For questions 1-5, 0 means none and 10 means very severe; for question 6, 0 means 0 hours and 10 means 2 or more hours. All questions refer to last week.

1. How would you describe the overall level of fatigue/tiredness you have experienced?

2. How would you describe the overall level of AS neck, back or hip pain you have had?

3. How would you describe the overall level of pain/swelling in joints other than neck, back or hips you have had?

4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?

5. How would you describe the overall level of morning stiffness you have had from the time you wake up?

6. How long does your morning stiffness last from the time you wake up?

Calculation of BASDAI: compute the mean of questions 5 and 6. Calculate the sum of the values of question 1–4 and add the result to the mean of questions 5 and 6. Divide the result by 5.

10.14.3 Medical Outcome Short Form Health Survey (SF-36) Version 2 (Acute Form)

The SF-36 is a widely used and extensively studied instrument to measure health-related quality of life among healthy subjects and patients with acute and chronic conditions. It consists of eight subscales that can be scored individually: Physical Functioning, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health (R97-1093). Two overall summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS) also can be computed (R96-1184). The SF-36 has proven useful in monitoring general and specific populations, comparing the relative burden of different disease, differentiating the health benefits produced by different treatments, and in screening individual subjects.

The purpose of the SF-36 in this study is to assess the HRQoL of subjects. Given the acute nature of this disease, version 2, with a 1-week recall period, will be used in this study.

References: R97-1093, R96-1184

10.14.4 FUNCTIONAL ASSESSMENT OF CHRONIC ILLNESS THERAPY-FATIGUE (FACIT-F)

The FACIT-Fatigue is a 13-item questionnaire (Cella 1993; Yellen 1997) that assesses self-reported fatigue and its impact upon daily activities and function.

The purpose of FACIT-Fatigue in this study is to assess the impact of fatigue on subjects with PsA.

Number of items: 13 items.

Response options/scale: Answers are based on a 5-point Likert scale. Responses of “not at all”, “a little”, “somewhat”, “quite a bit”, and “very much” are available for each question, and correspond to scores of 0, 1, 2, 3, and 4, respectively.

Recall period for items: 7 days.

Reference: R10-6433, R07-4311

10.14.5 Patient’s assessment of PsA pain intensity

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

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

“Please indicate with a vertical mark (|) through the horizontal line the most pain you had from your psoriatic arthritis today”.

10.14.6 Patient's global assessment of disease activity

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

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

"Considering all the ways psoriatic arthritis affects you, please indicate with a vertical mark (|) through the horizontal line how well you are doing today".

10.15 CLINICAL CRITERIA FOR DIAGNOSIS OF ANAPHYLAXIS

Anaphylaxis is highly likely when any one of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula)

    AND AT LEAST ONE OF THE FOLLOWING

    a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure *to a likely allergen for that patient* (minutes to several hours):

    a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

    b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

    c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

    d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to *known allergen for that patient* (minutes to several hours):

    a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*

    b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

PEF, Peak expiratory flow; *BP*, blood pressure.

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

Reference: R11-4890

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		12 October 2016
EudraCT number		2015-003625-34
BI Trial number		1311.5
Investigational Product		BI 655066/ABBV-066/risankizumab
Title of protocol		A randomised, double-blind, placebo-controlled, proof-of-concept, dose-ranging study of BI 655066/ABBV-066/risankizumab in patients with active psoriatic arthritis
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, CLINICAL TRIAL PROTOCOL SYNOPSIS, and all sections

Number of global amendment		1
Description of change 1		Add information for BI 655066/ABBV-066/risankizumab and AbbVie. All instances of BI drug or BI investigational product or BI 655066 found within the protocol refers to either names for this compound: BI 655066 or ABBV-066 or risankizumab except where outside documents or previous BI studies are referenced and only refers to BI 655066 (e.g., Investigator's Brochure, Study Manual, references, investigational drug product labels). All instances of BI, Boehringer Ingelheim, Boehringer Ingelheim International GmbH or Boehringer Ingelheim Pharmaceuticals, Inc found within the protocol are changed to Boehringer Ingelheim/AbbVie.
Rationale for change 1		The protocol has been amended to inform sites of a change in sponsor of the 1311.5 study in the US, and of an open label extension (OLE) study for 1311.5 study patients. The extension study will be sponsored by AbbVie as part of collaboration between Boehringer Ingelheim and AbbVie in the development of BI-665066/ABBV-066. The purpose of this amendment is to incorporate the changes summarized below as well as editorial changes. Risankizumab is the name of the compound.
Section to be changed		FLOW CHART
Description of change 2		Revision to visit schedule for OLE participants.
Rationale for change 2		Subjects that elect to enrol in the extension study may complete the 1311.5 study at V9 or V10 and therefore it is necessary to revise the visit schedule and the assessment period.
Section to be changed		ABBREVIATIONS
Description of change 3		Add abbreviation.

Number of global amendment		1
Rationale for change 3		This is an administrative change to add an abbreviation.
Section to be changed		2.2 TRIAL OBJECTIVES
Description of change 4		Addition of instruction in the assessment period for OLE study patients.
Rationale for change 4		Subjects that elect to enrol in the extension study may complete the 1311.5 study at V9 or V10 and therefore it is necessary to revise the visit schedule and the assessment period.
Section to be changed		2.3 BENEFIT – RISK ASSESSMENT
Description of change 5		Addition of rescue therapy instruction for patients that enrol in OLE.
Rationale for change 5		Therapy restriction required to maintain eligibility for OLE study.
Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change 6		Eligibility for OLE study and revision of study diagram.
Rationale for change 6		Explanation of open label study basic eligibility criteria and revised visit schedule and visual representation of trial design.
Section to be changed		3.1.1 ADMINISTRATIVE STRUCTURE OF THE TRIAL
Description of change 7		Update of sponsorship of the study. Update of administrative structure of the study.
Rationale for change 7		Administrative structure of the trial was updated to reflect AbbVie as sponsor in the US only and to reflect that data management will be done by BI according to BI SOPs and the statistical evaluation will be done by AbbVie according to AbbVie SOPs.
Section to be changed		3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP
Description of change 8		Revision of assessment period and visit schedule for patients that enrol in OLE.
Rationale for change 8		Explanation of revised assessment period and visit schedule for patients that enrol in OLE.
Section to be changed		3.3.4.1 Removal of individual patients
Description of change 9		Clarification and addition of eligibility instruction for OLE patients.

Number of global amendment		1
Rationale for change 9		Added to describe eligibility restrictions for participation in OLE.
Section to be changed		4.1.2 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS
Description of change 10		Added description of stratification within the study.
Rationale for change 10		Further clarification of study stratification.
Section to be changed		5.2 ASSESSMENT OF EFFICACY
Description of change 11		Correct table 5.2: 1, follow-up period starts at visit 8.
Rationale for change 11		This is an administrative change to correct table.
Section to be changed		5.3.3 SAFETY LABORATORY PARAMETERS
Description of change 12		Some laboratory parameters are better specified. Added Albumin/creatinine ratio in urine. Correct typos.
Rationale for change 12		Update to correct table.
Section to be changed		5.3.4 ELECTROCARDIOGRAM
Description of change 13		Source data for ECG is better specified.
Rationale for change 13		Update information for source data of ECG.
Section to be changed		5.4.1 ASSESSMENT OF PHARMACOKINETICS
Description of change 14		PK assessments revised to describe how summary statistics will be provided.
Rationale for change 14		Update to PK assessment.
Section to be changed		5.5.1 ASSESSMENT OF SOLUBLE AND CELLULAR BLOOD BIOMARKERS AND RNA
Description of change 15		Added additional types of analyses to be performed on samples.
Rationale for change 15		Update to clarify the additional types of cellular biomarker analyses that could be performed on the blood samples.
Section to be changed		5.5.2 BIOMARKER SAMPLE BANKING
Description of change 16		Added additional type of samples to be banked and additional analyses to be performed.
Rationale for change 16		Update to include PBMC samples and additional scope of sample analysis.
Section to be changed		5.5.3.2 Analytical determinations

Number of global amendment		1
Description of change 17		Update information for DNA banking samples.
Rationale for change 17		Updated protocol to reflect that DNA banking samples will be stored at Boehringer Ingelheim, AbbVie or third party delegate.
Section to be changed		5.6 OTHER ASSESSMENTS
Description of change 18		Update information for central read of MRI images.
Rationale for change 18		Update protocol to clarify that MRI images will be read in random order.
Section to be changed		6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS
Description of change 19		Clarify when patient reported outcomes (PROSs) are to be done.
Rationale for change 19		Update protocol to clarify that PROs have to be done first at a visit.
Section to be changed		6.2.3.1 Early treatment termination
Description of change 20		Description of eligibility for patients that enrol in OLE
Rationale for change 20		To ensure appropriate patients are enrolled in the OLE study
Section to be changed		6.2.3.2 Trial completion
Description of change 21		Added description of completion for patients that enrol in OLE
Rationale for change 21		Study completion revised for OLE patients.
Section to be changed		7.3.1 PRIMARY ENDPOINT ANALYSES
Description of change 22		Moved paragraph from section 7.4 to section 7.3.1.
Rationale for change 22		To accurately reflect the analysis process.
Section to be changed		7.3.4 SAFETY ANALYSES
Description of change 23		Safety analyses section update to reflect that AbbVie will produce summary tables and listings and to indicate that safety analyses will be based on AbbVie standards.
Rationale for change 23		Due to collaboration agreement.
Section to be changed		7.4. INTERIM ANALYSES
Description of change 24		Moved paragraph from section 7.4 to section 7.3.1. To inform that no interim analysis will be done.
Rationale for change 24		To accurately reflect the analysis process.
Section to be changed		10.2 JOINT ASSESSMENT
Description of change 25		Update instructions for joint count.

Number of global amendment		1
Rationale for change 25		Clarify that there is no extra rule for joint count of dactylitic digits.
Section to be changed		10.10 BASDAI (BATH AS DISEASE ACTIVITY INDEX)
Description of change 26		Moved from section 10.10 to section 10.14.2.
Rationale for change 26		To move information for BASDAI to the correct section.
Section to be changed		10.13 MNAPSI – MODIFIED NAIL PSORIASIS SEVERITY INDEX
Description of change 27		Update instruction of mNAPSI.
Rationale for change 27		Clarify that visual analog scale for global assessment of fingernails will not be done.
Section to be changed		10.14.2 BASDAI (BATH AS DISEASE ACTIVITY INDEX)
Description of change 28		Moved from section 10.10 to section 10.14.2.
Rationale for change 28		To move information for BASDAI to the correct section.

APPROVAL / SIGNATURE PAGE

Document Number: c03416278 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol

Title: A randomised, double-blind, placebo-controlled, proof-of-concept, dose-ranging study of BI 655066/ABBV-066/risankizumab in patients with active psoriatic arthritis

Signatures (obtained electronically)

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[redacted]		12 Oct 2016 15:59 CEST
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