Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c03357704-04**
EudraCT No.:	2014-005102-38	
BI Trial No.:	1311.4	
BI Investigational Product:	BI 655066/ ABBV-066 (risankizumab)	
Title:	BI 655066 / ABBV-066 (risankizumab) versus placebo **I**n a **M**ulticenter randomized double-blind study in patients with **M**oderate to severe c**h**ronic pl**a**que psoriasis evaluati**n**g the effi**c**acy and safety with randomized withdrawal and r**e**-treatment (IMMhance)	
Brief Title:	BI 655066 / ABBV-066 (risankizumab) in moderate to severe chronic plaque psoriasis with randomized withdrawal and re-treatment.	
Clinical Phase:	III	
Trial Clinical Monitor:	[redacted] Boehringer Ingelheim Pharmaceuticals 900 Ridgebury Road Ridgefield CT USA 06877 [redacted]	
Coordinating Investigator:	[redacted]	
Status:	Revised Protocol (based on Global Amendment #3)	
Version and Date:	**4.0**	**Date: 11-Oct-2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: **Boehringer Ingelheim**			
Name of finished product: **Not Applicable**			
Name of active ingredient: BI 655066/ ABBV-066 (risankizumab)			
Protocol date: 22-Oct-2015	**Trial number:** 1311.4		**Revision date:** **11-Oct-2016**

Title of trial:	BI 655066 / ABBV-066 (risankizumab) versus placebo **I**n a **M**ulticenter randomized double-blind study in patients with **M**oderate to severe c**H**ronic pl**A**que psoriasis evaluati**N**g the effi**C**acy and safety with randomized withdrawal and r**E**-treatment (IMMhance)
Coordinating Investigator:	[redacted]
Trial site(s):	Multicentre Trial conducted in approximately 10 countries
Clinical phase:	III
Objective(s):	The primary objectives of this trial are to assess the safety and efficacy of BI 655066 150 mg in comparison to placebo in patients with moderate to severe chronic plaque psoriasis with the primary efficacy evaluation at 16 weeks. Following drug withdrawal, the maintenance of response as well as the response to retreatment after relapse will be evaluated. In a subset of psoriasis patients with concomitant psoriatic arthritis, the signs and symptoms of psoriatic arthritis will be evaluated to assess improvement during the trial.
Methodology:	This is a confirmatory, multinational, multicenter, randomized, double-blind, placebo controlled study. Patients will be randomized at a ratio of 4:1 to either BI 655066 150 mg or to placebo. Randomisation will be stratified with to respect weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1)

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	All patients will receive the first dose of study medication on day 1 (Randomisation), the second dose at Week 4, and then every 12 weeks thereafter with the last dose at Week 88. After the end of treatment, patients will continue in the 16 week follow up period. Patients will be offered to roll over into an open label extension (OLE) trial, if they have completed the study and meet the inclusion criteria for the OLE trial at the End of Observation (EOO) visit.
No. of patients:	
total entered:	Approximately 500 patients
each treatment:	400 BI 655066, 100 placebo
Diagnosis :	Moderate to severe chronic plaque psoriasis
Main criteria for inclusion:	- Male or female patients with age ≥ 18 years at screening - Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. - Have stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis at both Screening and Baseline (Randomisation): • Have an involved body surface area (BSA) ≥ 10% and • Have a Psoriasis Area and Severity Index (PASI) score ≥ 12 and • Have a static Physician Global Assessment (sPGA) score of ≥ 3. - Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator

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Test product(s):	BI 655066
dose:	150 mg (2 syringes, 75mg each) at week 0, 4 and every 12 weeks
mode of administration:	s.c.
Comparator products:	Placebo
dose:	Not applicable
mode of administration:	s.c.
Duration of treatment:	88 weeks
Endpoints	Primary Endpoints: • Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16 • Achievement of an sPGA score of clear or almost clear (0 or 1) at Week 16 Key Secondary Endpoints: • Achievement of 75% reduction from baseline PASI score (PASI 75) at Week 16 • Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16 • Achievement of an sPGA score of clear (0) at Week 16 • Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16 • Achievement of an sPGA score of clear or almost clear (0 or 1) at Week 52 Other Secondary Endpoints: • Achievement of PASI 75 at Week 52 • Achievement of PASI 90 at Week 52

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	• Achievement of PASI 100 at Week 52 Note that all key and other secondary endpoints at Week 52 will only be assessed for patients re-randomised at Week 28.
Safety criteria:	Physical examinations, vital signs, 12 lead electrocardiogram (ECG), laboratory testing, adverse events, local tolerability
Statistical methods:	Co-primary analysis: The achievement of PASI 90 and sPGA of clear or almost clear at Week 16 are the co-primary endpoints and are binary variables with values of 0 or 1. The difference in proportion responding between the BI 655066 arm and placebo arm will be estimated and tested using the Cochran-Mantel-Haenszel risk difference estimate stratified by the randomisation factors of weight (≤ 100 kg versus >100 kg) and prior exposure to TNF antagonists (0 versus ≥1) with weights proposed by Greenland & Robins. Secondary analysis: The same methods for the primary analyses will be used to analyse all secondary endpoints since they are all binary endpoints. All hypotheses will be tested in a hierarchical order using two-sided tests with a type I error of 0.05.

FLOW CHART 1

Trial Period	Screening	Treatment																				Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21 EOT	Follow-up #1[12]	Follow-up #2 (EOO)
Week			4	8	12	16	20	24	28	32	36	40	44	48	52	58	64	70	76	82	88	94 EOT+ 6wks	104 EOT+ 16wks
Day	-42 to -7	1	28	56	84	112	140	168	196	224	252	280	308	336	364	406	448	490	532	574	616	658	728
Visit window (days)	N/A		±3	±7	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
Informed consent	X																						
Demographics	X																						
Medical history	X																						
Smoking , alcohol history	X																						
Psoriatic arthritis Medical History[19]	X																						
Inclusion-/exclusion criteria	X	X																					
% BSA involvement	X	X																					
Psoriasis therapy history	X																						
Height	X																						
Weight, waist circumference[9]	X								X						X				X				X
CASPAR for PsA[8]	X																						
Vitals	X	X[13]	X[13]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[4]	Xc	Xt	Xt	Xt	Xt	Xt	Xt	Xc	Xt	Xt	Xt	Xt	Xt	Xt	Xc	Xt	Xt	Xt	Xc	Xt	Xc	Xt	Xc
12 lead-ECG	X	X	X			X			X			X			X		X		X		X		X
Safety laboratory testing[14]	X	X	X			X			X			X			X		X		X		X		X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection Testing [23]	X														X								X
Pregnancy testing[1]	Xs	Xu	Xu			Xu			Xu			Xu			Xu		Xu		Xu		Xu		Xu
Optional DNA Banking[2,]		X																					
Randomisation via IRT[5]		X							X														
Contact IRT	X	X	X			X			X	X[11]	X[11]	X	X[11]	X[11]	X	X[11]	X	X[11]	X	X[11]	X		X
Administer trial drug[24]		X	X			X			X			X			X		X		X		X		
Local tolerability assessment			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood sampling for PK		X[7]	X[7]		X	X[7]			X[7]	X		X[7]			X[7]	X	X[7]	X	X[7]		X[7]		X
ADA assessment sampling		X[7]	X[7]			X[7]			X[7]			X[7]			X[7]		X[7]		X[7]		X[7]		X
Biomarker sampling[10,]		X	X			X			X			X			X		X		X		X		X
PASI, sPGA	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
NAPSI, PSSI, PPASI		X				X			X														
DLQI [3]		X			X	X																	
HAQ-DI, Pain VAS/ PtGA VAS[3]		X				X			X						X				X				X

Trial Period	Screening	Treatment																				Follow-up	
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21 EOT	Follow-up #1[12]	Follow-up #2 (EOO)
Week			4	8	12	16	20	24	28	32	36	40	44	48	52	58	64	70	76	82	88	94 EOT+ 6wks	104 EOT+ 16wks
Day	-42 to -7	1	28	56	84	112	140	168	196	224	252	280	308	336	364	406	448	490	532	574	616	658	728
Visit window (days)	N/A		±3	±7	±7	±3	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7
TJC/SJC, DAS28[16]		X				X			X						X				X				X
sPGA assessment of relapse[22]										X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[18]	X[18]	X[21]		
Termination of trial drug[15]																					X		
Trial completion																							X
Open label extension[6]																							X[6]
Vital Status[20]																							X

Flow Chart 1 Footnotes

1. Pregnancy Testing: Xs =serum testing; Xu= onsite urine testing; Serum pregnancy is done at screening and as a reflex when urine testing is positive.
2. Voluntary DNA banking sample will be stored after informed consent is given. This may be a separate informed consent or part of the main informed consent in accordance with local ethical and regulatory requirements. Refer to Section 5.5
3. PRO= Patient Reported Outcomes are performed electronically at clinic visits and completed by patients in a quiet place prior to any other visit procedure. The order will be as follows (see also Appendix 10.6 and Appendix 10.7):
   a) DLQI
   b) HAQ-DI [for psoriatic arthritis patients at selected sites]
   c) Pain VAS [for psoriatic arthritis patients at selected sites]
   d) Patient Global Assessment (PtGA) VAS [for psoriatic arthritis patients at selected sites]
4. Physical exams: T = targeted, C = complete. Refer to Section 5.3.1 for details.
5. Randomisation via IRT at Visit 2. Re-randomisation via IRT at Week 28 for Responders (sPGA =0 or 1). See Section 6.2.2
6. Patients who have completed the study (which is defined as patients completing the EOO visit within the specified window per the flow charts.) who have not discontinued drug prematurely and who also meet the eligibility criteria **will be offered to roll over into an open label extension (OLE) trial.** Refer to Clinical Trial Protocol (CTP) Section 6.2.3 for additional information on the OLE trial.
7. Blood samples for PK and Anti-drug antibodies (ADA) should be taken within 60 minutes before the subcutaneous injection (pre-dose).
8. At Visit 1 at selected study sites, patients with a positive history of PsA or suspected to have PsA will be further evaluated for PsA diagnosis based on CASPAR (ClASsification of Psoriatic Arthritis) criteria (R15-1001) See Appendix 10.6
9. For detailed instruction how to measure waist circumference see Section 5.3.1.1 of the protocol

10. Biomarker sampling should be done prior to administration of study drug at dosing visits. See Section 5.5 and lab manual for procedure
11. For those patients continuing in the double-blind portion of the trial an additional IRT call will be needed when patients in the randomized withdrawal part of trial reach sPGA≥3 at a non-dosing visit starting at Week 32. See also footnote # 17 and #18.
12. Follow-up Visit #1 is not required for patients discontinuing treatment early. After completing the EOT visit, these patients go right to EOO visit (end of treatment + 16 weeks). See Section 6
13. Vital signs will be assessed prior to treatment as well as approximately 5 and 60 minutes post dose (after last injection) at the first 2 dosing visits (V2, V3).
14. Blood samples should be taken after patient has fasted for at least 8 hours prior (except screening visit). If not fasted mark on laboratory requisition.
15. Patients that terminate trial medication early should remain in the trial and complete all remaining Treatment Period visits and, FU1 and FU2 Visits. Termination of trial medication eCRF should be completed and end of study registered as a non-completer in IRT. Refer to Section 6.2.3 for details and further instruction if patient cannot or will not continue in the trial.
16. Tender and swollen joint counts (TJC/SJC) and Disease Activity Score (DAS28) will be done at **selected sites for confirmed psoriatic arthritis patients (See Appendix 10.6)**
17. The patient will be switched to Flow Chart 2 if relapse occurs between Week 32 through Week 70 (inclusive). The R1 visit from the Flowchart 2 must be conducted instead of the current scheduled or unscheduled visit. See also Flow Chart 2 and Sections 3.1 and 6.2.2.
18. The patient will be switched to Flow Chart 3 if they relapse after week 70 through to week 82 (inclusive). The R1 visit from Flowchart 3 must be conducted instead of the current scheduled or unscheduled visit. See also Flow Chart 3 and Sections 3.1 and 6.2.2.
19. History for psoriatic arthritis is done on **all patients at all sites**
20. For patients who discontinue early, vital status should be collected every 12 months after discontinuation up to the original planned EOO.
21. Patients relapsing after Week 82 through Week 88 will immediately follow EOT procedures per Flow Chart 1 (see also Section 3.1 and 6.2.2).
22. For patients re-randomized at Week 28 continuing in the double blind treatment portion of the study, assessment of relapse is defined as having an sPGA ≥ 3. If the sPGA is ≥ 3, the result is entered into IRT and IRT will immediately dispense open label BI 655066.
23. Infection Testing: Note that at the Screening Visit (or prior to randomization) only TB testing is required. See Section 5.3.3:1 for a complete list of testing required.
24. Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at Visit 2 and for approximately one hour after the last injection at all other visits where drug is administered. Hypersensitivity reactions should be treated according to medical standards.

FLOW CHART 2 FOR RELAPSED AND RE-TREATED PATIENTS FROM WEEK 32 THROUGH WEEK 70

	Re-Treatment					Follow-up	
Relapse Visit	**R1**	**R2**	**R3**	**R4**	**R5 (EOT)**	**Follow-up #1**	**Follow-up #2 EOO**
Weeks of Re-Treatment		**4**	**8**	**12**	**16**	**EOT+ 6wks**	**EOT+ 16wks**
Day of Re-Treatment	**1**	**28**	**56**	**84**	**112**	**154**	**224**
Visit window (days)		**±3**	**±7**	**±7**	**±7**	**±7**	**±7**
Weight, waist circumference[4]	X						X
Vitals	X	X	X	X	X	X	X
Physical examination[2]	Xc	Xt	Xt	Xt	Xc	Xt	Xc
12 lead-ECG	X	X			X		X
Safety laboratory testing[5]	X	X			X		X
Adverse events	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
Infection Testing	X[11]						X
Pregnancy testing[1]	Xu	Xu			Xu		Xu
Contact IRT	X	X			X		X
Local tolerability assessment	X	X	X	X	X		
Blood sampling for PK	**X**[7]	**X**[7]			**X**[7]		X
ADA assessment sampling	**X**[7]	**X**[7]			**X**[7]		X
Biomarker sampling[8]	X	X			X		X
PASI, sPGA	X	X	X	X	X	X	X
HAQ-DI, Pain VAS/PtGA VAS[3]	X				X		X
TJC/SJC, DAS28[9]	X				X		X
Administer trial drug[12]	X	X(load)			X		
Termination of trial drug					X		
Trial completion							X
Open label extension[6]							X
Vital status[10]							X

Flow Chart 2 Footnotes

1. Pregnancy Testing: Xu= onsite urine testing. Serum pregnancy done as a reflex if urine test is positive.
2. Physical exams: T = targeted, C = complete. Refer to Section 5.3.1 for details
3. PRO= Patient Reported Outcomes are performed electronically at clinic visits and completed by patients in a quiet place prior to any other visit procedure. The order will be as follows (see also Appendix 10.6 and Appendix 10.7):
    a) HAQ-DI [for psoriatic arthritis patients at selected sites]
    b) Pain VAS [for psoriatic arthritis patients at selected sites]
    c) Patient Global Assessment (PtGA) VAS [for psoriatic arthritis patients at selected sites]
4. For detailed instruction how to measure waist circumference see Section 5.3.1.1 of the protocol
5. Blood samples should be taken after patient has fasted for at least 8 hours prior (except screening visit). If not fasted mark on laboratory requisition.
6. Patients who have completed the study (which is defined as patients completing the EOO visit within the specified window per the flow charts, who have not discontinued drug prematurely and who also meet the eligibility criteria) **will be offered to roll over into an open label extension (OLE) trial.** Refer to CTP Section 6.2.3 for additional information on the OLE trial.
7. Blood samples for PK and Anti-drug antibodies (ADA) should be taken within 60 minutes before the subcutaneous injection (pre-dose)
8. Biomarker sampling should be done prior to administration of study drug at dosing visits. See Section 5.5 and lab manual for procedure
9. Tender and swollen joint counts (TJC/SJC) and Disease Activity Score (DAS28) will be done at **selected sites for confirmed psoriatic arthritis patients (See Appendix 10.6)**
10. For relapsed and retreated patients following Flow Chart #2 and who discontinue early, Vital Status should be collected after discontinuation up to the new planned EOO per Flow Chart #2.
11. Infection Testing at R1 visit only for patients relapsing on or before Visit 15 (Week 52)
12. Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at Visit 2 and for approximately 1 hour after the last injection at all other visits where drug is administered. Hypersensitivity reactions should be treated according to medical standards.

FLOW CHART 3 FOR RELAPSE AND RE-TREATED PATIENTS AFTER WEEK 70 THROUGH WEEK 82

	Re-treatment		Follow-up	
Relapse Visit	**R1**	**R2 (EOT)**	**Follow-up #1**	**Follow-up #2 EOO**
Weeks of Re-Treatment		**4**	**EOT+ 6wks**	**EOT+ 16wks**
Day of Re-Treatment	**1**	**28**		
Visit window (days)		**±3**	**±7**	**±7**
Weight, waist circumference[4]	X			X
Vitals	X	X	X	X
Physical examination[2]	Xc	Xc	Xt	Xc
12 lead-ECG	X	X		X
Safety laboratory testing[5]	X	X		X
Adverse events	X	X	X	X
Concomitant therapy	X	X	X	X
Infection Testing				X
Pregnancy testing[1]	Xu	Xu		Xu
Contact IRT	X	X		X
Local tolerability assessment	X	X		
Blood sampling for PK	X[7]	X[7]		X
ADA assessment sampling	X[7]	X[7]		X
Biomarker sampling[8]	X	X		X
PASI, sPGA	X	X	X	X
HAQ-DI, Pain VAS/ PtGA VAS[3]	X	X		X
TJC/SJC, DAS28[9]	X	X		X
Administer trial drug[11]	X	X(load)		
Termination of trial drug		X		
Trial completion				X
Open label extension[6]				X
Vital status[10]				X

Note: Patients relapsing after Week 82 will immediately follow EOT procedures, and then return for Follow-up #1 and Follow-up #2. A loading dose will not be administered.

Flow Chart 3 Footnotes

1. Pregnancy Testing: Xu= onsite urine testing. Serum pregnancy done as a reflex if urine test is positive.
2. Physical exams: T = targeted, C = complete. Refer to Section 5.3.1 for details
3. PRO= Patient Reported Outcomes are performed electronically at clinic visits and completed by patients in a quiet place prior to any other visit procedure. The order will be as follows (see also Appendix 10.6 and Appendix 10.7):
    a) HAQ-DI [for psoriatic arthritis patients at selected sites]
    b) Pain VAS [for psoriatic arthritis patients at selected sites]
    c) Patient Global Assessment (PtGA) VAS [for psoriatic arthritis patients at selected sites]
4. For detailed instruction how to measure waist circumference see Section 5.3.1.1 of the protocol
5. Blood samples should be taken after patient has fasted for at least 8 hours prior (except screening visit). If not fasted mark on laboratory requisition.
6. Patients who have completed the study (which is defined as patients completing the EOO visit within the specified window per the flow charts) who have not discontinued drug prematurely and who also meet the eligibility criteria **will be offered to roll over into an open label extension (OLE) trial.** Refer to CTP Section 6.2.3 for additional information on the OLE trial.
7. Blood samples for PK and Anti-drug antibodies (ADA) should be taken within 60 minutes before the subcutaneous injection (pre-dose)
8. Biomarker sampling should be done prior to administration of study drug at dosing visits. See Section 5.5 and lab manual for procedure
9. Tender and swollen joint counts (TJC/SJC) and Disease Activity Score (DAS28) will be done at **selected sites for confirmed psoriatic arthritis patients (See Appendix 10.6)**
10. For relapsed and re-treated patients following Flow Chart #3 who discontinue early, Vital Status should be collected after discontinuation up to the new planned EOO per Flow Chart #3.
11. Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at Visit 2 and for approximately 1 hour after the last injection at all other visits where drug is administered. Hypersensitivity reactions should be treated according to medical standards.

TABLE OF CONTENTS

ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse events of special interest
ALT	Alanine transferase
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate transferase
AUC	Area under the Curve
BI	Boehringer Ingelheim
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CA	Competent Authority
CASPAR	ClASsification criteria for Psoriatic Arthritis
CK	Creatine Kinase
CK-MB	Creatine Kinase Muscle Brain
Cmax	maximal Concentration
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CRP	C-Reactive Protein
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DAS	Disease Activity Score
DEDP	Drug Exposure During Pregnancy
DILI	Drug induced liver injury
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcomes Assesssment
eCRF	Electronic Case Report Form
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme Linked Immunosorbent Assay
EOO	End of Observation
EOT	End of Treatment
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GRAPPA	The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAQ-DI	Health Assessment Questionnaire Disability Index
Hb	Hemoglobin
Hct	Hematocrit
HDL	High density lipoprotein
HIV	Human immunodeficiency virus

HIPAA	Health insurance portability and accountability act
HOMA-IR	Homeostatis model assessment of insulin resistance
IB	Investigator's Brochure
IC	Inhibitory Concentration
ICH	International conference on harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
INR	International normalized ratio
IL	Interleukin
IQR	Interquartile Range
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	Intravenous
LDL	Low density lipoprotein
LOCF	Last observation carried forward
mAb	Monoclonal Antibody
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed effect Model Repeat Measurement
Nab	Neutralizing Antibody
NAPSI	Nail Psoriasis Severity Index
NGAL	Neutrophil gelatinase associated lipocalin-2
NOAEL	No Observed Adverse Effect Level
NRI	No Response Imputation
OLE	Open label extension
OPU	Operative unit
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamics
PK	Pharmacokinetics
PoCC	Proof of Clinical Concept
PPASI	Palmoplantar Psoriasis Severity Index
PPD	Purified Protein Derivative
PPS	Per Protocol Set
PRO	Patient Reported Outcomes
PsA	Psoriatic Arthritis
PSI	Psoriasis Symptom Inventory
PSSI	Psoriasis Scalp Severity Index
PtGA	Patient Global Assessment
RBC	Red Blood Cells
RCTC	Rheumatology Common Toxicity Criteria
RDC	Remote Data Capture
REP	Residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
RRS-PPS	Re-Randomized Per Protocol Set
SAE	Serious Adverse Event
SAF	Safety Set
SD	Standard deviation
SOP	Standard Operating Procedures
s.c.	subcutaneous

sPGA	Static Physician Global Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
TJC/SJC	Tender or swollen joint count
TMF	Trial Master File
TNF	Tumor Necrosis Factor
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
VAS	Visual Analog Scale
VEGF	Vascular endothelial growth factor
WBC	White Blood cells

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

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

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

There is still clinical need for increased efficacy as the most effective anti-TNF and IL12/23 agents provide only 75% improvement in psoriasis in about 60-70% of patients, and these responses tend to be lost over time. While the anti-IL-17A agents provide better efficacy, they require monthly injections; thus, their long-term utility is still undetermined. BI 655066 is a humanized monoclonal antibody with high affinity for the p19 component of human IL-23 that specifically neutralizes IL-23. Proof of clinical concept (PoCC) for BI 655066 was demonstrated in a single dose phase I trial in 39 patients with moderate to severe plaque psoriasis, where 87% of patients achieved at least 75% reduction in Psoriasis Area and Severity Index (PASI 75) with no safety concerns (c02434648-01).

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

1.2 DRUG PROFILE

BI 655066 is a fully humanized monoclonal antibody (mAb) of the IgG1 subclass directed towards IL-23p19. The antibody has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity. BI 655066 binds with high affinity to human IL-23 and inhibits IL-23 stimulated IL-17 production at IC 50 concentrations below 10 pM, as compared with 167 pM for ustekinumab in the same system. BI 655066 does not affect IL-12 at a maximum tested concentration (33 nM) and it does not inhibit IL-12 stimulated IFN-γ production.

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

BI 655066 has been studied in approximately 200 patients with psoriasis without any unexpected adverse events or safety issue. Based on the efficacy and safety findings in the completed and ongoing studies, the risk benefit profile of BI 655066 is appropriate for initiation of Phase III studies. In Study 1311.1 (c02434648-01), a Phase I single rising dose trial in 39 patients with chronic plaque psoriasis, administration of BI 655066 either intravenously (i.v.) or subcutaneously (s.c.) was well tolerated. Over the 24 weeks following a single i.v. or s.c. administration of BI 655066, 65% (20/31) of patients experienced an AE compared with 88% (7/8) of patients receiving placebo. The most frequently reported AEs were mild to moderate upper respiratory tract infections, mild nasopharyngitis and mild to moderate headache. The severity of AEs did not appear related to the dose of BI 655066. Injection site reactions were reported in 2/18) patients receiving BI 655066 i.v., in 1/6 patients receiving placebo i.v. and in none of the patients receiving BI 655066 or placebo s.c.

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

After a single i.v. administration, BI 655066 geometric mean AUC_{0-inf} ranged from 2.93–1650 day*µg/mL and C_{max} from 0.311–110 µg/mL, with exposure increasing in a dose-proportional manner. Group mean clearance and terminal phase volume of distribution were 0.33 L/day and 10.8 L, respectively PK parameter variability, expressed as gCV (%) was <50%. After a single s.c. administration of BI 655066, maximal exposures were reached between 5-13 days and subcutaneous bioavailability was 73% (expressed as the ratio of geometric mean dose normalised AUC_{0-inf} after s.c. and i.v. administration).

For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB) (c01569420-06) which is included in the Investigator Site File (ISF).

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Psoriasis is a chronic inflammatory disease affecting 2% of the world population with significant impact on patient quality of life with significant systemic disease (R08-1089). IL-23 plays a key role in the pathophysiology of psoriasis through induction and maintenance of Th17 type cells that secrete inflammatory cytokines. BI 655066 is a humanized monoclonal antibody that specifically neutralizes the IL-23 axis. Proof of clinical concept (PoCC) for BI 655066 was demonstrated in a single dose phase I trial in 39 patients with moderate to severe plaque psoriasis where 87% of patients achieved at least 75% reduction in Psoriasis Area and Severity Index (PASI 75) with no safety concerns (c02434648-01).

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

2.2 TRIAL OBJECTIVES

The primary objectives of this trial are to assess the safety and efficacy of BI 655066 150 mg in comparison to placebo in patients with moderate to severe chronic plaque psoriasis. The primary efficacy evaluation will be performed at 16 weeks. In addition, the maintenance of response following drug withdrawal will be assessed after Week 28 through Week 104. Subsequent to drug withdrawal, patients who experience relapse will be retreated with BI 655066 to assess response after retreatment.
In addition, this trial will assess PK and the emergence of anti-drug antibodies (ADA) and their effect on efficacy and safety. Moreover, it will be explored how the use of BI 655066 may influence gene and protein expression levels and disease specific protein markers.

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

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

2.3 BENEFIT - RISK ASSESSMENT

Participation in this study may help to generate future benefit for larger groups of patients with psoriasis if BI 655066 proves to be successful in treating this disease. BI 655066 has been studied in approximately 200 patients with moderate to severe plaque psoriasis. In these studies, the majority of patients receiving BI 655066 achieved 90% improvement of their disease. The most common adverse events reported in these trials were mild symptoms of the upper respiratory tract, including nasal stuffiness, sore throat, influenza, and headache. These events were not considered to be related to drug treatment. Local reactions following subcutaneous administration of BI 655066 were uncommon, and limited to mild redness, swelling or induration at the injection site. No serious drug related adverse events were reported.

As with many immune modulating agents, BI 655066 may impair immune function resulting in a risk of infection. This will be monitored by collection of all AEs during the treatment and

observation periods. Patients with clinically important active infection will not be included in the study.
IL-23 inhibition is not known to increase the risk of TB infection or impair the response to TB infection in animal models (R15-5488; R15-5495). Thus, low risk patients with positive Quantiferon testing do not need to be treated with anti-tuberculosis therapy prior to receiving BI-655066, but should be carefully monitored for any sign of TB reactivation. Absence of TB reactivation, despite not receiving anti-tuberculosis prophylaxis will provide important information in humans as to whether TB testing is required prior to treatment with BI 655066 (R15-5497).

There is not enough information at this time to rule out a risk of cancer with BI 655066, but this risk is considered small with this type of compound because long-term experience with the anti-IL-12/23 mAb ustekinumab has not been associated with significant cancer risk. Patients will be monitored for signs and symptoms of malignancy at each visit.

Increases in major adverse cardiovascular events (MACE) including myocardial infarction, cerebrovascular accident, and cardiovascular death, reported initially with anti-IL-12/23 agents, such as ustekinumab, have not been observed in longer term studies. While the likelihood of increased MACE is small, all cardiovascular events (serious or non-serious) observed in this study will be adjudicated by an independent MACE Adjudication Committee.

A patient will have a 20% (1 in 5) chance in being randomized to the placebo arm. Patients assigned to placebo will have a low rate of response. These patients will be crossed over to active BI 655066 treatment at Week 16 of study participation. The knowledge gained from the placebo treatment group in a relatively short period of time can be used to control for bias and effect size. The delay in starting treatment does not diminish the potential benefit of treatment or introduce any risk. Patients will be monitored with study visits every 4 weeks through the end of the placebo period at Week 16.
Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients´ safety, see Section 5.3.6.1.

In conclusion, the benefit-risk profile is considered appropriate for this stage of clinical development. In order to recognize any safety signals as early as possible, an independent DMC will monitor all studies where patients are receiving BI 655066.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a confirmatory, multinational, multicenter, randomized, double-blind, placebo controlled, study that includes up to a 42 day screening period, an 88 week treatment period and a 16- week follow-up period. The primary objectives of this trial are to assess the safety and efficacy of BI 655066 in comparison to placebo in patients with moderate to severe chronic plaque psoriasis. The primary efficacy will be evaluated at 16 weeks. In addition, the maintenance of response following drug withdrawal in patients who respond to treatment prior to Week 28 will be assessed after Week 28 through Week 104. Subsequent to drug withdrawal, patients who experience relapse will be retreated with BI 655066 to assess response after retreatment.

In total, approximately 500 patients with moderate to severe chronic plaque psoriasis will be randomised and receive study treatment in this trial. A sufficient number of patients will be screened to meet this randomized goal. Patients are considered enrolled in the study once they have signed the informed consent.

Patients suitable after screening will be eligible to participate in this study and will be randomized at a ratio of 4:1 to one of two treatment arms as shown in Figure 3.1:1. Arm 1 refers to those patients originally randomized to BI 655066 and Arm 2 refers to those patients originally randomized to placebo. Randomisation will be stratified as listed in Section 7.6.

All patients will receive the first dose of study medication on day 1 (Randomisation), the second dose at Week 4, and then every 12 weeks thereafter with the last dose at Week 88.
After the end of treatment, patients will continue in the 16- week follow- up period.
At the Week 16 visit (primary endpoint), all patients randomized to Arm 2 (placebo) will start receiving 150 mg BI 655066 active treatment every 12 weeks and continue until the end of the treatment period. In order to maintain the blind, this will be performed in a blinded fashion at Week 16.
At the Week 28 visit, all patients will be assessed for responsiveness. Patients not meeting the protocol defined response criteria (sPGA is ≥ 2) (Week 28 non-responders), will receive open label BI 655066 150 mg from Week 28 until the end of the treatment period (Week 88), regardless of originally randomized treatment arm. Patients who meet the protocol defined responder criteria (sPGA of 0 or 1) (Week 28 responders), will continue to receive blinded drug. In Arm 1, patients will be re-randomized; in Arm 2, they will continue to receive blinded BI655066 treatment as described in Section 7.6.
Starting with Week 32, Week 28 responders will have their sPGA assessed for protocol defined relapse (sPGA of ≥ 3). Once a patient reaches a sPGA of ≥ 3, they will be switched to open label BI 655066. If this relapse occurs anytime between Week 32 through Week 70, the patients will follow Flow Chart #2 and be re-treated for 16 weeks. If this relapse occurs after Week 70 through Week 82, the patient will follow Flow Chart #3 and be re-treated for 28 days. If the relapse occurs after Week 82 through Week 88 the patient will immediately have the EOT procedures performed, including the final dose of study medication and continue into the 16-week Follow-Up Period. This process will be managed by IRT.

Patients will be offered to roll over into an open label extension (OLE) trial, if they have completed the study and meet the inclusion criteria for the OLE trial at the End of Observation (EOO) visit. See Section 6.2.2 and Section 6.2.3.

Patients who discontinue from the trial will **not** have the possibility to participate in the OLE study.
There will not be an interim analysis from a statistical standpoint however a primary endpoint analysis will be conducted after the last patient has been in the study for 52 weeks (or discontinued). See Section 7.4.

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 (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.

Part A is defined as the induction and response period from initial randomisation through Week 28. Part B is defined as the withdrawal and re-treatment period from Week 28 through Week 88.

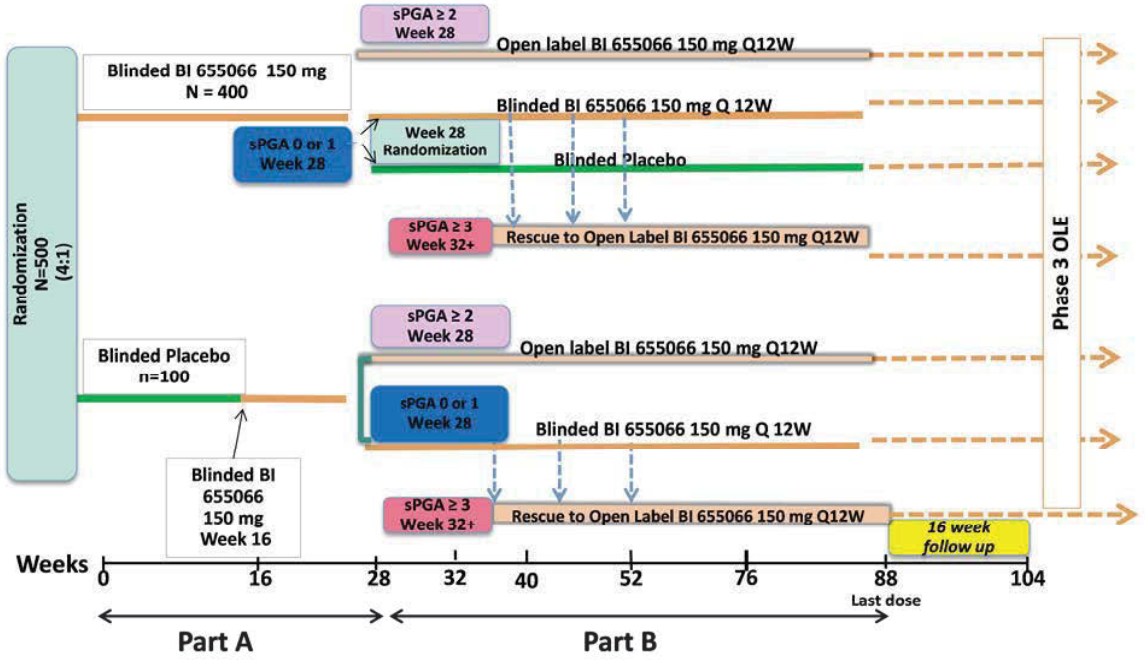


Figure 3.1:1 Trial Design

3.1.1 Administrative structure of the trial

The trial is sponsored by AbbVie in the USA and Boehringer Ingelheim (BI) for all other non-USA participating 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 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.

Data Management will be done by BI according to BI SOPs and the Statistical Evaluation will be done by AbbVie according to their SOPs.
Tasks and functions assigned in order to organise, manage, and evaluate the trial will be defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

The organisation of the trial in the participating countries will be performed by the respective local BI-organisation (Operative Unit (OPU) or by a Contract Research Organisation (CRO) 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 Coordinating Investigator will be responsible to coordinate 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 ISF.
Details of the trial supplies including responsible institutions are given in Section 4 of this protocol.

The ISF will be maintained at the sites as required by local regulation and BI-SOPs. A copy of the essential ISF documents will also be kept as an electronic TMF document according to BI SOPs.

A central laboratory service and vendors for ECG, eCOA and an IRT (Interactive Response Technology) will be used in this trial. Details will be provided in the applicable manuals available in the ISF.

3.1.2 Data Monitoring Committee (DMC)

A data monitoring committee (DMC), independent of the Sponsor will be established to assess the progress of the clinical trial, including unblinded safety assessments at specified intervals, and to recommend to the Sponsor whether to continue, modify, or stop the trial.
Any efficacy data provided to the DMC will only be used for DMC's obligation to assess the full benefit-to-risk of the treatments. Thus, no statistical penalty will be imposed since efficacy analyses will not be the basis for any potential early trial termination.
Measures are in place to ensure blinding of the Sponsor and all other trial participants. The Sponsor will remain blinded until after the last patient completes the Week 52 visit. See Section 7.4 for more information. The tasks and responsibilities of the DMC will be specified in a charter. The DMC will maintain written records of all its meetings.

3.1.3 MACE Adjudication Committee

An independent adjudication committee will be used to adjudicate all observed cardio- and cerebro-vascular and thrombotic events reported during the conduct of the study to assure

consistent assessment of major adverse cardiovascular events (MACE).This review will be blinded to treatment allocation; the events that are to be adjudicated and the adjudication process will be detailed in the MACE Adjudication Committee Charter.

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

This is a randomized double blind, placebo controlled, parallel design study. This design is appropriate for assessing the safety and efficacy of BI 655066 compared to placebo in patients with moderate to severe chronic plaque psoriasis. While there is a low rate of response with placebo treatment, it is important to have a placebo control early in the study to control for confounding factors, such as potential investigator bias or regression to the mean in PASI scoring.
In order to enroll patient participants, it is necessary to allow patients initially assigned to placebo to receive active treatment. Thus, only adverse events reported during the first 16 weeks of the trial can be directly compared to placebo. In this trial, patients originally randomized to BI 655066 who are considered to be BI 655066 responders will be re-randomized to receive either placebo or continued BI 655066 starting at Week 28. Patients in this phase of the study will be assessed for an additional 76 weeks for a total of 104 weeks. This is necessary to adequately capture the loss of response for patients taking BI 655066. Furthermore, patients losing response will be retreated with BI 655066 and response after retreatment will be assessed.

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 500 patients is planned to be randomized in this trial. A sufficient number of patients will be screened to meet this randomized goal. Patients will be recruited at multiple investigative sites in multiple countries. Approximately 85 sites are planned with approximately 5-10 patients to be randomized per site. Recruitment will be competitive.

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

3.3.1 Main diagnosis for trial entry

Patients must have moderate to severe chronic plaque psoriasis, defined as ≥ 10% body surface area involvement, a Psoriasis Area and Severity Index ≥ 12 and static Physician Global Assessment score ≥ 3.

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

   *Women **of** childbearing potential are defined as:

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

2. Age ≥ 18 years at screening

3. Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) at least 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient.

4. Have stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis at both Screening and Baseline (Randomisation);

   - Have an involved body surface area (BSA) ≥ 10% and
   - Have a Psoriasis Area and Severity Index (PASI) ≥ 12 and
   - Have a static Physician Global Assessment (sPGA) score of ≥ 3.

5. Must be a candidate for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator

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

3.3.3. Exclusion criteria

1. Patients with

   - nonplaque forms of psoriasis (including guttate, erythrodermic, or pustular)

   - current drug-induced psoriasis (including a new onset of psoriasis or an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium)

   - active ongoing inflammatory diseases other than psoriasis and psoriatic arthritis that might confound trial evaluations according to the investigator's judgment

2. Previous exposure to BI 655066

3. Currently enrolled in another investigational study or less than 30 days (from screening) since completing another investigational study (participation in observational studies is permitted).

4. Use of any restricted medication as noted in Table 4.2.2.1:1 or any drug considered likely to interfere with the safe conduct of the study.

5. Major surgery performed within 12 weeks prior to randomisation or planned within 12 months after screening (e.g. hip replacement, removal aneurysm, stomach ligation,).

6. Known chronic or relevant acute infections, such as HIV (Human Immunodeficiency Virus), \viral hepatitis, or tuberculosis. QuantiFERON® TB test or Purified Protein Derivative (PPD) skin test will be performed during screening. Patients with a positive test result 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, patients who are at low risk of reactivation, defined by local guidelines and investigator judgment, do not need to be treated with prophylactic anti-tuberculosis prior to or during the trial.

7. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.

8. Evidence of a current or previous disease (including chronic alcohol or drug abuse), medical condition other than psoriasis, surgical procedure (i.e., organ transplant), medical examination finding (including vital signs and ECG), or laboratory value at the screening visit outside the reference range that in the opinion of the Investigator, is clinically significant and would make the study participant unable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data.

9. History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients.

10. Women who are pregnant, nursing, or who plan to become pregnant while in the trial.

11. Previous enrolment in this trial.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

All patients have the right to withdraw from the study at any time without the need to justify their decision. The investigator has the right to remove patients from the study for 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.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Charts and Section 6.2.3.

An individual patient is to be withdrawn from study medication 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 study medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- Development of a toxicity or adverse event that warrants BI 655066 discontinuation including but not limited to SAEs or SUSARs
- If prohibited medication is used during the study for any indication, the patient must discontinue use of the prohibited medication if he/she wants to continue in this study. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.
- If the patient experiences an intolerable increase of psoriasis during the course of the trial the patient will be discontinued from the trial to receive rescue treatment as deemed appropriate by the investigator.

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

If a patient becomes pregnant during a trial, the study medication needs to be discontinued, and the patient will complete EOT Visit procedures, and Follow-up 2 (EOO) Visit procedures. The patient will be followed up until birth or otherwise termination of the pregnancy.
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 withdrawal (e.g. adverse events) must be recorded in the eCRF. These data will be included in the trial database and reported.

Vital Status
For randomized patients leaving the study early (before the planned EOO in their current applicable flow chart), vital status should be collected every 12 months after discontinuation up to the planned EOO.

3.3.4.2 Discontinuation of the trial by the sponsor

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

1. Failure to meet expected enrolment goals overall or at a particular trial site,

2. Emergence of any efficacy/safety information that could significantly affect continuation of the trial, or any other administrative reasons, i.e. problems with availability of the study medication, discontinuation of development of BI 655066
3. Violation of GCP, the CTP, or a Contract disturbing the appropriate conduct of the trial.

The investigator / 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/or Placebo to match BI 655066 will be administered subcutaneously. All products will be supplied by Boehringer Ingelheim.

4.1.1 Identity of BI investigational product and reference product

Table 4.1.1:1 BI 655066

Substance	BI 655066: Anti-human IL-23p19 mAb
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form	Anti-human IL-23p19 mAb
Molecular weight	Approximately 148 kDa
Unit strength:	75 mg BI 655066 in a pre-filled syringe (concentration 90 mg/mL)
Posology	Week 0, Week 4, then every 12 weeks with last injection at Week 88
Route of administration:	Subcutaneous injection

Table 4.1.1:2 Placebo to BI 655066

Substance:	Placebo to match BI 655066
Pharmaceutical formulation:	[redacted]
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form	N.A
Molecular weight	N.A
Unit strength:	Sodium chloride solution in a pre-filled syringe
Posology	Week 0, Week 4, then every 12 weeks with last injection at Week 88
Route of administration:	Subcutaneous injection

4.1.2 Method of assigning patients to treatment groups

During Visit 2 and after the patient's eligibility has been confirmed, the treatment will be assigned via Interactive Response Technology (IRT). To facilitate the use of the IRT, the Investigator will receive all necessary instructions.
Patients will be randomised to receive BI 655066 150 mg or matching placebo in a ratio of 4:1. Randomisation will be stratified by weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1).
At each subsequent visit where study medication is to be administered the site is required to complete the medication resupply module in the IRT. At randomisation as well as subsequent medication administration visits, IRT will assign medication numbers. Site personnel will enter the medication numbers in the eCRF.

Re-randomisation will occur at Week 28 for those patients who have met the responder criteria in Arm 1 (c.f. Section 7.6). Re-randomisation will be stratified by weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1). For Week 28 responders in Arm 2, blinded BI 655066 treatment will be assigned from IRT to maintain blinding.
Details regarding the use of the IRT are described in the site-user manual available in the ISF.

4.1.3 Selection of doses in the trial

The dose selection strategy for phase III involved analyses of data from the completed phase I study (Trial 1311.1), (c02434648-01) the ongoing phase II study (Trial 1311.2), (c03272682-01) and PK-PD modelling of all available data from phase I and II.
The phase I and phase II data demonstrated an exposure-response relationship for BI 655066 where doses less than 0.25 mg/kg (intravenously or subcutaneously) were associated with lower clinical efficacy (assessed as decrease from baseline in the PASI score) while doses greater than 1.0 mg/kg achieved near maximal efficacy.

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

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

PK-PD Modelling to Support Dose Selection

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

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

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

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

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

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

PK-PD analyses indicated no relevant reduction in efficacy when the dose was changed from 180 mg to 150 mg (based on interpolation). In summary, taking into consideration expert advisor recommendation and prescriber preferences, the proposed dosing for BI 655066 in the upcoming phase 3 trials is 150 mg at Weeks 0 and 4, followed by every 12 weeks. This regimen is anticipated to provide a favourable risk-benefit profile with a dosing schedule that is consistent with standard clinical practice.

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

4.1.4 Drug assignment and administration of doses for each patient

IRT will be used to allocate medication to patients. At randomisation as well as subsequent medication administration visits, IRT will assign medication numbers. At visits where study medication is to be administered (Refer to Flow Chart) study sites will be required to complete the appropriate module in the IRT system.

Study medication will be administered exclusively at the study site, by the investigator or authorized study personnel (e.g. study nurse).

BI 655066 and/or matching placebo will be administered as a subcutaneous injection in the abdomen, thighs, gluteal regions, or upper arms.
Injections should be at least 2 cm. apart and should not be close to a vein. The injection sites should avoid sites of psoriasis involvement as well as sites where the skin is tender, bruised, erythematous, or indurated, and should be alternated to other areas for subsequent doses.

Injections will be given in a double blind fashion with each patient receiving 2 injections of BI 655066 or matching placebo administered within approximately 5 minutes at each dosing visit as indicated in the Flow Charts.

In the eCRF, the study drug administration time is always the time of the first injection.

Further information regarding the technique of injection and injection materials (syringes, needles) will be provided in the ISF.

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

The injections at each dosing visit are presented in Table 4.1.4: 1.

Table 4.1.4:1 Dosing schedule

	Day 1 + Week 4	Week 16	Week 28, 40, 52, 64, 76, 88
Arm 1 **BI 655066 150 mg**	(2) [redacted] ml (75 mg) BI 655066 (blinded)	(2) [redacted] ml (75 mg) BI 655066 (blinded)	(2) [redacted] ml (75 mg) blinded or open label BI 655066 Or (2) PTM [redacted] ml (75 mg) BI 655066 (blinded)
Arm 2 Placebo to BI 655066 150 mg	(2) PTM [redacted] ml (75 mg) BI 655066 (blinded)	(2) [redacted] ml (75 mg) BI 655066 (blinded)	(2) [redacted] ml (75 mg) blinded or open label BI 655066

PTM= Placebo to match

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

During "Part A" of this trial all patients receive double-blind treatment. Patients, investigators and everyone involved in trial conduct or analyses of this double-blind study will remain blinded with regard to the randomized treatment assignments.

Arm 1 refers to patients originally randomized to BI 655066, and Arm 2 refers to patients originally randomized to placebo at Visit 2.

At Week 28, the start of "Part B", non-responders (sPGA≥ 2) from Arm 1 and 2 will receive open label drug and will know future treatments are BI 655066.
At Week 28, responders (sPGA of 0 or 1) from Arm 1 in "Part A" will be re-randomized to either maintain treatment of BI 655066 or to receive placebo; these treatments will also be double-blinded to ensure that patients and investigators remain blinded to re-randomized treatment during "Part B." To maintain blinding, if a patient in Arm 2 reaches a sPGA of 0 or 1 at Week 28, she/he will continue to receive blinded BI 655066 treatment assigned from IRT.

After the last patient has been in the study for 52 weeks (or has discontinued), the Sponsor will be unblinded in order to summarize the trial. Blinded treatment assignments will not be disseminated to the sites, investigators, and patients until the end of study database lock.

The randomisation code will be kept secret by Clinical Trial Support up to database lock. Refer to Section 4.1.5.2 for rules of breaking the blinding code for an individual or for all patients in emergency situations.
The randomisation codes will be provided to bioanalytics prior to last patient out to allow them to exclude PK samples taken from placebo patients from the bioanalytical analyses.
Bioanalytics will not disclose the randomisation code or the results of their measurements until the study is officially unblinded.
Serum drug levels and demographic data together with treatment assignments and dosing information may be made available to individuals outside of the trial team for the purpose of PK dataset generation and analysis in accordance with sponsor's standard procedures.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator / Pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unblinding must be documented in the source documents and/or appropriate CRF page along with the date and the initials of the person who broke the code.
If the treatment code for a patient is broken, the sponsor must be informed immediately.
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.

For Japan only:
In this blinded trial, an emergency code break will be available to the Investigator via the IRT system. This code break may only be accessed in emergency situations when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or if required to assure the safety of trial participants. Each site receives a manual from the IRT provider that contains instructions on how to
unblind the treatment of a patient via the IRT (via 24-hour Emergency helpline). If the code break for a patient is accessed, the sponsor must be informed immediately. The reason for accessing the code break, together with the date, must be documented on the appropriate eCRF page. In case a third party needs to break the code when the Investigator cannot be reached, the code can be opened by calling emergency code manager.

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.

There are approximately four re-supply campaigns planned. IRT will manage the inventory and re-supply of study medication.

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 local clinical monitor (as provided in the list of contacts) must be contacted immediately.
Trial medication must be securely stored, e.g. in a locked refrigerator or at a pharmacy. The medication may only be dispensed to trial patients according to the CTP by authorized personnel as documented in the trial staff list.

4.1.8 Drug accountability

Drug supplies will be provided by the sponsor.
The Investigator < and/or > pharmacist < and/or > investigational drug storage manager will receive the investigational drugs delivered by the Sponsor when the following requirements are fulfilled:

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

All unused medication must be returned to the sponsor. Used medication will be destroyed per local guidelines. Account must be given for any discrepancies.

Receipt, usage, and return must be documented. Account must be given for any discrepancy. 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 all unused or partially used drug supplies are not remaining in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

There are no special emergency procedures to be followed.

Stable doses of concomitant therapies for chronic conditions, for which neither the condition nor the treatment are judged to exclude the patient from participation (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.

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

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medications (or classes of medications) listed in Table 4.2.2.1:1 must not be taken for the specified times prior to randomisation and for the whole duration of the study.
If prohibited medication is used during the study for any indication, the patient must discontinue use of the prohibited medication if he/she wants to continue in this study. If a patient receives a live virus during the study, they must be discontinued.

Table 4.2.2.1:1 Restricted medications

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

[1] No restriction on corticosteroids with only a topical effect (e.g. inhalant corticosteroids to treat asthma or corticosteroid drops used in the eye or ear).

[2] **Exception**: Topical steroids of US class 6 (mild, such as Desonide) or US class 7 (least potent, such as hydrocortisone) will be permitted for use limited to the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to clinic visits when PASI is assessed.

4.2.2.2 Restrictions on diet and life style

Patients should be fasted for at least 8 hours prior to the collection of all safety laboratory samples starting with 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 need to follow inclusion criterion 1 in Section 3.3.2 of this CTP and the informed consent form with regard to acceptable contraception.

4.3 TREATMENT COMPLIANCE

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

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

- Achievement of ≥ 90% reduction from baseline PASI score (PASI 90) at Week 16
- Achievement of an sPGA score of clear or almost clear (0 or 1) at Week 16

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

None of the primary endpoints are safety issues.

5.1.2 Secondary Endpoints

None of the Secondary endpoints are safety issues.

Key Secondary Endpoints:
The key secondary endpoints are as follows:

- Achievement of 75% reduction from baseline PASI score (PASI 75) at Week 16
- Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16
- Achievement of an sPGA score of clear (0) at Week 16
- Achievement of a Dermatology Life Quality Index (DLQI) score of 0 or 1 at Week 16
- Achievement of an sPGA score of clear or almost clear (0 or 1) at Week 52

Other Secondary Endpoints:
The secondary endpoints are as follows:

- Achievement of PASI 75 at Week 52
- Achievement of PASI 90 at Week 52
- Achievement of PASI 100 at Week 52

Note that all key and other secondary endpoints at Week 52 will only be assessed for patients re-randomised at Week 28.

5.1.3. Further Endpoints

The further endpoints are as follows:

- Achievement of PASI 50 at all visits collected
- Achievement of PASI 75 at all visits collected
- Achievement of PASI 90 at all visits collected
- Achievement of PASI 100 at all visits collected
- Time until the first achievement of PASI 50, PASI 75, PASI 90,and PASI 100

- Time until loss of PASI 50, PASI 75, PASI 90, and PASI 100 response for patients re-randomised at Week 28
- Change and percent change from baseline in PASI at all visits collected
- Absolute PASI of < 3 at all visits collected
- Achievement of an sPGA score of clear or almost clear at all visits collected
- Achievement of an sPGA score of clear at all visits collected
- Time until the first achievement of sPGA of 0 or 1
- Time until loss of sPGA of 0 or 1 response for patients re-randomised at Week 28
- Time until sPGA score of ≥ 3 (relapse) for patients re-randomised at Week 28
- Change from baseline in DLQI at all visits collected
- Achievement of a DLQI score of 0 or 1 at all visits collected
- Achievement of a reduction of 5 or more points from baseline in DLQI score at all visits collected
- Change from baseline in HAQ-DI at all visits collected, in patients selected for PsA assessment.
- Change and percent change from baseline on patient Pain VAS
- Change and percent change from baseline on patient Global Assessment VAS
- Change from baseline in Swollen or Tender Joint Count (28 joints) at all visits collected in patients selected for PsA assessment.
- Change from baseline in DAS28 at all visits collected in patients selected for PsA assessment.
- Change and percent change from baseline in Nail Psoriasis Severity Index (NAPSI) at all visits collected
- Change and percent change from baseline in Palmoplantar Psoriasis Severity Index (PPASI) at all visits collected
- Change and percent change from baseline in Psoriasis Scalp Severity Index (PSSI) at all visits collected
- Change of metabolic risk factors from baseline (waist circumference, body weight, HOMA-index)

See the Flow Chart for when the above measures are collected. The above endpoints will be analyzed, where appropriate, for re-randomized subjects after receiving open-label study drug for retreatment (Flow Chart 2 and 3).

5.2 ASSESSMENT OF EFFICACY

- The skin condition will be assessed by using the PASI, sPGA, and other relevant scores as described in CTP Section 5.1, Appendix 10, and the ISF.
- Symptoms, quality of life, and physical function will be assessed by DLQI and HAQ-DI.

Details of the efficacy assessments are listed in the Appendix (Section 10).

5.3 ASSESSMENT OF SAFETY

Safety will be assessed descriptively based on:

- Adverse events
- Serious adverse events

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

5.3.1 Physical examination

Complete physical examinations will be performed at visits noted in the Flow Charts.
A complete physical examination will include vital sign assessment, and general appearance as well as evaluation of all relevant organ systems.

A targeted physical examination will be performed at visits noted in the Flow Charts. This includes vital sign assessment as well as an evaluation of the organ systems associated with AE(s) symptoms or laboratory abnormalities.
Clinically relevant abnormal findings will be reported as baseline conditions or AE's.

5.3.1.1 Waist circumference

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

5.3.1.2. Body weight

The scale used to capture body weight for each patient should remain consistent during the trial. In order to get comparable body weight values, it should be performed in the following way:

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

5.3.2 Vital Signs

Vital sign evaluations will be performed at every visit as shown in the Flow Charts and 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 sign evaluations will be performed pre-dose. In addition at Visit 2 and Visit 3 vital sign evaluations will be taken at approximately 5 minutes post-dose (5 minutes after last injection) and approximately 60 minutes post-dose (60 minutes after last injection).
Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at Visit 2 and for approximately 1 hour after the

last injection at all other visits where drug is administered. Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further injections might be considered and will be agreed on between investigator and BI clinical monitor.

5.3.3 Safety laboratory parameters

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

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.
Laboratory results (i.e. all safety laboratory and clinical laboratory data relevant for current clinical practice of psoriasis patients) 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 inside or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit laboratory kit and should be repeated until normalisation or stabilisation or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria (R13-3515).

Table 5.3.3:1 Laboratory tests

Category	**Test name**
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hb (HbA1c) Red Blood Cell Count/ Erythrocytes Reticulocyte Count White Blood Cells / Leukocytes Platelet Count/ Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Basophils (relative and absolute count) Monocytes (relative and absolute count) Lymphocytes (relative and absolute count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (Stabs) Neutrophils, polymorphonuclear (PMN) Eosinophils Basophils Monocytes Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin time (INR) Fibrinogen
Enzymes	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, (**Only if CK is elevated**) Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN Uric acid Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Bilirubin Direct (**if total is elevated**) Bilirubin Indirect (**if total is elevated**) Troponin (**Reflex when CK is elevated)** Albumin C-Reactive Protein (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol (calculated) HDL-Cholesterol HOMA-IR (**V2, V9, V15, V19, EOO)**
Urine Pregnancy test[1]	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test[2]	Human Serum Chorionic Gonadotropin

Table 5.3.3:1 Laboratory tests

Category	**Test name**
Hormones **(screening)**	TSH, **(free T3 and free T4 in case of abnormal TSH results)**
Autoantibodies **(screening)**	Rheumatoid Factor
Urinalysis (Stix)	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. Crystals., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urinalysis	Albumin (quantitative) Creatinine Albumin/Creatinine ratio
Infection Testing (**Screening [3] V15, EOO)**	Hepatitis B Surface Antigen (qualitative) Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON®-TB[3]

1. Urine pregnancy test performed on-site at all dosing visits (pre-dose) as well as EOT and EOO. (**only for female patients of childbearing potential)**
2. Serum pregnancy test at screening as well as confirmation of positive urine pregnancy test. (**only for female patients of child bearing potential at screening as well as reflex for positive urine pregnancy test)**
3. **At Screening only TB testing is required.** There is the site option to perform a PPD skin test, although this will not be provided or performed at Central Lab

5.3.4 Electrocardiogram

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

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 will be read and evaluated by a central vendor. The study site will be informed about the results of the assessment of the ECG obtained at screening and if there are findings that would exclude the patient from study participation according to Exclusion Criterion #8.
The electronic version of the ECG is regarded as source data.

ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected for safety reasons. Clinically significant abnormal findings will be reported as AE's.

Information about the details of ECG collection and the parameters assessed will be provided in the ISF.

5.3.5 Other safety parameters

5.3.5.1 Local Tolerability

Local tolerability at the administration sites of the subcutaneous injections will be assessed according to "swelling", "induration", "heat", "redness", "pain", or "other findings" at the specified visits during the treatment period according to the flow chart. On visits where drug is administered this assessment should be done pre-dose.
Clinically relevant findings will be reported as AE's.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

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

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

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

- results in death,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
  or
- Is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

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.

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.

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

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF and the RDC-system.
In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

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

Grade 1: MILD
Grade 2: MODERATE
Grade 3: SEVERE
Grade 4: LIFE-THREATENING

Causal relationship of AEs
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

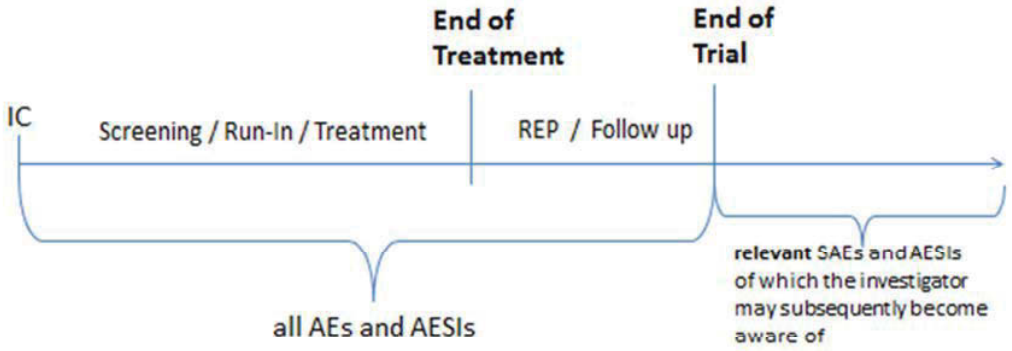
Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.
The causal relationship must be provided by the Investigator for all potential trial drugs, i.e. the BI trial drug and for all other trial drugs (such as any active comparator or placebo and for trial procedure).
For Japan, 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 in the eCRF by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period until a patient's end of trial participation, all AEs (serious and non-serious), and AESIs must be collected.
- After the individual patient's completion of trial:
  The investigator does not need to actively monitor the patient for AEs, but should only report relevant SAEs and relevant AESIs of which the investigator may become aware of.

The REP is defined as 15 weeks after the last trial medication administration. All AEs that occur during the treatment phase and throughout the REP will be considered as on treatment (see Section 7.3.4). Events that occur 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.

In Japan, all SAEs and AESIs must be reported immediately to the head of the trial site. With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

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, and the trial procedures outlined under Section 6.2.

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.

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

Pregnancy
In the rare case that a female 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.

If a patient becomes pregnant during a trial, the study medication needs to be discontinued, and the patient will complete the EOT Visit procedures and Follow-up 1 and Follow-up 2 (EOO) Visit procedures. The patient will be followed up until birth or otherwise termination of the pregnancy.

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

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

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

5.4 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.4.1 Assessment of Pharmacokinetics

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

5.4.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of analytic plasma concentrations, approximately 2.5 mL of blood will be taken at the time points listed in the Flow Chart under PK sampling.
Detailed instructions for pharmacokinetic sampling, handling, and shipment of plasma samples are provided in the laboratory manual.

5.4.2.2 Plasma sampling for ADA

For ADA assessment, approximately 2.5 mL of blood will be taken at the time points listed in the Flow Chart under ADA sampling. Detailed instructions for ADA sampling, handling, and shipment of plasma samples are provided in the laboratory manual.

5.4.3 Analytical determinations

BI 655066 concentrations will be determined by a validated Enzyme Linked Immunosorbent Assay (ELISA).
The presence of ADA to BI 655066 will be assessed via a tiered approach using a validated electrochemiluminescence assay (screening, confirmatory, and titration analysis as appropriate).

Samples that are confirmed positive may be further characterized in a validated neutralizing antibody (NAb) assay.

5.4.4 Pharmacokinetic-Pharmacodynamic Relationship

Refer to Section 7.3.6.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKERS

5.5.1 Assessment of soluble protein biomarkers in blood

Serum will be collected pre and post treatment with BI 655066 to assess changes in protein levels of disease specific markers such as but not limited to β-defensin 2, neutrophil gelatinase associated lipocalin-2 (NGAL) and S-100 A8 protein.
In addition changes in levels of biomarkers related to metabolic syndrome, such as leptin, resistin, TNFa, IL-6 and vascular endothelial growth factor (VEGF) will be explored.

Blood samples will be stored for a maximum of 3 years (under consideration of local legislation) upon signature of the final study report unless the patient agrees to long-term storage (15 years) of the biomarker samples for biomarker sample banking (Section 5.5.3).

5.5.1.1 Methods of sample collection

For the assessment of soluble protein biomarkers in serum, approximately 12.5 ml of blood will be collected at the time points indicated in the flow charts. Samples should be collected prior to the administration of study drug at dosing visits. For details on sample collection, processing 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 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.

5.5.2.1. Methods of sample collection

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

5.5.2.2. Analytical determinations

The DNA Banking sample, derived from the original blood sample, will be stored at AbbVie or a third party delegate (e.g. Boehringer Ingelheim Pharma GmbH & Co. KG; Birkendorfer Str. 65, 88397 Biberach, Germany). The stored DNA may be retrospectively analysed, e.g. to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions.

5.5.3 Biomarker sample banking

After completion of the study any unused serum, collected for biomarker sampling as listed in Section 5.5.1. may be used for further investigations, (e.g., additional biomarkers for immunological & inflammatory diseases) if informed consent for biomarker sample banking is agreed upon by the patient.
Declination to allow storage and use of these unused 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 termination.

5.6 OTHER ASSESSMENTS

Not applicable

5.7 APPROPRIATENESS OF MEASUREMENTS

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

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

6.0 INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All patients have to adhere to the visit schedule as specified in the Flow Charts. 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 scheduled. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.
For detailed description of the trial procedures, please refer to the Flow Charts.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Charts and the respective protocol sections. Refer to Section 5.3 and the Appendix Section 10 for explanations of the procedures. Additional details on select procedures are provided below.

Patients should be seen for all visits on the designated day within the allowed "visit window" as specified in the Flow Charts. Measurement of vital signs should precede blood sampling and be assessed pre-dose at all dosing visits. Patient reported outcomes (PROs) should be completed electronically during clinic visits by the patient on his/her own in the following order, as programmed in the electronic device:

(1) DLQI
(2) HAQ-DI [for psoriatic arthritis patients at selected sites]
(3) Pain VAS [for psoriatic arthritis patients at selected sites]
(4) Patient Global Assessment (PtGA) VAS [for psoriatic arthritis patients at selected sites]

PROs should be completed by the patient in a quiet area/room before any other visit assessments or treatments, and, when possible, before any interaction with the investigator or other members of the study team. Timing for downloading the data of PROs will be available in the ISF.

The following psoriasis efficacy assessments (PASI, sPGA, NAPSI, PPASI and PSSI) and psoriatic arthritis assessments (CASPAR and Tender or Swollen joint counts (TJC/SJC)) will be performed by a qualified efficacy assessor at the site by direct capture using an electronic device. Efficacy assessor qualifications and The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) training requirements will be available in the ISF.

Tuberculosis (TB) Testing
Patients will be tested for TB (Quantiferon or PPD) at Screening, Week 52 and EOO. Patients who test positive and are at low risk of TB reactivation, per local guidelines and investigator judgment, do not need to be treated with prophylactic anti-tuberculosis medication and can be entered or continue in the trial.

6.2.1 Screening period

After patients have been informed about the trial, written informed consent in accordance with GCP and the local legislation must be obtained prior to performing any study related procedures. Once they have consented, the patient is considered to be enrolled in the trial and have started screening. The patient should be recorded on the enrolment log and be registered

in IRT as a screened patient. Patients will be assigned a patient number and enrolment must be recorded in eCRF pages.
The Screening period is defined as the period from the Screening visit to Randomisation (first study drug administration). The screening period should be no longer than 42 days and no less than 7 days and will be used to assess eligibility of the patients and to taper the patients off disallowed medications. Thus patients will not be randomized until all screening procedures are completed and results are reviewed to verify study eligibility. Screening procedures may be extended to more than 1 physical visit if needed.

Re-Screening
Re-screening will not be permitted. Patients who fail screening following Visit 1 assessments should be registered as a screen failure in IRT within the protocol defined screening period.
For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to Flow Chart #1.

Demographics
Informed consent date, HIPAA status (US patients only), sex, ethnicity and race (if allowed by local law) will be collected and reported in the eCRF.

Baseline Conditions
Chronic diseases, current observable conditions, any new clinically relevant findings discovered from the Physical Exam, ECG, safety labs, and any condition requiring therapy (excluding psoriasis) will be reported on the Baseline Condition eCRF page.

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

Psoriatic Arthritis Diagnosis Assessment
At Visit 1 at pre-selected study sites, all patients with a positive medical history of psoriatic arthritis will be further evaluated for psoriatic arthritis (PsA) diagnosis based on CASPAR (ClASsification of Psoriatic Arthritis) criteria. See Appendix 10.6 for further details

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

6.2.2 Treatment period

The Treatment period consists of a maximum of 20 visits (Visits 2-21). Visit 2 is the Randomisation Visit and Visit 21 is end of treatment (EOT) visit, where the last dose of medication will be administered.

Unscheduled Visits
During the treatment period patients may be seen at an unscheduled visit if they experience deterioration of psoriasis (i.e. between Weeks 32 and 88 for patients in the double blind portion of the study to assess relapse), or have AEs that in the opinion of the investigator need intervention or repeated laboratory testing.

Safety laboratory testing
All visits after screening requiring safety laboratory sampling will be performed in a 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.

Pregnancy testing
Urine pregnancy testing for all woman of childbearing 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.

Psoriatic arthritis assessments (at selected study sites)
Refer to the Flow charts as well as Appendix 10.6 for timing and assessments.

C-Reactive protein (CRP)
Safety laboratory assessments include CRP testing. The result of the CRP will be used to calculate the DAS28 at the associated visit. See also Appendix 10.6.1.

At treatment period visits all the study procedures described in the Flow-Charts will be performed before the administration of the study medication.

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

Week 28 Visit
At Week 28, each patient's sPGA score will be entered into IRT. Refer to the ISF for details pertaining to IRT procedures and requirements.
All patients that are responding to treatment (sPGA of 0 or 1) at Week 28 will be dispensed blinded medication kits; see (Section 7.6.).
All patients who are non-responders (sPGA $\geq$ 2) at week 28, regardless of initial treatment arm, should continue in this trial and will be dispensed open label BI 655066 medication kits until the end of the treatment period (Week 88).

Randomized withdrawal period (Re-randomized patients)
Between Week 32 and Week 82, at scheduled or unscheduled visits, once any Week 28 responder's sPGA increases to $\geq$ 3 (relapse) the site will enter this result into IRT, and IRT will immediately dispense open label BI 655066 medication. The patient will immediately follow Flowchart #2 or Flowchart #3 depending on the time of relapse. The patient will be re-treated for a maximum of 16 weeks and then have the opportunity to roll-over to the OLE study for further treatment. (See Section 6.2.3). All patients following Flow Chart 2 or Flow Chart 3 will receive a loading dose 4 weeks after the first re-treatment.
Patients relapsing at either an unscheduled visit between Week 82 and Week 88 or at the scheduled Week 88 visit will have the EOT visit procedures performed and return for Follow-up 1 and Follow-up #2 visits as scheduled. A loading dose will not be administered. These patients will also have the opportunity to rollover to the OLE study (See Section 6.2.3)

6.2.3 Follow up Period and Trial Completion

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

The follow-up period within this trial is 16 weeks after receiving the last dose of study medication. Refer to the flow charts for the list of procedures required.

Early treatment and trial termination

If study medication is discontinued prior to the planned Flow Chart EOT visit, every effort should be made to have the patient continue in the trial and complete all of the remaining Treatment Period Visits, as well as Follow-Up 1 and Follow-Up 2 Visits. Trial termination should be completed at Follow-Up 2 Visit.

If a patient cannot or will not continue in the trial, the patient should complete EOT visit procedures instead of the planned treatment period visit and return to the clinic for Follow-Up 2/End of Observation (FU2/EOO) Visit 16 weeks after last dose of study medication.

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

Successful trial completion

Patients who complete treatment according to the applicable planned Flow Chart visit schedule will return to the clinic for Follow-up Visit 1, (6 weeks after last dose of study medication) and for the EOO visit (16 weeks after last dose of study medication). Trial completion is defined as patients completing the EOO visit within the specified window per the flow charts, and who have not discontinued drug prematurely. These patients should be registered as completed in IRT at the EOO visit. These patients will have the option to participate in the open label extension (OLE) trial once EOO procedures are completed.

Refer to ISF for OLE trial entry details.

Vital Status

For randomized patients leaving the study early (before the planned EOO in their current applicable flow chart), vital status should be collected every 12 months after discontinuation up to the planned EOO.

7.0 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a confirmatory, multicenter, randomized, double-blind, placebo controlled study with randomized withdrawal and re-treatment, evaluating the efficacy and safety of BI 655066 in patients with moderate to severe chronic plaque psoriasis. The primary objectives of this trial are to assess the safety and efficacy of BI 655066 in comparison to placebo in patients with moderate to severe chronic plaque psoriasis. The primary efficacy will be evaluated at 16 weeks. In addition, the maintenance of response following drug withdrawal will be assessed after Week 28 through Week 104. Subsequent to drug withdrawal, patients who experience relapse (sPGA ≥3) will be retreated with BI 655066 to assess response after retreatment. Randomisation will be stratified by weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1). Based upon these design considerations and the binary nature of the co-primary endpoints of PASI 90 and sPGA 0 or 1, the trial will be analysed using the Cochran-Mantel-Haenszel risk difference estimate stratified by the randomisation factors mentioned previously. Baseline refers to the measurement recorded at randomisation (Visit 2); if data at Visit 2 is missing or not collected per protocol, then data from Visit 1 will be considered baseline.

In addition, this trial will assess PK and the emergence of anti-drug antibodies (ADA) and their effect on efficacy and safety. Moreover, it will be explored how the use of BI 655066 may influence gene and protein expression levels and disease specific protein markers. More details on these analyses will be provided in the Trial Statistical Analysis Plan (TSAP).

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

Re-randomisation at Week 28 will also be stratified by weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1).

7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary hypotheses are that BI 655066 is different than placebo in achieving ≥ 90% reduction from baseline in the Psoriasis Area and Severity Index score (PASI 90) and sPGA of 0 or 1 at Week 16 in participants with moderate to severe chronic plaque psoriasis. For the primary analyses, this study has 2 treatment arms:

Arm 1 – Patients randomised at visit 2 to receive 150 mg of BI 655066
Arm 2 – Patients randomised at visit 2 to receive placebo

For Part B of the trial, patients randomised to receive BI 655066 at visit 2 and have an sPGA response of 0 or 1 at Week 28 will be re-randomised to one of the following treatment arms:

Arm A – Patients re-randomised to continue to receive BI 655066 during Part B
Arm B – Patients re-randomised to receive placebo during Part B

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

1. BI 150 mg (Arm 1) is not different from placebo (Arm 2) with respect to PASI 90 or sPGA 0 or 1 response at Week 16
2. BI 150 mg (Arm 1) is not different from placebo (Arm 2) with respect to PASI 75 response at Week 16
3. BI 150 mg (Arm 1) is not different from placebo (Arm 2) with respect to PASI 100 response at Week 16
4. BI 150 mg (Arm 1) is not different from placebo (Arm 2) with respect to achieving an sPGA score of clear (0) at Week 16
5. BI 150 mg (Arm 1) is not different from placebo (Arm 2) with respect to achieving a DLQI score of 0 or 1 at Week 16.

For the re-randomized patients, the following null hypothesis will be performed with a type I error of 0.05.

- Arm A (patients re-randomised to BI 655066) is not different from Arm B (patients re-randomised to placebo) with respect to sPGA 0 or 1 response at Week 52.

7.3 PLANNED ANALYSES

The efficacy analyses will be based on the intent-to-treat principle, comprising all participants who were randomized and received at least one dose during the trial. Misrandomized patients are by definition screening failures and therefore are not included in the intended to treat population. Efficacy analyses will be based on the planned treatment (i.e., the treatment assigned at randomisation); this set of patients is called the Full Analysis Set (FAS). Safety analyses will be based on the actual treatment received at the randomisation visit; this set of patients is called the Safety Set (SAF).
All efficacy analyses will be conducted on the FAS. All safety analyses will be conducted on the SAF.

Important violations of the protocol will include key inclusion and exclusion violations, incorrect medications taken, compliance with study medication, incorrectly re-randomized or not re-randomized, concomitant use of restricted medications, and any other violations of the protocol deemed important by the study team. All decisions concerning important protocol violations will be made prior to unblinding of the database. A per-protocol set (PPS) will be defined excluding patients with violations that affect Week 16 efficacy. A secondary re-randomized per-protocol set (RRS-PPS) will be defined excluding those patients with violations affecting Week 52 efficacy of randomized withdrawal. The hypothesis tests as described in Section 7.2 will be repeated on the PPS or RRS-PPS populations, as appropriate.

7.3.1 Primary endpoint analyses

The achievement of PASI90 at Week 16 is the first co-primary endpoint and is a binary variable with values of 0 or 1. The difference in proportion responding between the BI 150 mg arm and placebo arm will be estimated and tested using the Cochran-Mantel-Haenszel risk difference

estimate stratified by the randomisation factors of weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1) with weights proposed by Greenland & Robins, which is calculated as follows:

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

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

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

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

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

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

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

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

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

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

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

If there is a stratum for a treatment group that has 0 patients in it, the 0 count will be replaced by 0.1 in order to prevent dividing by 0 in the above equations, as suggested in Greenland & Robins (R09-1299). Pairwise comparisons of the BI 150 mg arm and placebo arm will include both a p-value and 95% confidence interval.

The achievement of an sPGA score of clear or almost clear at Week 16 is the second co-primary endpoint and is a binary variable with values of 0 or 1. The analysis of the sPGA co-primary endpoint will be identical to that of the PASI90 co-primary endpoint detailed above.

7.3.2 Secondary endpoint analyses

Key Secondary Endpoints:

The achievement of PASI75 at Week 16 is a binary variable with values of 0 or 1. The analysis of this endpoint will be identical to that of the PASI90 co-primary endpoint detailed in Section 7.3.1.

The achievement of PASI100 at Week 16 is a binary variable with values of 0 or 1. The analysis of this endpoint will be identical to that of the PASI90 co-primary endpoint detailed in Section 7.3.1.

The achievement of an sPGA score of clear at Week 16 is a binary variable with values of 0 or 1. The analysis of this endpoint will be identical to that of the PASI90 co-primary endpoint detailed in Section 7.3.1.

The achievement of a DLQI score of 0 or 1 at Week 16 is a binary variable with values of 0 or 1. The analysis of this endpoint will be identical to that of the PASI90 co-primary endpoint detailed in Section 7.3.1.

The achievement of an sPGA score of clear or almost clear at Week 52 is a binary variable with values of 0 or 1. The analysis of this endpoint will be identical to that of the PASI90 co-primary endpoint detailed in Section 7.3.1. Note that this endpoint will only be analysed for patients re-randomised at Week 28 (i.e., only for Arm A and Arm B defined in Section 7.2).

Other Secondary Endpoints:
All of the other secondary endpoints are binary variables with values of 0 or 1. The analysis of these endpoints will be identical to that detailed in Section 7.3.1.
Note that all other secondary endpoints will only be analysed for patients re-randomised at Week 28 (i.e., only for Arm A and Arm B defined in Section 7.2).

7.3.3 Further endpoint analyses

Further endpoints will be summarized, with number and proportion of responders for dichotomous endpoints and mean, median, SD and IQR presented for continuous variables.
Time to onset of *Endpoint*, the time to event will be calculated as:

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

Time to Loss of *Endpoint* will only be performed for patients that are re-randomised at Week 28 (i.e., Arms A and B defined in Section 7.2), where day 0 is defined as the date of the Week 16 visit. Time to loss is defined using the following algorithm:

a) Never attains *Endpoint* (Failure at day 0)
b) After achieving *Endpoint*, patient will be a failure if they subsequently do not achieve *Endpoint* and either discontinue from the study or switch therapy while still not achieving *Endpoint*. Time to failure will be calculated using date of first failure to achieve *Endpoint*.
c) Patients that take prohibited meds to treat Psoriasis will be counted as failures at the time when they first take the prohibited med.
d) Patients that switch therapy while maintaining response will be censored at their last measurement prior to switching treatment. A switch from active medication to Placebo does not consititute a change in treatment.
e) Patients who maintain *Endpoint* throughout the study will be censored at their last measurement.

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

All Time to Event endpoints will be presented using Kaplan-Meier curves with comparisons made between treatment groups using stratified Log-Rank test. Further information will be provided in the TSAP.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA) coding dictionary. Standard AbbVie summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 15 weeks days after the last dose of trial medication, will be assigned to the treatment period for evaluation.
All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on AbbVie standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. 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 on the analysis of safety will be given in the TSAP.

7.3.5 Pharmacokinetic analyses

Descriptive statistics of BI 655066 concentration measurements by treatment group and visit will be provided.
Pharmacokinetic data will be analyzed using population pharmacokinetic approaches. For this purpose, data may also be combined with data from other trials.

7.3.6 Pharmacodynamic analysis

No formal analysis of pharmacokinetic-pharmacodynamic relationships is planned. As the data from previous trials with BI 655066 suggest a pharmacokinetic (PK)-pharmacodynamic (PD)

relationship for efficacy endpoints such as PASI, population PK-PD analyses will be performed. For this purpose, data may also be combined with data from other trials. Model-based analyses will be planned and documented separately according to internal and external guidelines and SOPs. Other exploratory analyses of drug concentration, biomarker or safety data may be performed using data obtained as part of this trial.

All modeling activities will be planned and documented separately according to internal and external guidelines and SOP.

7.3.7 Biomarker analyses

Changes in serum protein 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

There will not be an interim analysis from a statistical standpoint. An analysis will be conducted after the last patient either has been in the study for 52 weeks or discontinues from the study. All primary and key secondary endpoints are collected by Week 52; hence no alpha adjustment is required at this analysis. For this analysis all efficacy endpoints and safety will be analysed. The Sponsor will be unblinded to perform this analysis. Blinded treatment assignments will not be disseminated to the sites, investigators, and patients until the end of study database lock. If needed, more details about this analysis will be specified in the TSAP.

7.5 HANDLING OF MISSING DATA

Every effort should be made to collect complete data at all visits.

The following rules will be used to impute for missing data:
- For all non-binary endpoints, last observation carried forward (LOCF) will be used to impute missing values
- For all binary endpoints (i.e. endpoints that are either 1 (patient responded) or 0 (patient did not respond)):
    - If no data after that visit*, then impute as failure (NRI [No Response Imputation])
    - If data at visits* before and after, only impute as success if both visits are successes; else impute as failure

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

Missing items from the PRO questionnaires will be handled according to the measure instructions (Section 10.7). If there is no data for a particular visit, then it will be imputed following the same rules as described above.
Sensitivity analyses to assess the robustness of the hypothesis testing results will include the following methods where applicable:
- LOCF (for binary endpoints)
- Logistic regression

- Mixed effect Model Repeat Measurement (MMRM) (for continuous endpoints)
- Multiple imputation (for binary endpoints)

Of note, for randomized withdrawal analyses, subjects who received retreatment will be counted as non-responders in all visits after the date of retreatment.

7.6 RANDOMISATION

At Visit 2, patients will be randomized in blocks to double-blind treatment to either BI 655066 150 mg or placebo in a 4:1 ratio. Randomisation will be stratified with respect to weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1).

At week 28, patients will be separated into "responder" and "non-responder" groups. A patient will be considered as a "responder" if the week 28 sPGA is clear or almost clear (0 or 1); otherwise the patient will be considered a "non-responder".

Among responders, patients originally randomized to BI 655066 150 mg (Arm 1) will be re-randomized in a 1:2 ratio to either 150 mg of BI 655066 or placebo in a second double-blinded portion (Part B) of the trial. Re-randomisation will be stratified by weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥1). Patients originally randomized to placebo (Arm 2) will continue to receive blinded study drug every 12 weeks in Part B of the trial, to maintain the blind to the original randomized treatment arm.

Regardless of originally randomized treatment group, non-responders will receive open label BI 655066 every 12 weeks, starting at Week 28, for the remainder of the trial. BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomisation lists will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block sizes will be documented in the Clinical Trial Report (CTR). Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

This study is designed to show a difference between BI 655066 and placebo in terms of PASI90 response and sPGA scores of clear or almost clear at Week 16. However, this study was also powered to show a difference in sPGA response at Week 52 between the patients randomized to continue on BI 655066 vs. patients randomized to placebo at Week 28.

Based on the interim results from 1311.2 (c03272682-01), it is assumed at most 10% of the patients in the re-randomized BI 655066 arm will lose sPGA response of clear or almost clear (0 or 1) at Week 52 whereas approximately 25% of patients in the re-randomized placebo arm will lose response. Using a 1:2 re-randomisation scheme (BI 655066:placebo), 102 patients in the BI 655066 arm and 204 patients in the placebo arm will provide at least 90% power to detect the difference in sPGA response rate at Week 52. Assuming that 80% of patients on BI 655066 at baseline will achieve sPGA of clear or almost clear at Week 28, the total sample size required for the initial BI 655066 arm at Visit 2 is (102)(3)÷0.8=383. See Table 7.7:1 for more sample size calculations to have at least 90% power.

Table 7.7:1 Sample sizes for randomized withdrawal comparison

Response Rate at Week 52			**Randomisation ratio at Week 28 active:placebo = Total N**	**Total N at randomisation**
Active	**Placebo**	**Delta**	**1:2**	
90%	72.5%	17.5%	79:158 = 237	297
90%	75%	15%	102:204 = 306	383
90%	77.5%	12.5%	138:276 = 414	518

Calculated using ADDPLAN Version 6.0.4.

Thus 400 patients in the original BI 655066 arm, provide at least 90% power for the randomized withdrawal comparison. Using a 4:1 randomisation will yield a total sample size of 500 = 400:100 for BI 655066: placebo.

Based on the outcome from trials 1311.1 and 1311.2, the PASI90 response rate at Week 16 is assumed to be at least 65% in the BI 655066 arm and approximately 5% for placebo. For sPGA clear or almost clear at Week 16, the response rate for the BI 655066 arm is assumed to be at least 80% and approximately 5% for placebo. This trial will have >99% power for comparing each BI 655066 arm to placebo on both of these endpoints.

All calculations were performed using ADDPLAN Version 6.0.4, an Aptiv Solutions Company.

8.0 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), relevant BI Standard Operating Procedures (SOPs), the EU regulation 536/2014, the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.
The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial patients against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a general rule, no trial results should be published prior to finalization of the Clinical Trial Report.
Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF.
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

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."

<u>The following paragraph pertains to Japan only</u>:
The Investigator must give a full explanation to trial patients including the items listed below in association with the use of the patient information form, which is prepared avoiding the use of technical terms and expressions. The patient is given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor via remote data capture. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available. For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with identification of critical data and processes. An Integrated Quality and Risk Management Plan documents the strategies involved with the implementation of onsite, offsite and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to patient safety and data quality. Trial oversight is achieved by regular review of a report of risk, which then influences any monitoring adaptations.
The Investigator / institution will permit trial-related monitoring, audits, IRB / IEC review and regulatory inspection, providing direct access to all related source data / documents. eCRF and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the Sponsor's clinical trial monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all eCRF, and written informed consents.

8.3.3 Storage period of records (Applicable to Japan only)

Trial site(s):
The trial site(s) must retain the source documents and essential documents for a period defined by the Japanese GCP regulation and trial site's contract with the sponsor.

Sponsor:
The Sponsor must retain the essential documents according to the Sponsor's SOPs.
When it is no longer necessary for the trial site to retain the source documents and essential documents, the Sponsor must notify the head of trial site.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the Sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore, a unique reference document for the evaluation of listedness needs to be provided. For the study drug BI 655066, this is the current version of the Investigator's Brochure (c01569420-06), which is provided in the ISF.
No AEs are classified as listed for matching placebo, trial design, or invasive procedures

8.4.2 Expedited reporting to health authorities and IEC / IRB

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

8.5 STATEMENT OF CONFIDENTIALITY

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

8.6 END OF TRIAL

The end of the trial is defined as written in Section 6.2.3.
The IEC / competent authority in each participating EU member state will be notified about the end or early termination of the trial.
For Japan: When the trial is completed, the Investigator should inform the head of the trial site of the completion in writing, and the head of the trial site should promptly inform the IRB and Sponsor of the completion in writing.

8.7 PROTOCOL VIOLATIONS

This Section is applicable to 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

This Section is applicable to 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 PASI DEFINITIONS AND USE

The PASI is an established measure of clinical efficacy for psoriasis medications. (R96-3541) The PASI is a tool that 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, the four main body areas are assessed: **head (h), trunk (t), upper extremities (u) and lower extremities (l).** These correspond to 10, 30, 20 and 40% of the total body area respectively.
The **area of psoriatic involvement** of these four areas (Ah, At, Au, and Al) is given a numerical value: 0 = no involvement, 1 = <10%, 2 = 10 to <30%, 3 = 30 to <50%, 4 = 50 to <70%, 5 = 70 to <90%, and 6 = 90 to 100% involvement.
The **signs of severity, erythema (E), infiltration (I) and desquamation (D)** of lesions are assessed using a numeric scale 0-4 where 0 is a complete lack of cutaneous involvement and 4 is the severest possible involvement; scores are made independently for each of the areas, h, t, u and l and represents a composite score for each area. An illustration of judging erythema follows: 0 = no erythema, 1 = slight erythema, 2 = moderate erythema, 3 = striking erythema, and 4 = exceptionally striking erythema.
The PASI score is calculated according to the following formula:
PASI = 0.1(Eh+Ih+Dh)Ah + 0.3(Et+It+Dt)At + 0.2(Eu+Iu+Du)Au + 0.4(El+Il+Dl)Al

10.2 STATIC PHYSICIAN GLOBAL ASSESSMENT (SPGA)

The 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 (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.

Erythema

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

Induration (plaque elevation)

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

Scaling

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

Scoring:

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

sPGA Rating Scale for Overall Psoriatic Disease

Score	Short description	Detailed description
0	**clear**	No signs of psoriasis. Post-inflammatory hyper/hypopigmentation 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

The scale used was static, i.e., it referred exclusively to the patient's 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.

10.3 NAPSI – NAIL PSORIASIS SEVERITY INDEX

The NAPSI assesses how much of the fingernail is affected with psoriasis with scores ranging from 0 to 80. (R16-2654)
If a patient has nail psoriasis, the physician will assess the nail psoriasis at each protocol defined time point. Fingers (5) on each hand will be individually examined for two distinct assessments and are graded as follows:

Nail Matrix Assessment:

0 = None
1 = present in 1 quadrant of nail
2 = present in 2 quadrants of nail
3 = present in 3 quadrants of nail
4 = present in 4 quadrants of nail

Nail Bed Assessment:

0 = None
1 = present in 1 quadrant of nail
2 = present in 2 quadrants of nail
3 = present in 3 quadrants of nail
4 = present in 4 quadrants of nail

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

10.4 PPASI – PALMOPLANTAR PSORIASIS SEVERITY INDEX

The PPASI provides a numeric scoring for psoriasis affecting the hands and feet with scores ranging from 0 to 72. It is a linear combination of percent of surface area of hands and feet that are affected and the severity of erythema, induration, and desquamation.
If a patient has palmoplantar psoriasis, the physician will assess the psoriasis at each protocol defined time point. Both palms and soles on each hand and foot will be individually assessed for erythema, induration, desquamation and percentage of area affected as follows:

Erythema, Induration and Desquamation:

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

Percent of Palm and Sole Area Covered:

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

The PPASI is a composite score and will be computed for each palm and sole, left and right and is derived from the sum of the scores for erythema (E), induration (I) and desquamation (D) multiplied by the score recorded for the extent of palm and sole area involved. PPASI is calculated as follows: (sum of scores for E+I+D)*Area *0.2(location: right palm) + (sum of scores for E+I+D)*Area *0.2(location: left palm) + (sum of scores for E+I+D)*Area *0.3(location: right sole) + (sum of scores for E+I+D)*Area *0.3(location: left sole). The range is 0 to 72.

10.5 PSORIASIS SCALP SEVERITY INDEX (PSSI)

If a patient has scalp psoriasis, the physician will assess the erythema (redness), induration (hardness), desquamation (shedding of skin) and percent of scalp covered at each protocol defined time point. (R16-2653).

Erythema, Induration and Desquamation:

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

Percent of Scalp Covered:

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

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

10.6 DIAGNOSIS AND ASSESSMENTS FOR PATIENTS WITH PSORIATIC ARTHRITIS (AT SELECTED SITES ONLY)

At Visit 1 at selected study sites, patients with a positive history of PsA or suspected to have PsA will be further evaluated for PsA diagnosis based on CASPAR (ClASsification of Psoriatic Arthritis) criteria (R15-1001).

To be classified has having PsA, a patient must have inflammatory articular disease (joint, spine, or entheseal) with at least 3 points total from the 5 categories in Table 10.6: 1, All trial participants will have 2 points assigned due to evidence of current psoriasis per trial entry criteria and will require at least one additional point for diagnosis of PsA.

Table 10.6:1 CASPAR criteria

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

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

- HAQ-DI (see Appendix 10.7.2)
- Pain VAS (see Appendix 10.7.3)
- Patient global assessment VAS (see Appendix 10.7.4)
- Tender or Swollen joint counts (TJC/SJC) on 28 joints (refer to Table 10.6: 2)
- Entry of data for calculation of DAS28 on electronic device (Refer to Appendix 10.6.1)

During the treatment period and EOO the following will continue to be performed at the visits noted in the Flow Charts if the TJC/SJC is ≥3 at Visit 2.

- HAQ-DI (see Appendix 10.7.2)
- Pain VAS (see Appendix 10.7.3)
- Patient global assessment VAS (see Appendix 10.7.4)
- Tender or Swollen joint counts (TJC/SJC) on 28 joints (refer to Table 10.6: 2)
- Entry of data for calculation of DAS28 on electronic device (Refer to Appendix 10.6.1)

Table 10.6:2 Tender or Swollen Joint Count (28)

Joint	Right		Left	
	Tender	Swollen	Tender	Swollen
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				
Knee				

Metacarpal-phalangeal joints (MCP); Interphalangeal joints (IP); Proximal interphalangeal joints (PIP)
Tenderness and swelling will be evaluated as “0” absent or “1” present.

10.6.1 Disease Activity Score in 28 Joints (DAS 28)

DAS28, which stands for "disease activity score," is a modified version of the original DAS. DAS28 will be calculated using a formula that includes the number of tender joints and swollen joints (28 joints), CRP (C-reactive protein) and a patient self-assessment (patient global health-VAS).

DAS 28 will be calculated using the following formula from the electronic device where the VAS pertains to the patient’s global assessment of disease VAS:

- DAS28=0.56*$\sqrt{}$ (tender joint count) + 0.28*$\sqrt{}$ (swollen joint count) + 0.36*Ln(CRP+1) + 0.014* (patient global assessment VAS) + 0.96

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

10.7 HEALTH OUTCOMES/QUALITY OF LIFE

10.7.1 Dermatology Life Quality Index

The DLQI is a patient-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment (R05-2548). The DLQI has a one-week recall period. Response categories include "not relevant" (score of 0), "not at all" (score of 0), "a little" (score of 1), "a lot" (score of 2) and "very much" (score of 3). Question 7 is a "yes"/ "no" question where "yes" is scored as 3.

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

The DLQI will be analysed under six headings as follows (R05-2548):

Domain	Question Number	Score
Symptoms and feelings	Questions 1 and 2	Score maximum 6
Daily activities	Questions 3 and 4	Score maximum 6
Leisure	Questions 5 and 6	Score maximum 6
Work and school	Question 7	Score maximum 3
Personal relationships	Questions 8 and 9	Score maximum 6
Treatment	Question 10	Score maximum 3

DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0-1 = no effect on patient's life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on patient's life. The higher the score, the more the quality of life is impaired. If the answer to one question in a domain is missing, that domain is treated as missing. If 2 or more questions are left unanswered (missing), DLQI total score is treated as missing. A 5-point change from baseline is considered a clinically important difference.

DERMATOLOGY LIFE QUALITY INDEX

DLQI

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

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

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

Please check you have answered EVERY question. Thank you.

10.7.2 Health Assessment Questionnaire Disability Index (HAQ-DI)

The HAQ-DI will be self-administered by the patient [for psoriatic arthritis patients at selected sites] at visits indicated in the flowchart.

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

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

HEALTH ASSESSMENT QUESTIONNAIRE

PATKEY#_____
QUESTDAT_____

Name_____ **Date**_____

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

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

PMSVIS_____
RASTUDY_____
QUESTNUM_____

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

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

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

DRSGASST_____
RISEASST_____

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

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

EATASST_____
WALKASST_____

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

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

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

____Raised toilet seat ____Bathtub bar
____Bathtub seat ____Long-handled appliances for reach
____Jar opener (for jars previously opened) ____Long-handled appliances in bathroom
____Other (Specify: _____)

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

____Hygiene ____Gripping and opening things
____Reach ____Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

10.7.3 Pain VAS

The Pain VAS will be self-administered by the patient [for psoriatic arthritis patients at selected sites] at visits indicated in the flowchart.

The patient's assessment of pain will be performed using a horizontal 15cm visual analog scale (VAS), ranging from 0 (no pain) to 100 (severe pain) after the question:

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

10.7.4 Patient global assessment VAS

The patient global assessment VAS will be self-administered by the patient [for psoriatic arthritis patients at selected sites] at visits indicated in the flowchart.

The patient's global assessment of disease activity will be performed using a horizontal 15cm VAS, ranging from 0 (very well) to 100 (very poor) after the question:

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

11. DESCRIPTION OF GLOBAL AMENDMENTS

Number of global amendment		1.0
Date of CTP revision		11-Mar-2016
EudraCT number		2014-005102-38
BI Trial number		1311.4
BI Investigational Product(s)		BI 655066
Title of protocol		BI 655066 (risankizumab) versus placebo **I**n a **M**ulticenter randomized double-blind study in patients with **M**oderate to severe c**h**ronic pl**a**que psoriasis evaluati**n**g the effi**c**acy and safety with randomized withdrawal and r**e**-treatment (IMMhance)
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		Flow Chart 1
Description of Change		1. Added Infection Testing (TB) to Screening. 2. Footnote #23 added for clarification to TB. 3.ADA sampling added to Week 4 4. Footnote #5, Visit 28 corrected to Week 28 5. Footnote #17, Visit 32 and Visit 70 corrected to Week 32 and Week 70 6.Text regarding hypersensitivity removed from Footnote #13 and placed accordingly in a new footnote #24 7. Line item “biologic therapy history” changed to “psoriasis therapy history 8. Footnote #22 was re-worded

		9. % BSA involvement added as a line item
Rationale for change		1.Request from Health Authorities 2. Request from Health Authorities 3. Request from Health Authorities 4. Error in original CTP 5. Error in original CTP 6. Clarification 7. Clarification 8. Clarification 9. % BSA is collected on the electronic device at screening and prior to randomization as an inclusion criteria
Section To be changed		All Flow Charts
Description of change		1. Footnote #6 The criterion for missing more than 1 study treatment was removed from the completer definition for entry into the OLE study. "Patients who have completed the study (which is defined as patients completing the EOO visit within the specified window per the flow charts.) and who also meet the eligibility criteria will be offered to roll over into an open label extension (OLE) trial. 2. Footnote #7- PK and ADA samples are to be taken **within** 60 minutes before the subcutaneous injection 3. Footnote #3 Re-written as well as DLQI removed from flow chart 2 and 3 footnote 3
Rationale for change		1. Clarification 2. Clarification 3. DLQI not needed for flow Chart #2 and Flow Chart #3. Also footnote as originally written was redundant
Section to be changed		Flow Charts 2 and 3 (Footnote #10)
Description of change		Vital Status information: patients must follow their current flow chart for 'planned EOO")
Rational for change		Clarification for relapsed and re-treated patients with respect to Vital Status as they follow Flow

		Charts 2 and 3 which do not have an EOO at 104 weeks.
Section to be changed		Flow Chart #2 and Flow Chart #3
Description of change		Removed DLQI from Footnote #3
Rationale for change		Error in original CTP footnote
Section to be changed		Section 2.3-Benefit Risk Assessment
Description of change		Provided justification for not treating latent TB
Rationale for change		Due to update of Exclusion #6 for TB
Section to be changed		Section 3.1.2-Data Monitoring
Description of change		Clarification on how efficacy data will be used upon submission to the DMC as well as additional information on unblinding
Rationale for change		Clarification
Section to be changed		Section 3.1.3, MACE Adjudication Committee
Description of change		Added “thrombotic events”
Rationale for change		Clarification
Section to be changed		Section 3.3.3- Exclusion Criteria #6
Description of change		Updated exclusion criteria to clarify latent TB and treatment for TB. ”Patients with a positive test result 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, patients who are at low risk of reactivation, defined by local guidelines and investigator judgment, do not need to be treated with prophylactic anti-tuberculosis prior to or during the trial”.
Rationale for change		Due to inclusion of TB testing at Screening
Section to be changed		Section 3.3.4.1, Removal of Individual Patients
Description of change		1.Patients discontinuing treatment early should remain in the study

		2. Updated Vital Status to clarify that EOO is the current applicable flow chart
Rationale for change		1. When possible patients should continue with remaining visits 2. To clarify and distinguish relapse and re-treated patients following flow charts #2 and #3
Section to be changed		Section 4.1.4, Drug assignment and administration
Description of change		Added additional areas and wording for subcutaneous injection "(gluteal and upper arms) as well as contralateral to PK/ADA sampling"
Rationale for change		Omitted from original CTP
Section to be changed		Table 4.2.2.1:1, restricted medications
Description of change		1.Added the following medications tofacitinib (Xeljanz®), apremilast (Otezla®) 2. Removed efalizumab (Raptiva®)
Rational for Change		1.Additional medications requiring washout 2. Medication not available
Section to be changed		Section 5.1.3-Further Endpoints
Description of change		Added "absolute PASI of <3 at all visits collected
Rationale for change		Change to CTP
Section to be changed		Laboratory Table 5.3.3:1
Description of Change		The requirement for TB at screening was added to the Infection Testing category and footnote #3
Rationale for change		Request from Health Authorities
Section to be changed		Section 6.2, Details of Trial Procedures
Description of change		Added a paragraph for TB testing: "Patients will be tested for TB (Quantiferon or PPD) at Screening, Week 52 and EOO. Patients who test positive and are at low risk of TB reactivation, per local guidelines and investigator judgment, do not need to be treated with prophylactic anti-tuberculosis medication and can be entered or continue in the trial".
Rational for change		New screening procedure and information on

		treatment upon testing positive.
Section to be changed		Section 6.2.1, Screening period
Description of change		The maximum of 2 visits that a patient may need for screening was deleted
Rationale for change		Patients may require more than 2 visits to the clinic during screening
Section to be changed		Section 6.2.3, Follow-up Period and Trial Completion
Description of change		1.Vital status- patients must follow their current flow chart for EOO 2. Removed criteria for missing one dose for eligibility for OLE study 3.Patients discontinuing treatment early should continue in the study
Rationale for change		1.Clarification for relapse and re-treated patients following FC#2 and FC#3 2. Clarification 3. Added for Clarification
Section for change		Section 7.2 Null and Alternative Hypothesis
Description of change		Separated out re-randomized hypothesis from hypotheses tested on all randomized patients
Rationale for change		The re-randomized portion of the trial can be treated as a separate study and thus tested with its own alpha = 0.05.
Section for change		Section 7.3- Planned Analysis
Description of change		1.Clarifying the definition of analysis sets 2. deleted wording that IPV's would be provided in TSAP and added verbiage about IPVs and PPS sensitivity analyses 3. Added "The hypothesis tests as described in Section 7.2 will be repeated on the PPS or RRS-PPS populations, as appropriate".
Rationale for change		In response to questions from Health Authorities.
Section for change		Section 7.4-Interim analysis
Description of change		Removal of DMC information

Rationale for change		Redundant as included in DMC section
Section for change		Section 7.5 Handling of Missing data
Description of change		Removed sentence that additional information may be included in TSAP and added information pertaining to the sensitivities analyses that will be done
Rationale for change		Provide as much information concerning primary and secondary endpoints to be pre-defined in the protocol.
Section to be changed		Appendix 10.6
Description of change		Order of PsA assessments changed at Visit 2
Rationale for change		To match order of assessments on the electronic device and due to requirement to perform joint counts last
Section for change		Section 1.2, Drug Profile, Listedness Section 8.4.1, and Unpublished Reference Section 9.2
Description of change		Document ID for the new version of the Investigator Brochure has changed to “c01569420-06”
Rationale for change		Updated Document ID
Section for change		Published Reference Section 9.1
Description of change		Three references added,R15-5488, R15-5495, R15-5497
Rationale for change		Due to addition information added to Section 2.3
Section for change		Pages 1,2 Title pages
Description of change		Added risankizumab after BI 655066
Rationale for change		New name added for completeness

Number of global amendment		2.0
Date of CTP revision		28-Jul-2016
EudraCT number		2014-005102-38
BI Trial number		1311.4
BI Investigational Product(s)		BI 655066 (risankizumab)
Title of protocol		BI 655066 (risankizumab) versus placebo **I**n a **M**ulticenter randomized double-blind study in patients with **M**oderate to severe c**h**ronic pl**a**que psoriasis evaluati**n**g the effi**c**acy and safety with randomized withdrawal and r**e**-treatment (IMMhance)
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 and Synopsis
Description of change		Added (risankizumab) to BI investigational product on title page and to active ingredient section in Synopsis
Rationale for change		New name added for completeness
Section To be changed		Throughout document
Description of change		The following abbreviations are now spelled out due to first use in the text: ECG (synopsis); RDC (5.3.6.1); PPD (3.3.3); VEGF (5.5.1);ULN (5.3.6.1); GRAPPA (6.2); NRI, LOCF, MMRM (7.5); CTR (7.6); CTP (flowchart #1 footnote 6)
Rationale for change		Omitted from original CTP
Section to be changed		All Flow Charts
Description of Change		**a.** Added to footnote #6 " who have not discontinued drug prematurely" **b**. Revision to footnote #24 on FC #1, footnote #12 on FC #2 and footnote #11 on FC #3, "Patients

		should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at Visit 2 and for approximately one hour after the last injection at all other visits where drug is administered
Rationale for change		**a**. Additional criteria for a study completer and entry into OLE study **b**. Provide additional details of monitoring hypersensitivity with respect to injection times
Section To be changed		Flow Chart 1
Description of change		Added to Footnote #15 "Patients that terminate trial medication early should remain in the trial and complete all remaining Treatment Period visits and, FU1 and FU2 Visits. Termination of trial medication eCRF should be completed and end of study registered as a non-completer in IRT. Refer to Section 6.2.3 for details and further instruction if patient cannot or will not continue in the trial.
Rationale for change		Additional clarification needed for proper procedure when a patient discontinues treatment but remains in the study
Section to be changed		Flow Chart #1
Description of change		Added the following to Footnote #13 "(after last injection)"
Rationale for change		To clarify when vitals post dose are expected at Visits 2 and 3
Section to be changed		Abbreviations
Description of change		Added the following abbreviations: aPTT, CRO, PPD, RCTC, Nab, NGAL, VEGF, TJC/SJC, GRAPPA, CRP, PPS, RBC, RRS-PPS, NRI, MMRM, AP, BUN, CK, CK-MB, eGFR, GGT, Hb, Hct, HDL, LDL, TSH, INR, RDC Abbreviation PoC corrected to PoCC Abbreviation OPU corrected to "Operative"
Rationale for change		Omitted from original or CTP V 2.0
Section to be changed		Table of Contents
Description of change		Formatting update to title of sections 5.3.5.1, 5.4.2.1, 5.4.2.2, 5.5.1.2 and 7.3.7 in order to show in the table of contents
Rationale for change		Formatting error in original CTP
Section to be changed		Section 3.1- Overall Trial Design and Plan
Description of change		Section re-written and Figure 3.1:1 was replaced with new trial design. In summary: At the Week 28 visit, all patients will be assessed for responsiveness. Patients not meeting the protocol defined response criteria (sPGA is ≥ 2) (Week 28 non-responders), will receive open label BI 655066 150 mg from

		Week 28 until the end of the treatment period (Week 88), regardless of originally randomized treatment arm. Patients who meet the protocol defined responder criteria (sPGA of 0 or 1) (Week 28 responders), will continue to receive blinded drug. In Arm 1, patients will be re-randomized; in Arm 2, they will continue to receive blinded BI655066 treatment as described in Section 7.6. Starting with Week 32, Week 28 responders will have their sPGA assessed for protocol defined relapse (sPGA of ≥ 3).
Rationale for change		This change is to be implemented to ensure that no bias is introduced by knowing patients' original treatment assignment after the Week 28 visit
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		"a primary endpoint analysis will be conducted after the last patient has been in the study for 52 weeks (or discontinued)". The previous wording was "when the last patient completes the Week 52 visit.
Rationale for change		To incorporate the possibility that patients may discontinue from the study prior to Week 52.
Section to be changed		Section 3.1.1 Administrative structure of the trial
Description of change		Operating unit changed to Operative Unit
Rationale for change		Protocol template error
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		The word "necessarily" was added to: "Discontinuation of study medication should not necessarily lead to withdrawal from the study".
Rationale for change		Clarification as patients that discontinue study medication should complete all study visits and procedures as initially planned, if possible
Section to be changed		3.3.4.2
Description of change		Bullet #2 re-written to "Emergence of any efficacy/safety information that could significantly affect continuation of the trial, or any other administrative reasons, i.e. problems with availability of the study medication, discontinuation of development of BI 655066 Original Bullet #3 removed "Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial (including those based on DMC recommendation)
Rationale for change		Error in original CTP
Section to be changed		Section 4.1.2 Methods of assigning patients to treatment groups
Description of change		Section re-written according to new study design to

		be consistent with section 3.1
Rationale for change		Design change
Section to be changed		Section 4.1.3 Selection of doses in the trial
Description of change		650666 changed to 655066
Rationale for change		Error in original CTP
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		**a**. Added that the 2 injections need to be administered within approximately 5 minutes. **b**. Added that the IMP time in the eCRF is the time of injection # 1. **c**. Added the underlined words to the sentence; "Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours <u>after the last injection</u> at Visit 2 and for approximately one hour <u>after the last injection</u> at all other visits where drug is administered. **d.** Deleted: (contra-lateral to that used for PK/PD samples) from sentence "BI 655066 and/or matching placebo will be administered as a subcutaneous injection in the abdomen, thighs, gluteal regions, or upper arms".
Rationale for change		**a,b**. Provide clarity and further details on timing of injections and eCRF completion **c**.To specify timing of monitoring hypersensitivity with respect to injection times. **d.** not required as PK samples are only taken pre-dose (trough)
Section to be changed		4.1.5.1 Blinding
Description of change		Section re-written according to new study design to be consistent with section 3.1, clarifying the criteria for receiving open label drug and knowing future treatments are BI 655066.
Rationale for change		New study design as noted in section 3.1
Section to be changed		4.2.2.3 Restrictions regarding women of childbearing potential
Description of change		Deleted reference to Section 3.3.3, and corrected to 3.3.2
Rationale for change		Error in original protocol
Section to be changed		5.1.3 Further endpoints
Description of change		Text added "The above endpoints will be analyzed,

		where appropriate, for re-randomized subjects after receiving open-label study drug for retreatment (Flow Chart 2 and 3)".
Rationale for change		To clarify that these endpoints will also be analyzed among retreatment patients at visits collected.
Section to be changed		5.3.2 Vital Signs
Description of change		The underlined wording was added to the following sentences. "In addition at Visit 2 and Visit 3 vital sign evaluations will be taken at approximately 5 minutes post-dose (5 minutes after last injection) and approximately 60 minutes post-dose (60 minutes after last injection). "Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at Visit 2 and for approximately one hour after the last injection at all other visits where drug is administered
Rationale for change		To specify timing of vitals relative to injection times and also timing of monitoring hypersensitivity with respect to injection times.
Section to be changed		Table 5.3.3:1 laboratory tests
Description of change		Added absolute count to differential Added "activated to aPTT Deleted "MB" from Troponin reflex Added "calculated" to LDL Deleted "creatinine" from urinalysis stix Added "creatinine" to urinalysis Added Albumin/creatinine ratio to Urinalysis
Rationale for change		Was omitted from original CTP or needed further clarification
Section to be changed		6.2 Details of Trial Procedures At Selected Visits
Description of change		Added paragraph to note that efficacy questionnaires are direct data capture on an electronic device
Rationale for change		Omitted from original CTP
Section to be changed		Section 6.2.2, Week 28 Visit and Randomized withdrawal period (Re-randomized patients)
Description of change		Wording revised due to implementation of continuing blinded treatment
Rationale for change		Design change for Week 28
Section to be changed		Section 6.2.2 Treatment period
Description of change		Added "a maximum of" 20 visits
Rationale for change		Clarification as patients who relapse and get retreated may have less visits during treatment depending on time of relapse
Section to be changed		Section 6.2.3 Early Treatment and trial termination
Description of change		Further instructions given for staying in the trial or terminating from the trial when a patient ends treatment early

Rationale for change		Update to original CTP
Section to be changed		Section 6.2.3 Successful Trial Completion
Description of change		Added "and who have not discontinued drug prematurely" to definition of trial completion
Rationale for change		Clarifying definition of trial completion
Section to be changed		Section 7.1
Description of change		"or not collected per protocol" was added to the last sentence in first paragraph
Rationale for change		clarification
Section to be changed		Section 7.3 Planned Analyses
Description of change		Second to last sentence of last paragraph wording "the patients included in the Week 52 assessment of randomized withdrawal " Replaced with "affecting Week 52 efficacy of randomized withdrawal.
Rationale for change		To clarify that this per-protocol set will exclude patients with violations affecting their efficacy evaluation, not affecting patients in general.
Section to be changed		7.3.3 Further endpoint analyses
Description of change		"descriptively" removed from "Further endpoints will be summarized descriptively
Rationale for change		"summarized" already means that descriptive/summary statistics will be provided, the word "descriptively" seems duplicated here and is removed.
Section to be changed		7.4 Interim Analyses
Description of change		**a**. Updated to "An analysis will be conducted after the last patient either has been in the study for 52 weeks or discontinues from study". **b**. Updated to: "hence no alpha adjustment is required at this analysis".
Rationale for change		**a.** To incorporate the possibility that patients may discontinue from the study prior to Week 52. **b.** To clarify that this analysis will not require type-I error rate adjustment.
Section to be changed		7.5 Handling of Missing Data
Description of change		**a.** Added "Of note, for randomized withdrawal analyses, subjects who received retreatment will be counted as non-responders in all visits after the date of retreatment." **b.** Added "the following methods where applicable" to the end of this sentence, "Sensitivity analyses to assess the robustness of the hypothesis testing results will include":
Rationale for change		**a.** To clarify that patients who received retreatment will be counted as non-responders, since the decision

		of retreatment is due to lack of efficacy. **b.** To clarify that the listed methods for sensitivity analyses will be conducted based on data availability and method validity, because not all methods are applicable at all cases.
Section to be changed		7.6 Randomisation
Description of change		Section re-written according to new study design to be consistent with section 3.1
Rationale for change		CTP update
Section to be changed		Table 7.7.1
Description of change		Changed PBO to “placebo”
Rationale for change		“placebo” used throughout CTP
Section to be changed		Section 9.1 Published References
Description of change		Added R16-2653 and R16-2654
Rationale for change		Omitted from original CTP
Section to be changed		10.3 NAPSI-Nail Psoriasis Severity Index
Description of change		Addition of Reference number R16-2654
Rationale for change		Update to CTP
Section to be changed		10.4 PPASI-Palmoplantar psoriasis severity index
Description of change		Correction of wording from “scored” to “scores”
Rationale for change		Correction
Section to be changed		10.5 Psoriasis scalp severity index (PSSI)
Description of change		Addition of Reference number R16-2653
Rationale for change		Omitted from original CTP
Section to be changed		10.7.1 Dermatology life quality index (DLQI)
Description of change		Correction of response categories
Rationale for change		Update from original CTP
Section to be changed		3.1 Overall Trial Design and Plan and 4.1.5.1 Blinding
Description of change		Removed wording noting that data for all patients through week 16 must be entered into the eCRF prior to the patients receiving treatment at the week 28 visit."
Rationale for change		As this amendment removes the blind break for week 28 responders, this is no longer a requirement and is accordingly removed from the protocol.

Number of global amendment		3.0
Date of CTP revision		11-Oct-2016
EudraCT number		2014-005102-38
BI Trial number		1311.4
BI Investigational Product(s)		BI 655066/ABBV-066 (risankizumab)
Title of protocol		BI 655066 (risankizumab) versus placebo **I**n a **M**ulticenter randomized double-blind study in patients with **M**oderate to severe c**h**ronic pl**a**que psoriasis evaluati**n**g the effi**c**acy and safety with randomized withdrawal and r**e**-treatment (IMMhance)
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	X	

Section To be changed		Title page and synopsis
Description of change		The compound name was revised to add "ABBV-066" to BI 655066 (risankizumab)
Rationale for change		In February 2016, AbbVie entered into a license agreement with BI related to risankizumab, and in October 2016, the US IND for risankizumab transitioned from BI to AbbVie. This protocol change reflects that AbbVie will now be the Sponsor of this study in the US, as well as the modifications to certain study conduct responsibilities as a result of that license agreement are listed as separate changes below.
Section To be changed		Section 3.1.1
Description of change		1. Changed sponsor from Boehringer Ingelheim (BI) to AbbVie in the USA and BI for non-USA participating countries.
Rationale for change		2. Changed text to specify Statistical Evaluation will be done by AbbVie according to their SOPs.
Section To be changed		Section 3.3.4.2

Description of change		Updated text to "AbbVie/Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons".
Rationale for change		Refer to rational for first change listed
Section To be changed		Section 5.5.2.2
Description of change		Changed DNA banking sample storage from Boehringer Ingelheim to "AbbVie or a third party delegate (e.g. Boehringer Ingelheim Pharma GmbH & Co. KG; Birkendorfer Str. 65, 88397 Biberach, Germany)".
Rationale for change		Refer to rational for first change listed
Section To be changed		Section 7.3.4
Description of change		Changed text to specify that AbbVie summary tables and listings will be produced and analyses based on AbbVie standards.
Rationale for change		Refer to rational for first change listed