16.0 Appendices

16.1 Study Information

16.1__1 Protocol and Protocol Amendments

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:	PPD Boehringer Ingelheim Pharmaceuticals 900 Ridgebury Road Ridgefield CT USA 06877 PPD	
Coordinating Investigator:		
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:	PPD
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.

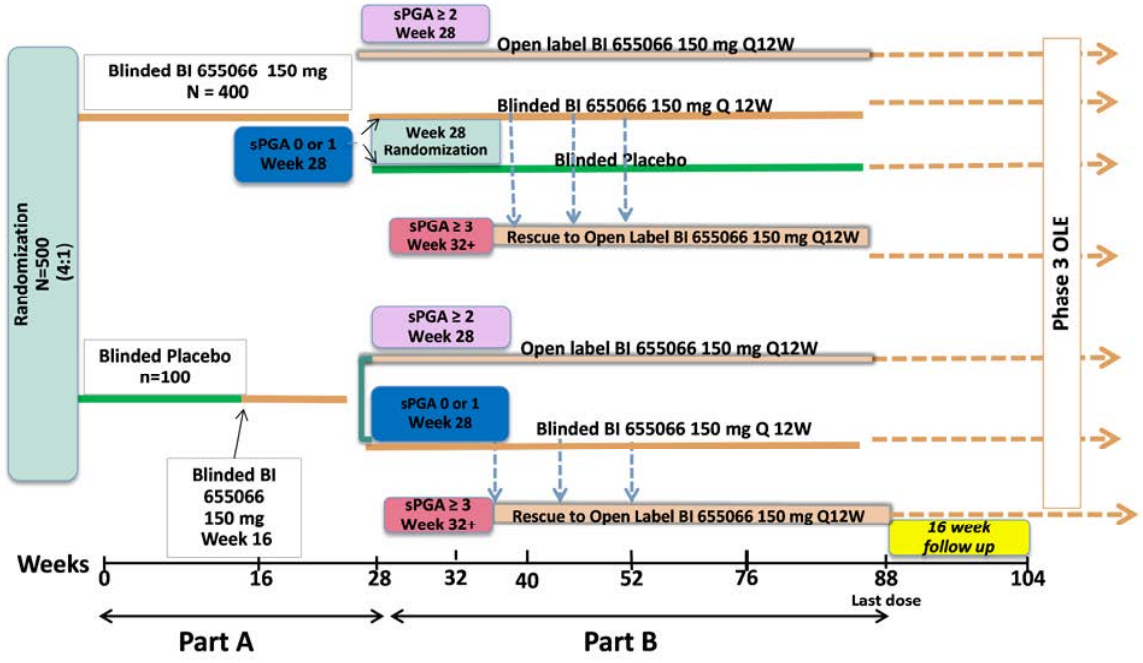


Figure 3.1:1 Trial Design

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:	Injection solution of BI 655066 in CC mM succinate buffer, pH CCI CCI mM sorbitol and CCI % polysorbate 20, presented in a 1 mL syringe pre-filled with 0.87 ml (dispensed volume is 0.83 ml)
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form	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:	0.9% sodium chloride solution, presented in a 1 mL syringe pre-filled with 0.87 mL (dispensed volume is 0.83 mL)
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form	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) 0.87 ml (75 mg) BI 655066 (blinded)	(2) 0.87 ml (75 mg) BI 655066 (blinded)	(2) 0.87ml (75 mg) blinded or open label BI 655066 Or (2) PTM 0.87 ml (75 mg) BI 655066 (blinded)
Arm 2 Placebo to BI 655066 150 mg	(2) PTM 0.87 ml (75 mg) BI 655066 (blinded)	(2) 0.87 ml (75 mg) BI 655066 (blinded)	(2) 0.87ml (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.

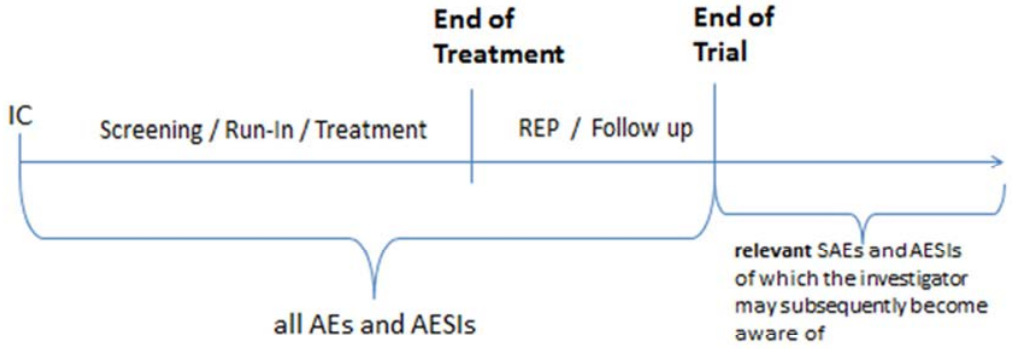
Yes: There is a reasonable causal relationship between the investigational product administered and the AE.
No: There is no reasonable causal relationship between the investigational product administered and the AE.
The causal relationship must be provided by the Investigator for all potential trial 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_____

HAQADMIN_____

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.

QUESTYPE_____

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

PMSVIS_____
RASTUDY_____

	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?	____	____	____	____
ARISING				
Are you able to:				
- Stand up from a straight chair?	____	____	____	____
- Get in and out of bed?	____	____	____	____
EATING				
Are you able to:				
- Cut your meat?	____	____	____	____
- Lift a full cup or glass to your mouth?	____	____	____	____
- Open a new milk carton?	____	____	____	____
WALKING				
Are you able to:				
- Walk outdoors on flat ground?	____	____	____	____
- Climb up five steps?	____	____	____	____

QUESTNUM_____

DRESSNEW_____

RISENEW_____

EATNEW_____

WALKNEW_____

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

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

DRSGASST_____
RISEASST_____

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

_____ Dressing and Grooming
_____ Arising
_____ Eating
_____ Walking

EATASST_____
WALKASST_____

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

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

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

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

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

____Hygiene
____Reach
____Gripping and opening things
____Errands and chores

HYGNASST_____
RCHASST_____
GRIPASST_____
ACTVASST_____

10.7.3 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 In a Multicenter randomized double-blind study in patients with Moderate to severe chronic plaque psoriasis evaluating the efficacy and safety with randomized withdrawal and re-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 after the last injection at Visit 2 and for approximately one hour after the last injection 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

APPROVAL / SIGNATURE PAGE

Document Number: c03357704 **Technical Version Number:4.0**

Document Name: clinical-trial-protocol

Title: Bi 655066/ABBV-066 (risankizumab) vs. placebo in a multicenter randomized double-blind study in patients with moderate to severe chronic plaque psoriasis evaluating the efficacy and safety with randomized withdrawal and re-treatment (IMMhance)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Clinical Monitor	PPD	12 Oct 2016 19:17 CEST
Author-Trial Statistician		12 Oct 2016 19:51 CEST
Approval-Clinical Program Leaders		12 Oct 2016 20:16 CEST
Author-Trial Clinical Pharmacokineticist		12 Oct 2016 20:18 CEST
Approval-Therapeutic Area Head		12 Oct 2016 22:41 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed

16.1__9 Documentation of Statistical Methods

1.0 Title Page

Statistical Analysis Plan

Study 1311.4

Risankizumab Versus Placebo in a Multicenter Randomized Double-Blind Study in Patients with Moderate to Severe Chronic Plaque Psoriasis Evaluating the Efficacy and Safety with Randomized Withdrawal and Re-Treatment (IMMhance)

Date: 12 Sep 2017

Version 2.0

2.0 Table of Contents

List of Tables

List of Figures

3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analysis to be completed by the AbbVie Clinical Statistics Department for study Protocol 1311.4 dated 28 July 2016.

This SAP will provide details to further elaborate statistical methods as outlined in the Protocol 1311.4 and will describe analysis conventions to guide the statistical programming work. The SAP will be signed off before the study database is locked.

Analyses will be performed using SAS® version 9.4 (SAS Institute, Inc., Cary, NC 27513) or higher using the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Primary Study Objective

The primary objective of the initial randomized phase of the study (Part A1; see Section 4.2) is to assess the efficacy of risankizumab 150 mg in comparison to placebo in subjects with moderate to severe chronic plaque psoriasis. The primary objective of the second randomized phase of the study (Part B; see Section 4.2) is to evaluate the maintenance of response with continuous risankizumab treatment compared with withdrawal of treatment.

The primary efficacy evaluation will be performed at 16 weeks. The maintenance of response following drug withdrawal will be assessed after Week 28 through the end of the study (primary evaluation at Week 52). Subsequent to drug withdrawal, subjects who experience relapse will be retreated with risankizumab to assess response after retreatment.

Evaluations of risankizumab efficacy and safety in various populations will be performed in the study to provide a full picture of risankizumab benefits and risks. These populations and the intent of the related analyses is specific in Section 5.2.

In addition, this trial will assess pharmacokinetics (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 risankizumab may influence gene and protein expression levels and disease specific protein markers. PK and ADA analyses, as well as DNA banking, exploratory biomarker, and metabolic risk factor analyses, will not be included in this SAP.

4.2 Design Diagram

This is a confirmatory, multinational, multicenter, randomized, double-blind, placebo controlled study with randomized withdrawal and retreatment, evaluating the safety and efficacy of risankizumab 150 mg subcutaneous (SC) in patients with moderate to severe chronic plaque psoriasis.

The study consists of an up to 42 day screening period, a 16-week double-blind, placebo-controlled initial treatment period (Part A1), a 12-week treatment period (Part A2), an up to 60-week continuous treatment and treatment withdrawal period (Part B) with possible retreatment with risankizumab for up to 16 weeks, and a 16 week follow-up period.

Part A1: A 16-week double-blinded, placebo-controlled treatment period during which subjects will be randomized at a ratio of 4:1 to one of two treatment arms as shown in Figure 1. Arm 1 refers to those subjects originally randomized to risankizumab and Arm 2 refers to those subjects originally randomized to placebo. The first dose of study drug will be administered on Day 1 (Visit 2; Baseline) and the second dose will be administered at Week 4. The randomization will be stratified with respect to weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1).

Part A2: A 12-week treatment period. At Week 16, all subjects will receive one dose of risankizumab 150 mg.

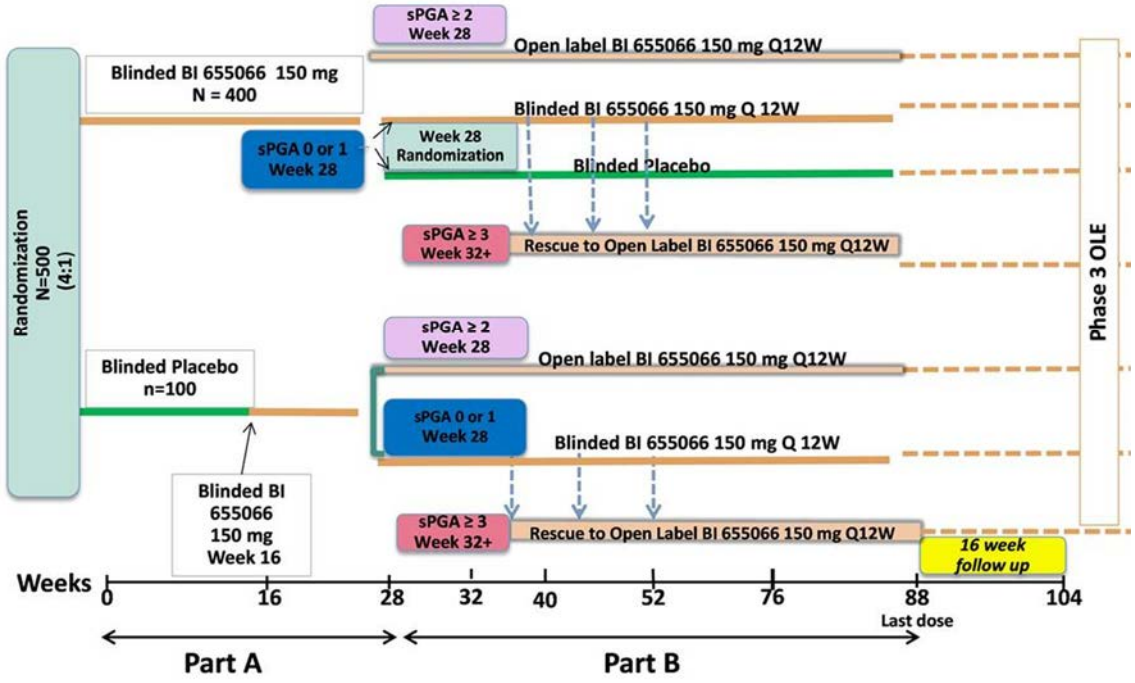
Part B: At Week 28, non-responders (static Physician Global Assessment [sPGA] ≥ 2) will receive open label risankizumab 150 mg every 12 weeks with a last dose at Week 88 (end-of-treatment, EOT), while responders (sPGA of 0 or 1) from Arm 1 will be

re-randomized in a 1:2 ratio to either maintain risankizumab 150 mg or matching placebo every 12 weeks with a last dose at Week 88 (EOT). The re-randomization will be stratified with respect to weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1). Responders from Arm 2 will continue to receive blinded risankizumab 150 mg every 12 weeks with a last dose at Week 88 (EOT) to maintain the blind. Throughout the SAP, "re-randomized" or "re-randomization" refers to the randomization at Week 28 among subjects from Arm 1 of Part A.

Retreatment: Starting from Week 32, subjects experiencing relapse (defined as an sPGA of ≥ 3), will receive open label risankizumab 150 mg. If this relapse occurs anytime between Week 32 through Week 70, open label risankizumab 150 mg will be administered at 0, 4, and 16 weeks (EOT) after relapse. If this relapse occurs after Week 70 through Week 82, open label risankizumab 150 mg will be administered 0 and 4 weeks (EOT) after relapse. If the relapse occurs after Week 82 through Week 88 the subject will immediately have the EOT procedures performed, including the final dose of study drug.

Follow-Up Period: Subjects who have completed their EOT visit will be followed up for 16 weeks. Follow-up Visit 1 is scheduled at 6 weeks after EOT. And Follow-up Visit 2 is scheduled at 16 weeks after EOT, which is the end of observation (EOO) visit. Subjects who have completed the EOO visit within the specified window, who have not discontinued drug prematurely, and who also meet the eligibility criteria will be offered to roll over into an open label extension study.

Figure 1. Trial Design



BI 655066 is risankizumab.

4.3 Sample Size

This study is designed to show a difference between risankizumab and placebo in terms of achieving 90% reduction in Psoriasis Area and Severity Index (PASI 90) response and sPGA of clear or almost clear (sPGA of 0 or 1) at Week 16. This study was also powered to show a difference in sPGA response at Week 52 between the subjects re-randomized to continue on risankizumab vs. subjects randomized to placebo at Week 28.

Based on the interim results from Study 1311.2, it is assumed at most 10% of the subjects in the re-randomized risankizumab arm and approximately 25% of subjects in the re-randomized placebo arm will lose response. Using a 1:2 re-randomization scheme (risankizumab:placebo), 102 subjects in the risankizumab arm and 204 subjects 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 subjects initially randomized to risankizumab at baseline will achieve sPGA of 0 or 1 at Week 28, the total sample size required for the initial risankizumab arm at Visit 2 is (102)(3) ÷ 0.8 = 383.

A total sample size of 500 = 400:100 for risankizumab: placebo was planned at Visit 2.

Based on the outcome from Trials 1311.1 and 1311.2, the PASI 90 response rate at Week 16 is assumed to be at least 65% in the risankizumab arm and approximately 5% for placebo. For sPGA clear or almost clear at Week 16, the response rate is assumed to be at least 80% for the risankizumab arm and approximately 5% for placebo. This trial will have > 99% power for comparing risankizumab arm to placebo on both of these endpoints.

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

4.4 Interim Analysis

Unblinded data will be reviewed during the study by an independent data monitoring committee (DMC). The membership, roles and responsibilities and activities of the DMC will be defined in a written charter. The DMC will include representatives from external safety experts who do not directly involve in the study. Clinical site personnel and the study team will remain blinded to the randomized treatment assignments during the course of the study. Communications from the DMC to the study team will not contain information that could potentially unblind the study personnel. Since there is no efficacy analyses for early stopping, no alpha adjustment is needed.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Efficacy Population:

Intent-to-Treat (ITT) Population: The ITT Populations will be used for the efficacy analyses in different parts.

- The ITT Population in Part A1 (ITT_A1) is defined as all subjects who are randomized at Baseline. This Population will be analyzed for the efficacy of initial treatment.
- The ITT Population in Part A2 from Arm 1 (ITT_A2) is defined as all subjects who were randomized to Arm 1 at Baseline. Data from Part A2 will be used to evaluate the mid-term efficacy.
- The ITT Population across Part A2 and B from Arm 2 (ITT_ARM2) is defined as all subjects who were randomized to Arm 2 at Baseline and received at least one dose of study drug on or after Week 16. This Population will be analyzed for short and long term efficacy without initial loading dose.
- The ITT Population in Part B for re-randomized subjects (ITT_B_R) is defined as all subjects who were randomized to Arm 1 and re-randomized at Week 28. The ITT_B_R Population will mainly be used to compare efficacy of continued treatment with risankizumab vs withdrawal from the treatment. The risankizumab arm will also be summarized (including data after retreatment) for long-term efficacy with the option of re-load.
- The ITT Population in Part B for Arm 1 non-responders at Week 28 (ITT_B_NR) is defined as all subjects who were randomized to Arm 1 at Baseline, were non-responders (sPGA $\geq$ 2) at Week 28, and receive at least one dose of risankizumab on or after Week 28. This population will be summarized for potential delayed response.
- The ITT Population for Part B placebo patients who received retreatment (ITT_B_PBO_RT) is defined as all subjects who were re-randomized to placebo and received at least one dose of retreatment with open label risankizumab after relapse, and have the opportunity to have retreatment Week 16 assessments.

- The ITT Population for Part B risankizumab patients who receive retreatment (ITT_B_RZB_RT) is defined as all subjects who were re-randomized to risankizumab and received at least one dose of retreatment with open label risankizumab after relapse, and have the opportunity to have retreatment Week 16 assessment. The population will be summarized to examine the efficacy of re-treatment with loading dose upon relapse on risankizumab.

ITT Populations will be analyzed by the treatment group as randomized.

In addition, additional analysis will be performed on ITT_B_R subjects who are re-randomized to risankizumab 150 mg, in which all evaluations after re-randomization (including evaluations after retreatment with open label risankizumab after relapse) will be included along with the blinded assessments to evaluate the efficacy of continuous treatment.

Per-Protocol (PP) Population: To evaluate the impact of protocol deviations on the primary and ranked secondary endpoints, additional analyses will be performed on the Per-protocol Populations. The Per-protocol Population will include those who were most compliant with the protocol in ways that could impact the primary and ranked secondary endpoints. Final results and the criteria for exclusion of subjects will be finalized prior to database lock for data pertaining to the DB period.

The PP Population at Part A1 (PP_A1; a.k.a. the PPS in study Protocol 1311.4) is defined as all subjects from the ITT_A1 Population who meet all the following criteria:

- Subjects must receive at least 75% of planned study drug injections, per randomization, in Part A1.
- Subjects must have either a PASI or sPGA assessment post-baseline in Part A1.
- Inclusion Criterion 4: Subjects must have stable moderate to severe chronic plaque psoriasis at baseline:
  - Have an BSA ≥ 10% and
  - Have a PASI ≥ 12 and

- Have an sPGA ≥ 3.

Primary and ranked secondary efficacy endpoints at Part A1 at Week 16 will be analyzed on the PP_A1 Population.

The PP Population at Part B for re-randomized subjects (PP_B_R; a.k.a. RRS-PPS in study Protocol 1311.4) is defined as all subjects from the ITT_B_R Population who meet all the following criteria:

- Subjects must receive at least 75% of planned study drug injections, per re-randomization, in Part B.
- Subjects must have at least one sPGA assessment post re-randomization in Part B.
- Subjects must have sPGA < 2 at re-randomization.

The primary efficacy endpoint for Part B at Week 52 and ranked secondary endpoint for Part B at Week 104 will be analyzed on the PP_B_R Population.

PP Populations will be analyzed by the treatment group as randomized (or re-randomized).

Safety Population:

The Safety Populations will be used for safety analyses in different study parts.

Each ITT population will have a corresponding safety population (Safety) of the same study part, which includes all subjects who receive at least one dose of study drug during the analysis period.

Complete safety tables will be provided for the Safety_A1 Population and the Safety_B_R population. Only AE overview tables will be provided for other safety populations.

The Safety Population will be analyzed based on the actual treatment received at the randomization visit (Part A) and at the re-randomization visit (Part B).

In addition, an All Risankizumab Treated Population (ALL_RZB) is defined as all subjects who receive at least one dose of risankizumab in the study. The ALL_RZB Population will be used for safety analyses. Complete safety tables will be provided in the ALL_RZB Population.

Table 1. Notations for Treatment Groups

Population	Treatment Code	Definition
ITT_A1/PP_A1/ Safety_A1	RZB	Subjects who randomized to risankizumab 150 mg.
	PBO	Subjects who randomized to placebo.
ITT_A2/Safety_A2	RZB/RZB	Subjects who randomized to risankizumab 150 mg.
ITT_ARM2/ Safety_ARM2	PBO/RZB	Subjects who randomized to placebo and received at least one dose of study drug on or after Week 16.
ITT_B_R/PP_B_R/ Safety_B_R	RZB/RZB/RZB	Subjects who re-randomized to risankizumab 150 mg at Week 28.
	RZB/RZB/PBO	Subjects who re-randomized to placebo at Week 28.
ITT_B_NR/Safety_B_NR	RZB/RZB/RZB	Subjects who randomized to risankizumab and are non-responders at Week 28.
ITT_B_PBO_RT/ Safety_B_PBO_RT	RZB/RZB/PBO/RZB	Subjects who received open-label risankizumab 150 mg as retreatment, after re-randomized to placebo in Part B.
ITT_B_RZB_RT/ Safety_B_RZB_RT	RZB/RZB/RZB/RZB	Subjects who received open-label risankizumab 150 mg as retreatment, after re-randomized to risankizumab in Part B.
ALL_RZB	RZB	Subjects who received at least one dose of risankizumab 150 mg.

5.2 Variables Used for Stratification of Randomization

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

Subjects originally randomized to risankizumab 150 mg (Arm 1) who are responders at Week 16 will be re-randomized at Week 28 in a 1:2 ratio to either risankizumab 150 mg or placebo. Re-randomization will also be stratified with respect to weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1).

6.0 Analysis Conventions

Definition of Baseline

The last non-missing measure collected on or before the date of the first dose of study drug injection will be used as Baseline for summary of demographics and disease characteristics, efficacy analyses, and safety analyses in each period, with the exception that:

- The last evaluation on or prior to the first dose date of risankizumab will be used for the safety analyses for Safety_ARM2 and ALL_RZB populations.
- For all vital sign assessments, only assessments prior to first dose time will be considered, since vital signs are to be assessed both pre- and post-dose in some visits.

For subjects who are randomized but do not take any study drug during the study, the last non-missing measurement collected on or before the date of randomization will be used as Baseline.

Definition of Final Observation (Applicable to Safety Analyses)

Final observation for the Part A1 is defined as:

- The last non-missing observation collected within 105 days following the last dose of study drug in Part A1, for subjects who were not dosed in Part A2.
- The last non-missing observation collected on or before the first dose date of study drug on or after Week 16 and within 105 days following the last dose of study drug in Part A1, for subjects who were dosed in Part A2. For vital sign assessments, only assessments prior to the first dose of study drug injection in Part A2 will be included in the analysis for Part A1.

Final observation for the Part A2 is defined as:

- The last non-missing observation collected within 105 days following the Week 16 dose of study drug in Part A2, for subjects who were not dosed in Part B.
- The last non-missing observation collected on or before the first dose date of Part B, or within 105 days following the last dose of study drug in Part A2, whichever comes first, for subjects who were dosed in Part B. For vital sign assessments, only assessments prior to the first dose of study drug injection in Part B will be included in the analysis for Part A2.

Final observation in Part B is defined as the last non-missing observation collected within 105 days following the last dose of study drug, and on or prior to the date first dose of retreatment with risankizumab for relapsed subjects, with the following exception:

For vital sign assessments, only assessments prior to the first dose of retreatment will be included in the analysis for Part B.

Final observation in the retreatment period is defined as the last non-missing observation collected within 105 days after the last dose of retreatment with risankizumab.

Final observation in the entire study is defined as the last non-missing observation collected within 105 days after the last dose of study drug.

Definition of Rx Days (Days Relative to the Date of First Dose of Study Drug)

Rx days are calculated for each time point relative to the date of first dose of study drug. They are defined as the number of days between the day of the first dose of study drug and the specific time point. Rx days are negative values when the time point of interest is prior to the first study drug dose day. Rx days are positive values when the time point of interest is on or after the first study drug dose day. The day of the first dose of study drug is defined as Rx Day 1, while the day prior to the first study drug dose is defined as Rx Day –1 (there is no Rx Day 0).

For analysis in each Part (A1, A2, or B), the Rx Day is calculated relative to the first dose of study drug in the specific study Part. For analysis across Part A2 and Part B, the Rx days are calculated relative to the date of first dose of risankizumab injection in Part A2.

Definition of Analysis Windows

All time points and corresponding time windows are defined based on Rx Days.

For efficacy analyses, local tolerability, ECG, laboratory parameters, and vital sign variables, analysis windows are constructed using the following algorithm:

- Determine the nominal Rx day for each visit (e.g., Week 4 [4 weeks after Baseline visit] equals Rx Day 29).
- In order to include all post baseline data, the first post-baseline interval starts on the first day after the first dose of study drug (Rx Day 2).
- Determine the window around a specific nominal Rx day by adding or subtracting half of the interval between adjacent visits (e.g., days between Week 2 and Week 4 is 14). The threshold between adjacent visits is determined by splitting the interval evenly between the visits. If the resulting split is between Rx days, then the threshold is determined as the midpoint between the adjacent visits. If the resulting split is on an Rx day, then the threshold is determined as being between that Rx day and the Rx day prior to it (e.g., the split between Week 2 and Week 4 would be between Rx Days 22 and 23).
- If more than one assessment is included in a time window the assessment closest to the nominal day will be used. If there are two observations equidistant to the nominal day, the one after the nominal day will be used in analyses. If more than one assessment is included on the same day, then the worst assessment on that day will be used in analyses, except those specified in Section 11.0.

The protocol specified visits and corresponding time windows used in the efficacy analyses, local tolerability, ECG, laboratory parameters, and vital sign variables, are

presented in the following Table 2, Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, Table 9, Table 10, Table 11, Table 12, Table 13, Table 14, Table 15 and Table 16.

Table 2. Visit Windows for Analysis of PASI, sPGA, Local Tolerability, and Vital Signs in Part A1 (ITT_A1/PP_A1/Safety_A1 Populations)

Window Label	Target Day	Interval
Baseline	1	≤ 1[a]
Week 4	29	[2, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 127[b]]

Rx Day calculated relative to first dose date of study drug. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. There is no baseline for local tolerability measurements. If time is collected in vital signs, restrict to records prior to the first dose of study drug.

b. The minimum of upper bound and first dose date of study drug on or after Week 16 (and within 105 days of last dose for safety analyses). If time is collected in vital signs, restrict to records prior to the first dose of study drug on or after Week 16.

Table 3. Visit Windows for Analysis of DLQI in Part A1 (ITT_A1/PP_A1 Populations)

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 12	85	[2, 99]
Week 16	113	[100, 127[a]]

Rx Day calculated relative to first dose date of study drug. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. The minimum of upper bound and first dose date of study drug on or after Week 16.

Table 4. Visit Windows for Analysis of Safety Laboratory Tests and ECG in Part A1 (Safety_A1 Population)

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 4	29	[2, 71]
Week 16	113	[72, 155[a]]

Rx Day calculated relative to first dose date of study drug. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. The minimum of upper bound and first dose date of study drug on or after Week 16 (and within 105 days of last dose for safety analyses).

Table 5. Windows for Analysis of Efficacy Variables Collected Only at Week 16 After Baseline in Part A1 (ITT_A1 Population)

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 16	113	[2, 225[a]]

Rx Day calculated relative to first dose date of study drug. For subjects randomized but not dosed, Rx Day calculated relative to Randomization.

a. The minimum of upper bound and first dose date/time on or after Week 16 study drug.

Table 6. Visit Windows for Analysis of PASI and sPGA in Part A2 (ITT_A2 Population)

Window Label	Target Day	Interval
Entry of A2	1	≤ 1
Week 20	29	[2, 43]
Week 24	57	[44, 71]
Week 28	85	[72, 99[a]]

Rx Day calculated relative to the date of Week 16 visit.

a. The minimum of upper bound and first dose date on or after the first re-randomized dose for subjects with re-randomization or the first open label risankizumab dose for those who were not re-randomized.

Table 7. Visit Windows for Analysis of Efficacy Variables Only Collected at Week 28 in Part A2 (ITT_A2 Population)

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 28	85	[2, 169[a]]

Rx Day calculated relative to the date of Week 16 visit.

a. The minimum of upper bound and first dose date on or after the first re-randomized dose for subjects with re-randomization or the first open label risankizumab dose for those who were not re-randomized.

Table 8. Visit Windows for Analysis of PASI and sPGA, Local Tolerability, and Vital Signs in Part B (ITT_B_R/ITT_B_NR/PP_B_R/Safety_B_R/Safety_B_NR Populations)

Window Label	Target Day	Interval
Entry of B	1	≤ 1[a]
Week 32	29	[2, 43]
Week 36	57	[44, 71]
Week 40	85	[72, 99]
Week 44	113	[100, 127]
Week 48	141	[128, 155]
Week 52	169	[156, 190]
Week 58	211	[191, 232]
Week 64	253	[233, 274]
Week 70	295	[275, 316]
Week 76	337	[317, 358]
Week 82	379	[359, 400]
Week 88	421	[401, 442]
Week 94	463	[443, 498]
Week 104	533	[499, 568[b]]

Rx Day calculated relative to the first dose date of study drug in Part B. For subjects re-randomized but not dosed in Part B, Rx Day calculated relative to the IRT date of Re-randomization evaluation.

a. There is no local tolerability at re-randomization and after EOT. If time is collected in vital signs, restrict to records prior to the first dose of study drug in Part B.

Table 8. Visit Windows for Analysis of PASI and sPGA, Local Tolerability, and Vital Signs in Part B (ITT_B_R/ITT_B_NR/PP_B_R/Safety_B_R/Safety_B_NR Populations) (Continued)

b. The minimum of upper bound, the first dose date of retreatment with risankizumab for relapsed subjects (except the additional analysis as in footnote a), and within 105 days of last dose of study drug for safety analyses. If time is collected in vital signs, restrict to records prior to the first dose of retreatment.

Note: For additional PASI and sPGA analysis on ITT_B_R subjects re-randomized to risankizumab to evaluate continuous treatment, evaluations after retreatment with open label risankizumab will also be included along with blinded assessments.

Table 9. Visit Windows for Analysis of Safety Laboratory Tests and ECG in Part B (Safety_B_R/Safety_B_NR Populations)

Window Label	Target Day	Interval
Entry of B	1	≤ 1
Week 40	85	[2, 127]
Week 52	169	[128, 211]
Week 64	253	[212, 295]
Week 76	337	[296, 379]
Week 88	421	[380, 477]
Week 104	533	[478, 589[a]]

Rx Day calculated relative to the first dose date of study drug in Part B. For re-randomized subjects not dosed in Part B, Rx Day calculated relative to the IRT date of Re-randomization evaluation.

a. The minimum of upper bound and first dose date of retreatment with risankizumab for relapsed subjects (and within 105 days of last dose of study drug for safety analyses).

Table 10. Visit Windows for Analysis of Other Efficacy Endpoints Only Collected at Week 52, 76, and 104 in Part B (ITT_B_R/ITT_B_NR/PP_B_R Populations)

Window Label	Target Day	Interval
Entry of B	1	≤ 1
Week 52	169	[2, 253]
Week 76	337	[254, 435]
Week 104	533	[436, 631[a]]

Rx Day calculated relative to the first dose date of study drug in Part B. For re-randomized subjects not dosed in Part B, Rx Day calculated relative to the IRT date of Re-randomization evaluation.

a. The minimum of upper bound and first dose date of retreatment with risankizumab for relapsed subjects.

Table 11. Visit Windows for Analysis of PASI and sPGA Across Part A2 and B (ITT_ARM2 Population)

Window Label	Target Day	Interval
Entry of A2	1	≤ 1
Week 20	29	[2, 43]
Week 24	57	[44, 71]
Week 28	85	[72, 99]
Week 32	113	[100, 127]
Week 36	141	[128, 155]
Week 40	169	[156, 183]
Week 44	197	[184, 211]
Week 48	225	[212, 239]
Week 52	253	[240, 274]
Week 58	295	[275, 316]
Week 64	337	[317, 358]
Week 70	379	[359, 400]
Week 76	421	[401, 442]
Week 82	463	[443, 484]
Week 88	505	[485, 526]
Week 94	547	[527, 582]
Week 104	617	[583, 652]

Rx Day calculated relative to first dose date of risankizumab.

Table 12. Visit Windows for Analysis of Other Efficacy Endpoints Collected at Week 28, 52, 76, and 104 in Part A2 and B (ITT_ARM2 Population)

Window Label	Target Day	Interval
Entry of A2	1	≤ 1
Week 28	85	[2, 169]
Week 52	253	[170, 337]
Week 76	421	[338, 519]
Week 104	617	[520, 715]

Rx Day calculated relative to first dose date of risankizumab.

Table 13. Visit Windows for Analysis of PASI and sPGA During Retreatment with Risankizumab (ITT_B_PBO_RT/ITT_B_RZB_RT Populations)

Window Label	Target Day	Interval
Entry of RTS	1	≤ 1
Week 8R	57	[2, 85]
Week 16R	113	≥ 86

Rx Day calculated relative to first dose date of retreatment with risankizumab.

Table 14. Visit Windows for Analysis of Other Efficacy Variables Only Collected at EOT and EOO Visits During Retreatment with Risankizumab (ITT__B_PBO_RT/ITT_B_RZB_RT Populations)

Window Label	Target Day	Interval
Entry of RTS	1	≤ 1
Week 16R	113	≥ 2

Rx Day calculated relative to first dose date of retreatment with risankizumab.

Table 15. Visit Windows for Analysis of Vital Signs and Local Tolerability in the ALL_RZB Population

Window Label	Target Day	Interval
Baseline	1	≤ 1[a]
Week 4	29	[2, 43]
Week 8	57	[44, 71]
Week 12	85	[72, 99]
Week 16	113	[100, 155]
Week 28	197	[156, 239]
Week 40	281	[240, 323]
Week 52	365	[324, 407]
Week 64	449	[408, 491]
Week 76	533	[492, 575]
Week 88	617	[576, 673]
Week 104	729	[674, 785[b]]

Rx Day calculated relative to first dose date of risankizumab.

a. Local tolerability not measured at Baseline and at Week 104. If time is collected in vital signs, restrict to records prior to the first dose of risankizumab.

b. The minimum of upper bound and within 105 days of last dose of risankizumab.

Table 16. Visit Windows for Analysis of Safety Laboratory Tests and ECG in the ALL_RZB Population

Window Label	Target Day	Interval
Baseline	1	≤ 1
Week 4	29	[2, 71]
Week 16	113	[72, 155]
Week 28	197	[156, 239]
Week 40	281	[240, 323]
Week 52	365	[324, 407]
Week 64	449	[408, 491]
Week 76	533	[492, 575]
Week 88	617	[576, 673]
Week 104	729	[674, 785[a]]

Rx Day calculated relative to first dose date of risankizumab.

a. The minimum of upper bound and within 105 days of last dose of risankizumab.

The time windows specified in Table 17, Table 18, Table 19, Table 20, Table 21 and Table 22 will be used for the summary of study drug injections of each period.

Table 17. Visit Windows for Summary of Study Drug Injections for Part A1

Window Label	Target Day	Interval
Week 0	1	≤ 1
Week 4	29	[2, 57[a]]

Rx Day calculated relative to the first dose date of study drug.

a. Before the first dose date of study drug on or after Week 16.

Table 18. Visit Windows for Summary of Study Drug Injections for Part A2

Window Label	Target Day	Interval
Week 16	1	≤ 1

Rx Day calculated relative to the Week 16 dose date.

Table 19. Visit Windows for Summary of Study Drug Injections for Part B

Window Label	Target Day	Interval
Week 28	1	≤ 1
Week 40	85	[2, 127]
Week 52	169	[128, 211]
Week 64	253	[212, 295]
Week 76	337	[296, 379]
Week 88	421	[380, 463[a]]

Rx Day calculated relative to the first dose date of study drug in Part B.

a. Before retreatment.

Table 20. Visit Windows for Summary of Study Drug Injections for Subjects Retreated with Risankizumab for Relapse from Week 32 Through Week 70 (Inclusive)

Window Label	Target Day	Interval
Week 0	1	≤ 1
Week 4R	29	[2, 71]
Week 16R	113	[72, 155]

Rx Day calculated relative to the first dose date of retreatment.

Table 21. Visit Windows for Summary of Study Drug Injections for Subjects Retreated with Risankizumab for Relapse from Week 70 Through Week 82 (Inclusive)

Window Label	Target Day	Interval
Week 0	1	≤ 1
Week 4R	29	[2, 57]

Rx Day calculated relative to the first dose date of retreatment.

Table 22. Visit Windows for Summary of Study Drug Injections for Subjects Retreated with Risankizumab for Relapse After Week 82

Window Label	Target Day	Interval
Entry of retreatment	1	≤ 1

Rx Day calculated relative to the first dose date of retreatment.

Definition of Missing Data Imputation

No global imputation is taking place at the database level. Efficacy related imputations are outlined in Section 10.0. There is no imputation for missing values in the safety analyses.

Rounding of Numeric Results

Rounding will be performed for presentation of results. No rounding will be performed before or during analyses. The ROUND function of SAS will be used to round results.

When dichotomizing continuous variables, associated continuous variables will be rounded to 9 decimal points before applying the cutoff point to determine the response status (for example, percent change from baseline in PASI score will be rounded to 9 decimal places before comparing to 90%).

The mean and median will be rounded for presentation to 1 decimal more than the data entered into the database. The standard deviation will be rounded to 2 decimal places more than the data entered into the database. The minimum and maximum values will be presented as entered into the database.

Probabilities will be rounded to 3 decimal places before assignment of statistical significance and will be presented in rounded format. Probabilities that round to zero or are reported by SAS as zero will be presented as "< 0.001." Probabilities that round to 1 or are reported by SAS as 1 will be presented as "> 0.999."

7.0 Demographics, Baseline Characteristics, Medical History, and Previous/Concomitant Medications

7.1 Demographic and Baseline Characteristics

Demographics and Baseline characteristics will be summarized for each arm and for overall of the ITT populations. Continuous variables will be summarized with the number of non-missing observations by mean, standard deviation, first quartile, median,

third quartile, minimum and maximum values. Categorical data will be summarized using frequencies and percentages. Statistical tests will be performed to assess the comparability of the two arms at Randomization on ITT_A1 and at Re-Randomization on ITT_B_R. Per Protocol Populations will only be summarized in the accountability table. Treatment comparison will be made based on non-missing information. Continuous variables will be analyzed using one-way analysis of variance (ANOVA). Categorical variables will be analyzed using a two-sided Pearson's Chi-Square test (or an appropriate exact test if expected cell count < 5).

The following demographic and baseline parameters will be summarized.

Subject Demographics

- Sex (male, female)
- Age (years), defined as the number of years from date of birth to date of first drug
- Age categories (< 40 years, ≥ 40 – < 65 years, ≥ 65 years.)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multi Race)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Body weight (kg)
- Body weight category (≤ 100 kg, > 100 kg)
- Height (cm)
- BMI (kg/m^2)
- BMI category (< 25, ≥ 25 – < 30, ≥ 30)
- Prior exposure to TNF antagonists (0 versus ≥ 1)

General Baseline Characteristics

- PASI (Psoriasis Area and Severity Index)
- BSA (Body Surface Area)
- sPGA categories

- NAPSI (Nail Psoriasis Severity Index)
- PSSI (Psoriasis Scalp Severity Index)
- PPASI (Palmoplantar Psoriasis Area Severity Index)
- Dermatology Life Quality Index (DLQI)
- HAQ-DI (HAQ Disability Index)
- Pain VAS (Visual Analog Scale)/Patient Global Assessment (PtGA) VAS (Visual Analog Scale)
- TJC/SJC (Tender/Swollen Joints)
- DAS28 (Disease Activity)

Psoriasis and Cardiovascular History

- Psoriatic arthritis (diagnosed, suspected, no)
- Cardiovascular Diseases (myocardial infarction, angina pectoris, transient ischemic attack, stroke, deep vein thrombosis)
- Cardiovascular Risk Factors (hypertension, hyperlipidemia, diabetes mellitus, obesity)

General Use

- Smoking status (Never-smoked, Ex-smoker, Currently smokes)
- Alcohol status (Non-drinker, drinks – no interference with participation in trial, drinks – possible interference with participation in clinical trial)

Prior Treatment

- Psoriasis Biologic Treatment History – by Response to Prior Treatment
- Psoriasis Treatment – by Therapy Type (topical therapy, phototherapy, photochemotherapy, non-biologic systemic therapy, TNF antagonist, other biologic)

Also, Physical Exam and Pregnancy Test will be presented in listing format.

7.2 Medical History

Medical history will be summarized using body systems and condition/diagnosis as captured on the eCRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized for each treatment arm. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

7.3 Previous Treatment and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the first dose of study drug. A concomitant medication is defined as any medication that started prior to the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started after the first dose of study drug, but not after the last dose of study drug plus 21 days. The number and percentage of subjects who had taken medications will be summarized by generic drug name assigned by the World Health Organization (WHO) for both prior and concomitant medications.

7.4 Protocol Deviations

Number and percentage of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though she/he did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment or incorrect dose
- Subject who received excluded or prohibited concomitant treatment

8.0 Patient Disposition

The number of subjects for each of the following categories will be summarized, for overall and for each treatment group in the ITT_A1 Population:

- Number of subjects randomized
- Number of subjects treated during Part A1
- Number of subjects who completed Part A1
- Number of subjects who discontinued study drug during Part A1
- Number of subjects who prematurely discontinued from Part A1

The number of subjects for each of the following categories will be summarized, for overall and for each treatment group in the ITT_B_R population:

- Number of subjects re-randomized
- Number of subjects treated at Part B
- Number of subjects who completed the Part B
- Number of subjects who received retreatment with risankizumab during Part B at different time points
- Number of subjects who discontinued study drug during Part B
- Number of subjects who prematurely discontinued from the Part B

In addition, the reasons for premature discontinuation will be summarized with frequencies and percentages.

Disposition tables will also be summarized in the ITT_A2, ITT_ARM2, and ITT_B_NR Populations.

In addition to patient disposition, number of screening failures and reasons for screening failure will also be summarized among all screened subjects in a subject screening status table.

9.0 Study Drug Exposure and Compliance

Summary of study drug exposure will be provided for each treatment arm for all ITT_A1, ITT_A2, ITT_ARM2, ITT_B_R, and ITT_B_NR populations, and the ALL_RZB population. Study drug compliance will be summarized in ITT_A1, ITT_A2, and ITT_B_R populations.

Study drug exposure (days) will be summarized using the sample size, mean, standard deviation, minimum, median and maximum for each treatment part. In addition cumulative exposure of RZB will be also summarized in the ALL_RZB Population. Study drug exposure will be summarized as follows:

Study Drug Exposure (in Days) in Each Period:

Part A1:

For subjects who did not continue into Part A2:

- Date of last injection in Part A1 – Date of first injection in Part A1 + 84.

For subjects who continued into Part A2: the minimum of

- Date of first injection in Part A2 – Date of first injection in Part A1.
- Date of last injection in Part A1 – Date of first injection in Part A1 + 84 days.

Part A2:

For subjects who did not continue into Part B:

- Date of last injection in Part A2 – Date of first injection in Part A2 + 84 days.

For subjects who continued into Part B: the minimum of

- Date of first injection in Part B – Date of first injection in Part A2.
- Date of last injection in Part A2 – Date of first injection in Part A2 + 84 days.

Part B:

For subjects who did not receive retreatment with risankizumab: the minimum of

- Date of last injection in Part B – Date of first injection in Part B + 84 days.
- Cutoff date of 01 September 2017 – Date of first injection in Part B (only for the primary analysis after the last patient either has completed Week 52 visit or discontinues from the study)

For subjects who received retreatment with risankizumab: the minimum of

- Date of first injection of retreatment – Date of first injection in Part B.
- Date of last injection in Part B – Date of first injection in Part B + 84 days.
- Cutoff date (01 September 2017) – Date of first injection in Part B (only for the primary analysis after the last patient either has completed Week 52 visit or discontinues from the study)

ALL_RZB:

For subjects who were re-randomized to placebo in Part B and received retreatment with risankizumab: the minimum of

- Date of last injection of risankizumab in Part A – Date of first injection of risankizumab + 84 days + Date of last retreatment of risankizumab – Date of first retreatment of risankizumab + 84 days.
- Date of last injection of risankizumab in Part A – Date of first injection of risankizumab + 84 days + Cutoff date for retreatment (22 September 2017) – Date of first retreatment of risankizumab (only for the primary analysis after the last patient either has completed Week 52 visit or discontinues from the study).

For all other subjects: the minimum of

- Date of last injection of risankizumab – Date of first injection of risankizumab + 84 days.

- Cutoff date (01 September 2017) – Date of first injection of risankizumab (only for the primary analysis after the last patient either has completed Week 52 visit or discontinues from the study)

Compliance

There will be a summary of the number of subjects receiving study drug and dose at each study drug administration visit. This will be repeated on the cumulative number of doses.

When computing compliance at each scheduled time point, the denominator for each week will include all subjects in each analysis population who have not prematurely discontinued study drug prior to the scheduled study drug injection. Subjects who have prematurely discontinued the study drug but have not prematurely discontinued the study are not used in the denominator.

10.0 Efficacy Analysis

10.1 General Considerations

The treatment effect will be evaluated based on a two-sided significance level of 0.05 (when rounded to three decimal places).

The Primary Analysis for Period B re-randomized subjects will be conducted after the last patient either has completed Week 52 visit or discontinues from the study, and at the time approximate to the database lock of all other global pivotal Phase 3 psoriasis studies, whichever occurs later. All endpoints will be analyzed up to Week 52, with the following exception:

- Categorical endpoints related to PASI and sPGA, using the LOCF method (defined in Section 10.1.4), will be analyzed up to the last visit that at least one subject has observed PASI and sPGA measurements, respectively.

To best maintain the study integrity for data beyond Week 52, blinded treatment assignments will not be disseminated to the sites, investigators, and patients until the end of study database lock.

Efficacy variables will be summarized in all efficacy populations. The efficacy analysis will be conducted in the ITT_A1 and the ITT_B_R populations. Only the primary and ranked secondary variables will be analyzed for the per-protocol populations using primary approach to handle missing data as described below.

Subjects' actual weight category and prior TNF antagonist exposure will be used as the strata in the stratified analyses.

10.1.1 Analyses of Categorical Variables

For categorical variables, frequencies and percentages will be summarized. Treatment comparison will be conducted using a Cochran-Mantel-Haenszel (CMH) test with stratification factors as strata for the analysis. The CMH test will use weights proposed by Greenland & Robins, which is calculated as follows:

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

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

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

x_i denotes the number of patients with event in treatment_1 in stratum i, $i = 1, \cdots, u$

y_i denotes the number of patients with event in treatment_2 in stratum i, $i = 1, \cdots, u$

n_i denotes the number of patients on treatment_1 in stratum i, $i = 1, \cdots, u$

m_i denotes the number of patients on treatment_2 in stratum i, $i = 1, \cdots, u$

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

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

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

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

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

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

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

If there is a stratum for a treatment group that has 0 subjects in any cell in the contingency table, all cells from the stratum will be added by 0.1 in order to prevent dividing by 0 in the above equations, as suggested in Greenland & Robins.

10.1.2 Analyses of Continuous Variables

For continuous variables, the model based mean and standard error will be presented. The Baseline and visit means will also be presented for each treatment group for subjects who have both Baseline and post Baseline visit values. The treatment groups will be compared using ANCOVA with treatment group, Baseline value, and stratification factors in the model.

10.1.3 Analyses of Time-to-Event Variables

Time to first achievement of endpoints will only be performed in ITT_A1 up to Week 16. The time to event will be calculated as:

- Time to first achievement (with observed event) = [date of first achievement] – [date of first dose] + 1
- If a subject never attains Endpoint at the end of evaluation period, that subject's time to first achievement will be censored at the last visit where the variable was measured

Time to loss-of-response (and time to relapse) endpoints will only be performed in ITT_B_R Population among those who achieved response at Re-Randomization. The time to failure events will be calculated as:

- Subjects will be a considered as failures if they subsequently lost the response, or discontinue from the study due to AE of "Worsening of disease under study," or receive retreatment with risankizumab.
- Time to failure events = [date of failure] – [date of first dose in Part B] + 1
- Subjects who maintain Endpoint throughout the study, or discontinued from the study due to reasons other than above, will be censored at their last measurement.

Both time to first achieving endpoints and time to loss-of-response endpoints will be analyzed using Kaplan-Meier estimates for each treatment group. In the ITT_A1 and ITT_B_R populations, treatments will be compared using stratified Log-rank test.

10.1.4 Missing Data Imputations

Missing data will be imputed using the following methods for the efficacy analyses:

- Non-Responder Imputation (NRI): the NRI analysis will categorize any subject who does not have evaluation during a specific visit window as a non-responder for that visit. The only exception is when the subject is a responder both before and after a specific visit window, then the subject will be categorized as a responder for the visit. Only observations within the same analysis period will be used except for summary of ITT_A2 from ARM 1, where subjects' observation from Part A1 can be used since the treatment is the

same. The NRI will be the primary approach in the analyses of categorical variables.

- Last Observation Carried Forward (LOCF): The LOCF analyses will use the last observed non-missing evaluation (last completed non-missing evaluation, from composite endpoint) from the previous visit within the particular period for efficacy measures assessed to impute missing data at later visits in the same period. Baseline efficacy evaluations will not be carried forward. Of note, post-baseline observations from Part A1 can be carried forward to ITT_A2 subjects from ARM 1 since treatment is the same. LOCF will be the primary approach in the analyses of continuous variables, and the secondary approach in the analysis of categorical variables.
- As-Observed Cases (OC): The as-observed analysis will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the as-observed analysis for that visit. As-observed analysis will be the secondary approach in the analysis of continuous variables.
- Multiple Imputation (MI): The MI will be used as sensitivity approach to impute missing data in primary and ranked secondary endpoints. The variables to be included in the imputation model are listed below. If MI is not applicable due to the nature of our data (e.g., MCMC algorithm does not converge), logistic regression or mixed effect model repeat measurement (MMRM) methods will be applied as sensitivity approach, whichever applicable.

The Multiple Imputation analysis will be carried out in three steps.

- Imputation of missing data. The imputation will be generated for each efficacy endpoint measurement. The variables to be included in the imputation model are: Baseline disease severity (PASI and sPGA), Baseline weight (continuous variable), treatment group, actual prior TNF antagonist exposure, and measurements at each visit from randomization (or re-randomization) up to the end of the analysis period. For each endpoint, 20 'complete' datasets will be generated using SAS PROC MI. The imputed post-baseline measurements

will be rounded to the same precision as the observed data before the determination of responder status (e.g., PASI 90).

- Analysis of imputed data sets. A CMH test, stratified by stratification factors, will be used to analyze categorical endpoints in each imputed dataset.
- Synthesis of imputation and analysis results. SAS PROC MIANALYZE will be used to generate the final inferences of the risk difference between treatment groups.

Of note, subjects who discontinued due to AE of "Worsening of disease under study," or received retreatment with risankizumab for relapse during Part B, will be counted as non-responders in all visits thereafter in the NRI and MI analyses, and will have their last observation prior to discontinuation or retreatment with risankizumab carried forward in the LOCF analyses.

10.2 Primary Efficacy Analysis

10.2.1 Primary Efficacy Analysis in Part A

There are two co-primary endpoints to assess the efficacy of risankizumab 150 mg for the treatment of moderate to severe plaque psoriasis in Part A. These are as follows:

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

The primary null hypotheses are that risankizumab 150 mg is not different from placebo in achieving PASI 90 and in achieving sPGA of clear or almost clear at Week 16.

The achievement of PASI 90 at Week 16 is the first co-primary endpoint. The difference in proportion of subjects achieving PASI 90 between treatment arms will be estimated and tested using the Cochran-Mantel-Haenszel risk difference estimate stratified by the stratification factors of baseline weight (≤ 100 kg vs. > 100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1).

The achievement of a sPGA of clear or almost clear at Week 16 is the second co-primary endpoint. The analysis method for the sPGA co-primary endpoint will be identical to that of the PASI 90 co-primary endpoint detailed above.

The co-primary endpoints of PASI 90 and sPGA clear or almost clear need to be significant simultaneously. Both endpoints will be tested using a two-sided test with a type I error rate of 0.05.

The primary analysis will be carried out in the ITT_A1 Population and the PP_A1 Population. Non-responder imputation will be used as the primary approach for missing values. LOCF and MI will be performed as sensitivity analyses.

10.2.2 Primary Efficacy Analysis in Part B

Achievement of an sPGA of clear or almost clear (0 or 1) at Week 52 is the primary endpoint for Part B under re-randomization. This endpoint will be tested independently with a type I error rate of 0.05, for the ITT_B_R Population. A sensitivity analysis will also be performed on the same endpoint for the PP_B_R Population.

10.3 Secondary Efficacy Analyses

10.3.1 Ranked Secondary Efficacy Analysis

10.3.1.1 Ranked Secondary Efficacy Analysis in Part A

The ranked secondary endpoints in Part A are in ranked order as follows:

1. Achievement of ≥ 75% reduction from baseline PASI score (PASI 75) at Week 16
2. Achievement of 100% reduction from baseline PASI score (PASI 100) at Week 16
3. Achievement of sPGA of clear at Week 16
4. Achievement of DLQI score of 0 or 1 at Week 16

Ranked secondary endpoints above will be analyzed for the ITT_A1 Population. The same methods as discussed for the primary analyses will be used. The following null hypotheses will be tested in a hierarchical order using two-sided tests with a type I error of 0.05 only if the null hypothesis for the co-primary endpoints in Part A1 has been rejected:

1. Risankizumab is not different from placebo with respect to PASI 75 response at Week 16
2. Risankizumab is not different from placebo with respect to PASI 100 response at Week 16
3. Risankizumab is not different from placebo with respect to achieving an sPGA of clear at Week 16
4. Risankizumab is not different from placebo with respect to achieving a DLQI score of 0 or 1 at Week 16.

10.3.1.2 Ranked Secondary Efficacy Analysis in Part B

The ranked secondary endpoint for Part B is the achievement of sPGA of clear or almost clear (0 or 1) at Week 104.

This ranked secondary endpoint will be analyzed for the ITT_B_R Population. The same methods as discussed for the primary analyses will be used.

The null hypotheses below will be tested in a hierarchical order in the final analysis only, using two-sided tests with a type I error of 0.05 only if the null hypothesis for the primary endpoint in Part B has been rejected:

- Continuation of risankizumab is not different from switching to placebo with respect to sPGA of clear or almost clear (0 or 1) response at Week 104.

10.3.2 Other Secondary Efficacy Analysis

The other 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

Other secondary endpoints will be analyzed among the ITT_B_R Population.

10.3.3 Further Efficacy 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 to the first achievement of PASI 50, PASI 75, PASI 90, and PASI 100
- Time to loss of PASI 50, PASI 75, PASI 90, and PASI 100 response for subjects re-randomized at Week 28
- Change and percent change from baseline in PASI at all visits collected
- Achievement of PASI < 3 at all visits collected
- Proportion of subjects with at least 25% increase in PASI from baseline within 60 days after re-randomization for subjects re-randomized to placebo at Week 28
- Achievement of sPGA of clear or almost clear at all visits collected
- Achievement of sPGA of clear at all visits collected
- Time to the first achievement of sPGA of clear or almost clear
- Time to loss of sPGA of clear or almost clear response for subjects re-randomised at Week 28
- Time to sPGA of ≥ 3 (relapse) for subjects 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, among subjects with baseline DLQI ≥ 5
- Change from baseline in HAQ-DI at all visits collected, among subjects with PsA confirmed via ClASsification of Psoriatic Arthritis (CASPAR) and had baseline value > 0
- Achievement of a reduction of 0.3 or more from baseline HAQ-DI at all visits collected, among subjects with PsA confirmed via CASPAR and had baseline value ≥ 0.3
- Change and percent change from baseline on patient Pain VAS, among subjects with PsA confirmed via CASPAR and had baseline value > 0
- Achievement of a reduction of 10 or more from baseline Pain VAS at all visits collected, among subjects with PsA confirmed via CASPAR and had baseline value ≥ 10
- Change and percent change from baseline on patient Global Assessment VAS, among subjects with PsA confirmed via CASPAR and had baseline value > 0
- Change from baseline in Swollen or Tender Joint Count (28 joints) at all visits collected, among subjects with PsA confirmed via CASPAR and had baseline value > 0
- Change from baseline in DAS28 at all visits collected, among subjects with PsA confirmed via CASPAR and had baseline value > 0
- Change and percent change from baseline in Nail Psoriasis Severity Index (NAPSI) at all visits collected, in subjects with baseline NAPSI > 0
- Change and percent change from baseline in Palmoplantar Psoriasis Severity Index (PPASI) at all visits collected, in subjects with baseline PPASI > 0
- Change and percent change from baseline in Psoriasis Scalp Severity Index (PSSI) at all visits collected, in subjects with baseline PSSI > 0

10.4 Handling of Multiplicity

The statistical comparisons for the primary efficacy variable and the ranked secondary variables will be carried out in the hierarchical order. This means that statistically

significant results (P value ≤ 0.05) for the comparison in the higher rank (primary, then ranked secondary variables) are necessary to initiate the testing of the next comparison in the lower rank. Since a step-down procedure is used, each comparison will be tested at a significance level of 0.05 and overall alpha level of 0.05 will be preserved.

10.5 Efficacy Subgroup Analysis

To evaluate the consistency of the efficacy over demographic and other baseline characteristics, summaries and analyses will be performed for selected subgroups for the primary efficacy endpoints in Part A and the primary efficacy endpoint in Part B.

- Age group (< 40 years, ≥ 40 – < 65 years, ≥ 65 years)
- Sex (male, female)
- Race (white, non-white)
- Smoking (current, ex or never)
- BMI (normal: < 25, over weight: ≥ 25 – < 30, obese: ≥ 30)
- Region (US, Asia, Other)
- Baseline PASI score (by median)
- Baseline sPGA (3, 4)
- Psoriatic arthritis (yes [diagnosed or suspected], no)
- Ps Therapy History (Phototherapy or Photochemotherapy, TNF Antagonist, Other biologics, Non-biologic systemic therapy, All biologics, Naïve to all)

11.0 Safety Analysis

11.1 General Considerations

Safety analyses will include adverse events, laboratory, local tolerability, ECG, and vital sign measurements. Safety summaries will be provided using the safety population in each period as defined in Section 5.1. Comparison between risankizumab group and placebo group will be performed in the Safety Population in Safety_A1 and Safety_B_R populations. Continuous variables will be analyzed using one-way ANOVA and

categorical variables will be analyzed using Fisher's exact test. For analyses of AEs, only P values ≤ 0.100 when rounded to three digits will be presented.

Missing safety data will not be imputed.

11.2 Analysis of Adverse Events

11.2.1 Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as any event with an onset that is after the first dose of study drug and with an onset date within 105 days after the last dose of study drug in the analysis period, or prior to the first dose in the subsequent period for subjects who entered in to the subsequent period. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent, unless the adverse event start time is prior to the study drug start time with the following exception:

- If an AE onset date is the same as the first dose of Part B and the AE time is missing, the AE is considered TEAE for the Part A2.

If an incomplete onset date is collected for an adverse event, the event will be assumed to be treatment-emergent unless there is other evidence that confirms that the event is not treatment-emergent (e.g., the event end date is prior to the study drug start date).

Treatment-emergent adverse events (TEAE) for each safety population are defined as follows:

TEAEs of Safety_A1:

For subjects who do not enter Part A2, TEAEs are defined as any event with an onset after the first dose of study drug and no more than 105 days after the last dose of study drug.

For subjects who enter Part A2, TEAEs are defined as any event with an onset after the first dose of study drug and before the first dose of study drug in Part A2.

TEAEs of Safety_A2 for Subjects from ARM 1:

For subjects who do not enter Part B, TEAEs are defined as any event with an onset after the first dose of study drug in Part A2 and no more than 105 days after the last dose of study drug in Part A2.

For subjects who enter Part B, TEAEs are defined as any event with an onset after the first dose of study drug in Part A2 and prior to the first dose of study drug in Part B.

TEAE of Safety_ARM2:

TEAEs are defined as any event with an onset after the first dose of study drug in Part A2 or Part B and no more than 105 days after the last dose of study drug in the study.

TEAEs of Safety_B_NR:

TEAEs are defined as any event with an onset after the first dose of study drug in Part B and no more than 105 days after the last dose of study drug in the study.

TEAEs of Safety_B_R:

For subjects who do not receive retreatment with risankimumab, TEAEs are defined as any event with an onset after the first dose of study drug in Part B and no more than 105 days after the last dose of study drug in Part B.

For subjects who receive retreatment with risankimumab, TEAEs are defined as any event with an onset after the first dose of study drug in Part B and before the first dose of retreatment with risankimumab.

TEAEs of Safety_B_PBO_RT and Safety_B_RZB_RT:

TEAEs are defined as any event with an onset that is after the first dose of retreatment and no more than 105 days after the last dose of study drug.

TEAE of ALL_RZB:

TEAEs are defined as any event with an onset after the first dose of risankizumab through 105 days after the last dose of risankizumab, except for AEs with an onset during protocol-designed treatment gaps (i.e., placebo period) that was more than 105 days from the last dose of the previous risankizumab treatment and before the first dose of retreatment.

Summary tables will be presented as follows:

1. **Adverse Event Overview**

   The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event categories:

   - Any AE
   - Any AE that was assessed as related to study drug by the investigator
   - Any severe AE
   - Any serious AE (SAE)
   - Any serious AE that was assessed as related to study drug by the investigator
   - Any AE leading to discontinuation of study drug
   - Any AE leading to death
   - Any deaths
   - Areas of Safety Interest

2. **Adverse Events by System Organ Class and Preferred Term**

   TEAEs will be summarized and presented using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs). The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

   Subjects reporting more than one adverse event for a given MedDRA preferred term will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables). Subjects reporting

more than one type of adverse event within a SOC will be counted only once for that SOC. Subjects reporting more than one type of adverse event will be counted only once in the overall total.

In addition, the number and percentage of adverse events with causal relationship between the events and the study drug will be summarized using the same conventions described above.

3. Adverse Events by Maximum Severity

The severity grading of AEs follows Rheumatology Common Toxicity Criteria (RCTC).

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

Adverse events will also be summarized by maximum severity. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity (Life threatening). In this case, the subject will be counted under the "Life-threatening" category.

4. Adverse Events by Maximum Relationship

Adverse events will be summarized by maximum relationship to study drug, as assessed by the investigator. Relationship of an AE to study drug is assessed by the investigator and collected in the CRF as 'Yes' or 'No.' If a subject has an adverse event with unknown relationship, the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship of "No." If the subject has another occurrence

of the same adverse event with a relationship assessment of "Yes," the subject will be counted under the "yes" category.

A listing of all pretreatment (i.e., events start prior to the first study drug injection) serious adverse events will be provided.

The following tables are planned.

Treatment-emergent adverse events will be summarized as follows:

- Grouped by SOC and PT
- Grouped by SOC, PT and maximum relationship to study drug
- Grouped by SOC, PT and maximum severity

Treatment-emergent serious adverse events will be summarized as follows:

- Grouped by SOC and PT
- A by-subject listing will be provided

Pre-treatment serious adverse events will be summarized as follows:

- A by-subject listing will be provided

Treatment-emergent adverse events leading to death or premature discontinuation of study drug will be summarized as follows:

- Grouped by SOC and PT
- Separate listings by subject for deaths and premature terminations of study drug due to adverse events will be provided.

Treatment-emergent areas of safety interest will be summarized as follows:

- Grouped by SOC and PT
- A listing by subject will be provided.

Areas of Safety Interest:

Areas of Safety Interest groupings are listed in Table 23. These events are of interest due to a higher rate in the moderate to severe psoriasis population, or of interest for all Ig products or products in general.

The final list will be based on the most updated final version of risankizumab Product Safety Statistical Analysis Plan, which is consistent to the most updated risankizumab Risk Management Plan.

Table 23. Areas of Safety Interest

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Adjudicated CV Events	Major adverse cardiovascular events (MACE)	Adjudicated events	Display underlined terms defined by the following adjudicated terms: • CV Death which includes CETERM values: Fatal CV, Fatal PE, Fatal Non-Cardiac/Non-Neuro Arterial Thrombosis/ Thromboembolism, Undetermined Death, Not assessable death (cardiac/neuro/thrombotic), Fatal Stroke • Myocardial infarction • Stroke	Y
	Extended MACE	Adjudicated events	Display underlined terms from MACE and underlined terms below: • Hospitalization for Unstable Angina • Coronary Revascularization Procedures	N

Table 23. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Adjudicated CV Events (continued)	Other CV events	Adjudicated events	Display underlined terms defined by the following adjudicated terms: • Thrombotic events which includes CETERM values: Deep Vein Thrombosis, TIA, Pulmonary Embolism, Non-fatal Non-Cardiac/Non-Neurological Arterial Thrombosis/ Thromboembolism, Other Venous Thrombosis, specified (non-fatal) • Cardiac arrhythmia which includes CETERM of: Clinically Significant Arrhythmia • Congestive heart failure which includes CETERM of Heart Failure • Hypertensive emergency	N
Serious infections, TB, fungal and opportunistic infections (including herpes zoster)	Serious infections	Serious PTs of the CMQ (company MedDRA query) Infections (CMQ 80000018)	PTs	Y
	TB	Tuberculosis (including Investigations) CMQ (code 80000033)	PTs	Y
	Opportunistic infections	Opportunistic infections CMQ (code 80000073	PTs	N

Table 23. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Serious infections, TB, fungal and opportunistic infections (including herpes zoster) (continued)	Fungal infections	Fungal infections CMQ (code 80000063)	PTs	N
	Herpes Zoster	Herpes zoster CMQ (code 80000175)	PTs	N
Malignancies	All possible malignancies	Narrow – Malignancies (SMQ 20000090)	PTs	N
	Malignant Tumours	Narrow – Malignant tumours (SMQ 20000194)	PTs	Y
	Non-melanoma skin cancer (NMSC)	Broad – Skin malignant tumours (SMQ 20000204) excluding terms identified by the Melanoma CMQ (code 80000119)	PTs	N
	Malignant Tumours excluding NMSC	'Malignant Tumours excluding NMSC' is identified by the 'Malignant Tumours' search excluding terms identified by the 'Non-melanoma skin cancer (NMSC) search.	PTs	Y

Table 23. Areas of Safety Interest (Continued)

ASI Grouping	Categories (ASI)	Search Criteria	Terms to Display	Include in AE Overview (Y/N)
Hypersensitivity Reaction	Hypersensitivity	Narrow – Hypersensitivity (SMQ 20000214)	PTs	Y – serious events only
	Anaphylactic Reaction	Narrow – Anaphylactic reaction (SMQ 20000021)	PTs	N
Hepatic Events	Hepatic Events	Broad – Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ 20000013) Broad – Hepatitis, non-infectious (SMQ 20000010) Broad – Cholestasis and jaundice of hepatic origin (SMQ 20000009) Broad – Liver related investigations, signs and symptoms (SMQ 20000008) Narrow – Liver-related coagulation and bleeding disturbances (SMQ 20000015)	PTs	N

Adverse Event per 100 Patient-Years of Exposure

Adverse events occurring during the entire study will be presented by event rate per 100 patient-years. These will be presented for any TEAEs, serious adverse events, and Areas of Special Interest.

AEs per 100 patient-years of exposure is defined as the number of AEs divided by the total exposure in 100 patient-years. Note that one event per preferred term per day per subject will be counted in the calculation of the number of AEs (i.e., a preferred term will not be counted twice on the same day for the same subject). See the calculation method below.

$$100 \times \frac{\text{Number of TEAEs}}{\text{Total Patient Years}}$$

where total patient years is defined as the sum of the study drug exposure (defined as date of last dose – date of first dose + 105 days (5 half-lives)) of all subjects normalized by 365.25, and rounded to one decimal place.

11.2.2 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

Deaths and all SAEs will be presented in listing format. In addition, SAEs and AE leading to study drug discontinuation will be summarized by System Organ Class and MedDRA Preferred Term.

11.2.3 Safety Subgroup Analysis

The AE overview and AE by SOC and PT in Safety_A1 and Safety_B_R populations will also be analyzed with respect to the actual values of stratification factors:

- Dichotomous weight (≤ 100 kg vs. > 100 kg)
- Prior exposure to TNF antagonists (0 versus ≥ 1)

11.3 Analysis of Laboratory Data

For the assessments of laboratory data, values observed more than 105 days after the last dose of study drug will be excluded.

Listing and descriptive statistics of laboratory values over time, changes from baseline, and extreme abnormal value on treatment will be provided. Extreme abnormal value is the value which is most significantly away from the reference range. Frequency of subjects with transitions relative to reference range and listing of subjects with significant abnormal laboratory values will be presented as well.

Analyses will be conducted in the Safety_A1 Population, the Safety_B_R Population, and the ALL_RZB Population.

For subjects who were re-randomized to placebo in Part B, laboratory values evaluated after 105 days from the last dose of risankizumab in Part A and before the first dose of retreatment will not be included in the summaries for the ALL_RZB Population.

11.3.1 Variables and Criteria Defining Abnormality

Clinical laboratory tests conducted in the study are listed in Table 24.

Table 24. Clinical Laboratory Tests

Category	Test Name
Haematology	Hematocrit (Hct) Hemoglobin (Hb) Glycosylated Hb (HbA1c) White Blood Cells/Leukocytes Platelet Count/Thrombocytes
Diff. Automatic	Neutrophils (relative and absolute count) Eosinophils (relative and absolute count) Lymphocytes (relative and absolute count)
Enzymes	AST (GOT) ALT (GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) Gamma-Glutamyl Transferase (GGT/γ-GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium
Substrates	Glucose BUN Uric acid Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Albumin C-Reactive Protein (high sensitivity) Cholesterol, total Triglycerides LDL-Cholesterol (calculated) HDL-Cholesterol
Urinalysis (Stix)	Urine Protein Urine Glucose

11.3.2 Statistical Methods

Analysis of Quantitative Laboratory Parameters (Hematology and Chemistry)

Though the protocol indicates utilizing the Rheumatology Common Toxicity Criteria (RCTC) scale for grading laboratory values, given that the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) scale includes a more comprehensive list of laboratory values; the lab analyses based on the NCI CTCAE scale will be presented. Changes from Baseline to each scheduled visit and to the final value in continuous laboratory parameters will be summarized with the mean, standard deviation and median. The Baseline and visit/final value means will also be presented for subjects who have both the Baseline and visit/final values (see Section 6.0 for the definition of Baseline and final values).

If there are multiple post-baseline measurements on the same day, average value will be used.

Shift Tables

Shift tables for changes from Baseline according to the normal range will be provided for each hematology, and clinical chemistry parameter. Shifts from Baseline to the following endpoints will be considered: minimum value, maximum value and final value. Categories of "low or normal" and "high or normal" will be included at Baseline in addition to the categories of "low," "normal," "high" and "missing."

If there are multiple post-baseline measurements on the same day, the last value will be used.

Potentially Clinically Important Laboratory Values

Frequencies and percentages of subjects with post Baseline lab values meeting the following criteria in Table 25 and Table 26 will be summarized. Of note, a post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table 25. Criteria for Potentially Clinically Important Chemistry Values

		Definition of Potentially Clinically Important Current (Version 4) NCI CTCAE Grade 3 or Greater	
Chemistry Variables	**Units**	**Very Low**	**Very High**
TBL	mcmol/L		> 3.0 × ULN
SGOT/AST	U/L		> 5.0 × ULN
SGPT/ALT	U/L		> 5.0 × ULN
Albumin	g/L	< 20	
Glucose	mmol/L	< 2.2	> 13.9
Triglycerides	mmol/L		> 5.7
Creatinine	mcmol/L		> 3.0 × ULN
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Calcium	mmol/L	< 1.75	> 3.1
CPK	U/L		> 5.0 × ULN
Total Cholesterol	mmol/L		> 10.34
GGT			> 5.0 × ULN
ALP			> 5.0 × ULN

Note: A post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table 26. Criteria for Potentially Clinically Important Hematology Values

		Definition of Potentially Clinically Important Current (Version 4) Grade 3 or Greater
Hematology Variables	**Units**	**Very Low**
Hemoglobin	g/dL	< 8.0
Platelets count	10^9/L	< 50.0
WBC count	10^9/L	< 2.0
Neutrophils	10^9/L	< 1.0
Lymphocytes	10^9/L	< 0.5

Note: A post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

A separate listing will be provided that presents all of the subjects and values that are NCI CTCAE toxicity grade 3 or above. For each of these subjects, the whole course of the respective parameter will be listed. The NCI CTCAE grading is shown in Table 27 below:

Table 27. NCI CTCAE Grading

Test	Grade 1	Grade 2	Grade 3	Grade 4
SGPT/ALT increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
SGOT/AST increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
GGT increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
ALP increased	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
TBL increased	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 10.0 × ULN	> 10.0 × ULN
Creatinine increased	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN
CPK increased	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 10.0 × ULN	> 10.0 × ULN
Hemoglobin decreased	< LLN – 100.0 g/L	< 100.0 – 80.0 g/L	< 80.0	
Neutrophil count decreased	< LLN – 1.5 × 10^9/L	< 1.5 – 1.0 × 10^9/L	< 1.0 – 0.5 × 10^9/L	< 0.5 × 10^9/L
WBC decreased	< LLN – 3.0 × 10^9/L	< 3.0 – 2.0 × 10^9/L	< 2.0 – 1.0 × 10^9/L	< 1.0 × 10^9/L
Lymphocyte count decreased	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L

If there are multiple post-baseline measurements on the same day, the worst value will be used.

Liver Function Tests

Additional summaries will be presented for liver function tests including ALT or serum glutamic-pyruvic transaminase (SGPT), AST or serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, and total bilirubin. Each laboratory value will be categorized as follows:

- < 1.5 × ULN
- ≥ 1.5 × ULN – < 3.0 × ULN
- ≥ 3.0 × ULN – < 5.0 × ULN
- ≥ 5.0 × ULN – < 10.0 × ULN
- ≥ 10.0 × ULN – < 20.0 × ULN
- ≥ 20.0 × ULN

Shift tables of Baseline to the maximum (relative to the normal range, i.e., the largest multiple relative to the upper limit of normal) values, and from Baseline to final value will be presented using these categories. A listing of potentially clinically important liver function laboratory values will be provided. The listing will include all subjects who met any of the following four criteria:

- ALT ≥ 3 × ULN, or
- AST ≥ 3 × ULN, or
- Alkaline phosphatase ≥ 1.5 × ULN, or
- Total bilirubin ≥ 2 × ULN.

A listing of possible Hy's Law cases, defined as those who meet all of the following conditions will be provided:

- ALT > 3 × ULN or AST > 3 × ULN
- Associated with an increase in bilirubin ≥ 2 × ULN
- Alkaline phosphatase < 2 × ULN.

11.4 Analysis of Vital Signs and Weight

Analyses will be conducted in the Safety_A1 Population, the Safety_B_R Population, and the ALL_RZB Population.

For subjects who were re-randomized to placebo in Part B, vital sign values evaluated after 105 days from the last dose of risankizumab in Part A and before the first dose of retreatment will not be included in the summaries for the ALL_RZB Population.

11.4.1 Variables and Criteria Defining Abnormality

The following vital sign parameters will be assessed: Systolic blood pressure [mmHg], Diastolic blood pressure [mmHg], Pulse [beats per minute], Respiratory rate [breaths per minute], Temperature [°C], Weight [kg]. The following table presents the Criteria for Potentially Clinically Important Vital Sign Findings. Of note, a post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

Table 28. Criteria for Potentially Clinically Important Vital Sign Findings

Vital Sign	Category	Criteria for Potential Clinically Important Vital Signs
Systolic Blood Pressure	Low Value	≤ 90 mmHg and decrease ≥ 20 mmHg from Baseline
	High Value	≥ 160 mmHg and increase ≥ 20 mmHg from Baseline
Diastolic Blood Pressure	Low Value	≤ 50 mmHg and decrease ≥ 15 mmHg from Baseline
	High Value	≥ 105 mmHg and increase ≥ 15 mmHg from Baseline
Pulse	Low Value	≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High Value	≥ 120 bpm and increase ≥ 15 bpm from Baseline

Note: A post baseline value must be more extreme than the baseline value to be considered a potentially clinically important finding.

11.4.2 Statistical Methods

Changes from Baseline to each visit and to the final value in vital sign parameters will be summarized with the mean, standard deviation and median. The Baseline and final value means will also be presented for subjects who have both the Baseline and final values (see Section 6.0 for the definition of Baseline and final values).

For baseline, if there are multiple measurements on the same day, the last measurement prior to the first dose of study drug will be used as the Baseline vital sign value. If there are multiple post-baseline measurements on the same day, average value will be used.

For systolic blood pressure, diastolic blood pressure and pulse, a listing of all subjects with any vital sign value meeting criteria for potentially clinically important values will be provided. For each of these subjects, the whole course of the respective parameter will be listed. The number and percentage of subjects who have at least one value meeting criteria for potentially clinically important values will be provided for each selected vital sign parameter.

11.5 Analysis of ECG Parameters

The ECG parameters will be assessed as scheduled in the study protocol.

Summary statistics for mean change from baseline for corrected QT interval (QTc) using Bazett (QTcB) and Fridericia (QTcF) corrections, aggregated, will be provided by analysis visits.

- Values for both QTcF and QTcB interval measurements will be categorized into the following: ≤ 450 ms, > 450 ms, > 480 ms, > 500 ms, or missing. For the scheduled visits, as well as baseline, the number and percentage of subjects within each category will be presented. Additionally, for each category, the number and percentage of subjects with a maximum QTcF interval falling into the category will be presented; a similar summary will be presented for QTcB intervals.
- For QTcF and QTcB intervals, the changes from baseline will be categorized into the following: < 30 ms, 30 ≤ – < 60 ms, ≥ 60 ms, or missing. For the scheduled visits, the number and percentage of subjects within each category will be presented. Additionally, for each category, the number and percentage of subjects with a maximum change from baseline in the QTcF interval falling into the category will be presented; a similar summary will be presented for QTcB intervals.

Analyses will be conducted in the Safety_A1 Population, the Safety_B_R Population, and the ALL_RZB Population.

11.6 Local Tolerability

Local tolerability of the subcutaneous injection will be assessed by the investigator according to 6 items: swelling, induration, heat, redness, pain, and other findings. Proportion of subjects reporting each condition will be summarized.

Local tolerability will be summarized in the Safety_A1 Population and the Safety_B_R Population. In addition, the overall rate (with at least one occurrence) during the study will also be presented in the ALL_RZB Population.

12.0 Pharmacokinetic Analysis

Pharmacokinetic analysis is not covered in this SAP.

13.0 Biomarkers Analysis

Biomarker Analysis is not covered in this SAP.

14.0 Summary of Changes

14.1 Summary of Changes Between the Latest Version of Protocol and the Current SAP

- Defined analysis populations (including the Per-protocol population) in detail.
- Clarified independent null hypothesis test hierarchy in the ITT Population in Part B consisting re-randomized subjects.
- Added additional ranked secondary endpoint to the ITT Population in Part B consisting re-randomized subjects: achievement of sPGA of clear or almost clear (0 or 1) at Week 104.
- Pre-specified Areas of Safety Interest.

14.2 Summary of Changes Between the Previous Version and the Current Version of the SAP

Updated Table 25, Table 27, and Table 28 based on Integrated Summary of Safety SAP.

Updated the end day for inclusion concomitant medications, based on Integrated Summary of Safety SAP.

15.0 Appendix

None.

16.0 References

None.

17.0 List of Tables, Figures and Data Listings That are to Be Programmed

To be provided in a separate document.

Document Approval

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