


CLINICAL TRIAL PROTOCOL

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BI Trial No.:	1311.30	
BI Investigational Product:	Risankizumab, BI 655066	
Title:	BI 655066/ABBV-066 (risankizumab) versus adalimumab in a randomised, double blind, parallel group trial in Moderate to severe plaque psoriasis to assess safety and efficacy after 16 weeks of treatment and after inadequate adalimumab treatment response (IMMvent)	
Brief Title:	BI 655066/ABBV-066 (risankizumab) compared to active comparator (adalimumab) in patients with moderate to severe chronic plaque psoriasis	
Clinical Phase:	III	
Trial Clinical Monitor:	[REDACTED]	
Coordinating Investigator:	[REDACTED]	
Status:	Revised Protocol	
Version and Date:	Version: 4.0	Date: 17 Oct 2016
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CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		Boehringer Ingelheim	
Name of finished product:		Not applicable	
Name of active ingredient:		BI 655066 (risankizumab)	
Protocol date: 10 December 2015	Trial number: 1311.30		Revision date: 17 October 2016
Title of trial:	BI 655066/ABBV-066 (risankizumab) versus adalimumab in a randomized, double blind, parallel group trial in Moderate to severe plaque psoriasis to assess safety and efficacy after 16 weeks of treatment and after inadequate adalimumab treatment response (IMMvent)		
Coordinating Investigator:			
Trial site(s):	Multi-centre trial		
Clinical phase:	III		
Objective(s):	The main objective of this study is to assess the safety and efficacy of BI 655066 (risankizumab) compared to adalimumab in patients with moderate to severe chronic plaque psoriasis		
Methodology:	Active-controlled, double-blind, double dummy, randomized, parallel design comparison of BI 655066 and adalimumab over 44 weeks		
No. of patients:			
total entered:	600		
each treatment:	300		
Diagnosis :	Moderate to severe chronic plaque psoriasis		
Main criteria for inclusion:	<ul style="list-style-type: none"> - Male or female patients with age \geq 18 years at screening - Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. - Have stable moderate to severe chronic plaque psoriasis with or 		

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	without psoriatic arthritis at both Screening and Baseline (Randomisation): <ul style="list-style-type: none"> • Have an involved body surface area (BSA) \geq 10% and • Have a Psoriasis Area and Severity Index (PASI) score \geq 12 and • Have a static Physician Global Assessment (sPGA) score of \geq 3. <ul style="list-style-type: none"> - Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator - Must be a candidate for treatment with Humira® (adalimumab) according to local label. 		
Test product(s):	BI 655066		
dose:	150mg (2 syringes à 75mg) at Weeks 0, 4 and every 12 weeks		
mode of administration:	subcutaneous		
Comparator products:	Adalimumab		
dose:	80mg at randomisation; then 40mg at Weeks 1, 3, 5 and every other week.		
mode of administration:	subcutaneous		
Duration of treatment:	44 weeks		
Endpoints	Primary Endpoints <ul style="list-style-type: none"> - Achievement of \geq 90% reduction from baseline PASI score (PASI 90) at Week 16, - Achievement of an sPGA score of clear or almost clear at Week 16 Key Secondary Endpoints: <ul style="list-style-type: none"> - Achievement of \geq 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 \geq 90% reduction from baseline PASI score 		

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<p>(PASI 90) at Week 44 for those patients who are re-randomized at Week 16</p> <p>Other Secondary Endpoints</p> <ul style="list-style-type: none"> • Achievement of an sPGA score of clear or almost clear (0 or 1) at Week 44 • Achievement of sPGA score of clear (0) at Week 44 <p>Further endpoints:</p> <ul style="list-style-type: none"> • Achievement of PASI 50 at all visits collected • Achievement of PASI 75 at all visits collected • Achievement of PASI 90 at all visits collected • Achievement of PASI 100 at all visits collected • Time until the first achievement of PASI 50, PASI 75, PASI 90, PASI 100 and sPGA 0 or 1 • Time until loss of PASI 75, PASI 90, PASI 100 and sPGA 0 or 1 response • Change and percent change from baseline in PASI at all visits collected • Absolute PASI score 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 • Change from baseline in Dermatology Life Quality Index (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 Work Limitations Questionnaire (WLQ) at all visits collected • Change and percent change from baseline in Nail Psoriasis Severity Index (NAPSI) at all visits collected 			

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	<ul style="list-style-type: none"> • 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 • Response to individual questions on the self-administration questionnaire at each visit where BI 655066 active or placebo is self-administered • Change of metabolic risk factors from baseline (waist circumference, body weight, Homeostasis Model Assessment [HOMA] index) 		
Safety criteria:	Physical examination vital signs, 12-lead electrocardiogram (ECG), laboratory tests, adverse events and tolerability		
Statistical methods:	<p>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 the adalimumab 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.</p> <p>Secondary analysis: The same methods for the primary analyses will be used to analyze binary key secondary endpoints. In particular, the achievement of PASI 90 at Week 44 for patients re-randomized to continue adalimumab or switch to BI 655066 will be compared using the methods described above.</p> <p>The hypotheses comparing BI 655066 to adalimumab at Week 16 will be tested in hierarchical order using two-sided tests with a type I error of 0.05. In addition, the comparison of the achievement of PASI 90 at Week 44 for the re-randomized patients will be tested separately with a type I error of 0.05.</p>		

FLOW CHART

Trial Periods	Screen- ing	Randomized Treatment														FU
		V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	EOT	EOO
Week			1	3	4	8	12	16	20	24	28	32	36	40	44	EOT +4 ¹⁸
Day	-42 to -7	1	8	22	29	57	85	113	141	169	197	225	253	281	309	EOT +28 ¹⁸
Visit window (days)			±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7
Informed consent to main study and to optional study procedures ¹	X															
Demographics	X															
Medical history	X															
Smoking/alcohol history	X															
Psoriasis therapy history	X															
In-/exclusion criteria	X	X														
%BSA involvement	X	X														
Height	X															
Weight and waist circumference ²	X							X								X
Physical examination ³	X _C	X _T	X _T	X _T	X _T	X _T	X _T	X _C	X _T	X _T	X _T	X _T	X _T	X _T	X _C	X _C
Vital signs ⁴	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Infection screening ⁵	X														X	
Pregnancy testing ⁶	X	X			X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests ⁷	X	X			X			X			X				X	X
12 lead-ECG	X	X			X			X			X				X	X
Blood sampling for PK ⁸		X			X		X	X			X		X		X	
ADA sampling ⁸		X			X			X			X				X	
Blood sampling for Biomarkers ^{1,9}		X			X			X			X		X		X	
Local tolerability ¹⁰			X	X	X			X			X				X	

Trial Periods	Screen- ing	Randomized Treatment														FU
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	EOT	EOO
Week			1	3	4	8	12	16	20	24	28	32	36	40	44	EOT +4 ¹⁸
Day	-42 to -7	1	8	22	29	57	85	113	141	169	197	225	253	281	309	EOT +28 ¹⁸
Visit window (days)			±1	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±7
PASI / sPGA	X	X			X	X	X	X	X	X	X	X	X	X	X	
NAPSI / PPASI / PSSI		X						X							X	
DLQI and WLQ		X						X							X	
HCRU ¹¹		X			X	X	X	X	X	X	X	X	X	X	X	
Optional skin biopsy ^{1,12}		X					X									
Optional DNA banking ^{1,13}		X														
Randomization, Re-Randomisation ¹⁴		X						X ¹⁴								
Contact IRT	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Administration of trial drugs at study visits ¹⁵		X	X	X	X			X	X		X	X				
Self administration questionnaire for Study Drug BI 655066 (active or placebo) ¹⁶					X			X	X		X	X				
Dispensation of trial drugs to patient ¹⁷					X	X	X	X	X	X	X	X	X	X		
Termination of trial medication ²⁰															X	
Trial completion ¹⁸															X	X
Vital status ¹⁹																X

FOOTNOTES

1. After patients have been informed about the trial, written informed consent in accordance with ICH-GCP and the local legislation must be obtained prior to performing any study related procedures. A separate informed consent is required for optional study procedures if patients will participate in these optional study procedures which are DNA banking from blood samples, biomarker serum sample banking, skin biopsies and biomarker tissue sample banking from skin biopsies.
2. For detailed instructions how to measure waist circumference see [section 5.3.1.1](#) for waist circumference procedure.
3. Physical examination: C=complete, T=targeted. Refer to [Section 5.3.1](#).
4. Measurement of vital signs should precede blood sampling and be assessed pre-dose. Additional assessments will be done approximately 5 minutes post-dose (5 min. after last injection) and approximately 60 minutes post-dose (60 min. after last injection) at Visit 2 and Visit 5. Refer to [Section 5.3.2](#). Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at the Randomization Visit

and for approximately 1 hour after the last injection at all other study visits with drug administrations. Hypersensitivity reactions should be treated according to medical standards.

5. Refer to [table 5.3.3:1](#) for the list of infection screening tests and to Exclusion criterion 7 in [section 3.3.3](#)
6. Serum pregnancy testing at screening and if urine pregnancy test is positive. Urine pregnancy testing at randomization and will be continued as indicated in the [Flow Chart](#) (including EOT and EOO Visit) and should be done prior to administration of study drug in case there is dosing at study visits.
7. 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.
8. On dosing visits, PK and ADA samples should be taken approximately within 1 hour prior to administration of study drug.
9. Biomarker sampling should be done prior to administration of study drug at dosing visits.
10. Refer to [section 5.3.5](#) for details on local tolerability assessment.
11. Healthcare Resource Utilisation (HCRU): hospitalisations, emergency room visits and unscheduled outpatient or home visits will be captured (refer to [Section 5.6.3](#)).
12. At selected study sites, voluntary skin biopsy assessment will be conducted after separate informed consent is given. Collection should be done prior to administration of study drug at dosing visits. Refer to [Section 5.5.1](#).
13. Voluntary DNA Banking sample will be taken and stored after separate informed consent is given in accordance with local ethical and regulatory requirements. Refer to [section 5.5](#).
14. At Week 16, patients treated with adalimumab and with \geq PASI 50 and $<$ PASI 90 will be 1:1 re-randomized to continue on adalimumab or switch to BI 655066. Adalimumab patients below PASI 50 at Week 16 will be switched to BI 655066. Adalimumab patients with \geq PASI 90 at Week 16 will continue on adalimumab.
15. At Randomization (Visit 2) all study drugs will be administered by study personnel (2 injections BI 655066 active or placebo plus 2 injections adalimumab active or placebo).
At Visits 3 and 4 (Weeks 1 and 3) the patient self-administers 1 injection adalimumab (active or placebo) under supervision of study personnel.
At Visit 5 (Week 4), Visit 8 (Week 16), Visit 9 (Week 20), Visit 11 (Week 28) and Visit 12 (Week 32) the patient self-administers 2 injections BI 655066 (active or placebo) under supervision of study personnel (Refer to [Section 4.1.4](#) and [Figure 3.1: 1](#)).
16. Study personnel completes a questionnaire about self-administration of BI 655066 (active or placebo) by the patient (refer to [section 4.1.4](#), [5.6.2](#) and [Appendix 10.8](#))
17. Adalimumab (active or placebo) is dispensed to the patient for self-administration at home (at Weeks 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39 and 41). Time window for home administration should be \pm 3 days.
18. Patients who complete the randomized treatment period of study 1311.30 will be offered to roll over into an open label extension (OLE) trial if they fulfill the in- and exclusion criteria for the OLE trial. Those patients will have no Follow-up Visit in study 1311.30.
Patients who discontinue the randomized treatment period of study 1311.30 prematurely will complete EOT Visit procedures and return 16 (\pm 1) weeks after their last BI 655066 (active or placebo) administration for End of Observation (EOO) Visit.
Patients who complete the randomized treatment period of study 1311.30, but will not (or cannot) be included in the OLE study will have their EOO Visit 4 (\pm 1) weeks after their EOT Visit at Week 44 (this is at Week 48 \pm 1 week).
19. For randomised patients who will not participate in the OLE study and who withdraw from the study prior to their planned EOO Visit, vital status should be collected at 48 (+1) weeks after the Randomisation Visit.
20. Patients that terminate trial medication early should remain in the trial if possible, and complete all remaining study visit procedures if possible. Termination of trial medication should be completed in the e CRF and treatment discontinuation registered in IRT. Refer to [Section 6.2.3](#) for more details

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ABBREVIATIONS

ADA	Anti-drug antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine transferase
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate transferase
AUC	Area under the Curve
BIRDS	Boehringer Ingelheim Regulatory Documents for Submission
BLA	Biologic Licensing Application
BUN	Blood urea nitrogen
CCDS	Company Core Data Sheet
CI	Confidence Interval
CK	Creatine Kinase
CK-MB	Creatine Kinase Muscle Brain
C _{max}	Maximal concentration
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CV	Cardiovascular
DEDP	Drug Exposure During Pregnancy
DILI	Drug induced liver injury
DLQI	Dermatology Life Quality Index
DNA	Deoxyribonucleic Acid
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCOA	Electronic clinical outcome assessment
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme Linked Immunosorbent Assay
EOO	End of Observation
EOT	End of Treatment
ePRO	Electronic Patient Reported Outcome
EU	European Union
EudractCT	European Clinical Trials Database
FAS	Full Analysis Set
FC	Flow Chart
GCP	Good Clinical Practice
gCV	Geometric mean of Coefficient Variation
GGT	Gamma-Glutamyl Transferase

GOT	Glutamat Oxalacetate Transaminase
Hb	Hemoglobin
HCRU	Health Care Resource Utilization
Hct	Hematocrit
HDL	High density lipoprotein
HIPAA	Health insurance portability and accountability act
HIV	Human immunodeficiency virus
HOMA	Homeostatis model assessment
HPC	Human Pharmacology Centre
IB	Investigator's Brochure
IC	Inhibitory concentration
ICH	International conference on harmonisation
IEC	Independent Ethics Committee
IFN	Interferon
IgG	Immunogloblin G
IL	Interleukin
INR	International normalized ratio
IQR	Interquartile range
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
i.v.	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web-based Response System
LDL	Low density lipoprotein
LOCF	Last Observation Carried Forward
LoEE	List of Essential Element
mAb	Monoclonal antibody
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed effect Model Repeat Measurement
MST	Medical Sub team
NAb	Neutralizing Antibody
NAPSI	Nail Psoriasis Severity Index
NOAEL	No observed adverse effect level
NRI	No Response Imputation
OLE	Open label extension
OPU	Operative Unit
PASI	Psoriasis Area and Severity Index
Pbo	Placebo
PD	Pharmacodynamics
PK	Pharmacokinetics
p.o.	per os (oral)
PoCC	Proof of Clinical Concept
PPASI	Palmoplantar Psoriasis Area Severity Index
PPD	Purified Protein Derivative

PPS	Per Protocol Set
PSSI	Psoriasis Scalp Severity Index
q.d.	quaque die (once a day)
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
RNA	Ribonucleic Acid
RRS-PPS	Re-Randomized Per Protocol Set
SAE	Serious Adverse Event
SAF	Safety Set
s.c.	Subcutaneous
SD	Standard deviation
SmPC	Summary of product characteristics
SOPs	Standard Operating Procedures
sPGA	Static Physician Global Assessment
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TCM	Trial Clinical Monitor
TMF	Trial Master File
TNF	Tumor Necrosis Factor
TSAP	Trial Statistical Analysis Plan
TSH	Thyroid Stimulating Hormone
ULN	Upper limit of normal
US PI	United States Product Information
VEGF	Vascular endothelial growth factor
WBC	White blood cells
WLQ	Work Limitations Questionnaire

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

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

While the majority of psoriasis patients are managed initially with topical therapies, those with severe and/or refractory disease may require phototherapy and/or systemic therapy. Oral systemic agents provide modest efficacy, but increasingly patients are treated with biological agents, such as TNF-alpha inhibitors (etanercept, adalimumab) and the p40 IL12/23 inhibitor (ustekinumab) ([R14-5159](#)). While the clinical efficacy of ustekinumab indicates a role for both IL-12 and IL-23 in the pathogenesis of psoriasis ([R11-1547](#)), more recent data suggest that IL-23 is disproportionately involved in the maintenance of chronic psoriasis ([R11-1547](#)). IL-23 is thought to be involved in the pathophysiology of psoriasis via induction and maintenance of Th17 type cells, including type 17 T cells and other IL-23 responsive cells. This is supported by recent clinical data indicating that monoclonal antibodies that block IL-17, the cytokine produced by Th17 cells, have high efficacy in psoriasis.

There is still clinical need for increased efficacy as the most effective anti-TNF and IL12/23 agents provide only 75% improvement in psoriasis in about 60 -70% of patients and these responses tend to be lost over time. While the anti-IL-17 agents (i.e. secukinumab) provide better efficacy, they require monthly injections, thus their long term utility is still undetermined. BI 655066 is a humanized monoclonal antibody with high affinity for the p19 component of human IL-23A that specifically neutralizes IL-23. Proof of clinical concept (PoCC) for BI 655066 was demonstrated in a single dose phase I trial in 39 patients with moderate to severe plaque psoriasis where 87% of patients achieved at least 75% reduction in Psoriasis Area and Severity Index (PASI 75) with no safety concerns (1311.1, [c02434648](#)).

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

1.2 DRUG PROFILE

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

[REDACTED]

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

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

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

[REDACTED]

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

Psoriasis is a chronic inflammatory disease affecting 2% of the world population with significant impact on patient quality of life and associated with significant systemic disease. IL-23 plays a key role in the pathophysiology of psoriasis through induction and maintenance of Th-17 type cells that secrete inflammatory cytokines. BI 655066 is a humanized monoclonal antibody that specifically neutralizes the IL-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 (1311.1, [c02434648](#)).

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

2.2 TRIAL OBJECTIVES

The main objectives of this study are to assess the efficacy and safety of BI 655066 compared to adalimumab in patients with moderate to severe chronic plaque psoriasis. The primary efficacy evaluation will be performed at 16 weeks and an assessment of maintenance of response will be performed at 44 weeks. The study will also evaluate the efficacy of a 28 week treatment with BI 655066 in patients who were initially treated with adalimumab for 16 weeks, achieving insufficient or only partial response with adalimumab, and then switched to BI 655066 treatment from Week 16 to Week 44.

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.

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

2.3 BENEFIT - RISK ASSESSMENT

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

As with 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.

There is not enough information at this time to rule out a risk of cancer with BI 655066, but this risk is considered small with this type of compound as experience with the anti-IL 12/23 mAb ustekinumab has not suggested significant risk for cancer/serious infection.

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

All patients will receive active treatment in this study, either BI 655066 or adalimumab; there is no placebo comparator in this trial. Adalimumab (Humira[®]) is used as an established treatment for patients with moderate to severe psoriasis and has been on the market in many countries for many years. Adalimumab has an acceptable safety profile.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety, see also [Section 5.3.6.1](#).

In order to recognize any safety signals as early as possible, an independent Data Monitoring Committee (DMC) will monitor this study and all studies where patients are receiving BI 655066.

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

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This confirmatory multi-national, randomized, double-blind, double dummy, active controlled, parallel design study compares BI 655066 with adalimumab. In total, approximately 600 patients with moderate to severe chronic plaque psoriasis will be randomized in this trial.

Patients are included in the study once they have signed the informed consent. Patients suitable after screening will be eligible to participate in the 44 week treatment period and will be randomized at a ratio of 1:1 to one of 2 treatment arms (BI 655066 or adalimumab) shown in [Figure 3.1: 1](#).

Patients initially randomized to BI 655066 will stay on BI 655066.

At Week 16, patients initially on adalimumab and <PASI 50 will be switched to BI 655066.

At Week 16, patients initially on adalimumab and \geq PASI 90 will stay on adalimumab.

At Week 16, patients initially on adalimumab and \geq PASI 50 and <PASI 90 will be re-randomised 1:1 to receive either BI 655066 or adalimumab.

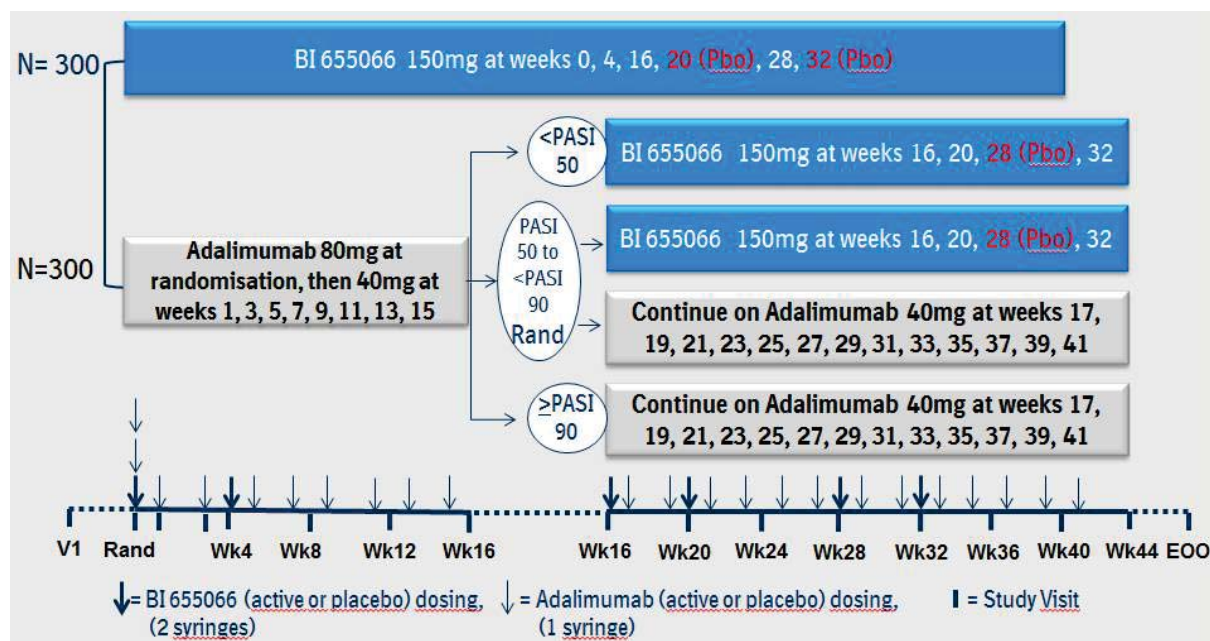


Figure 3.1: 1 Trial design

Patients will be blinded to treatment. Patients in each dose group will receive the same injections (active or placebo) at each designated time point, in order to maintain blinding.

Patients starting and continuing with BI 655066 active drug will receive 2 syringes of BI 655066 active drug (2 x 75mg) at randomization, at Weeks 4, 16 and 28 and placebo adalimumab at randomization (2 syringes) and 1 placebo adalimumab syringe at Weeks 1, 3, 5, 7, 9, etc. up to Week 41. These patients also receive 2 syringes of BI 655066 placebo at Weeks 20 and 32 to maintain blinding to the BI 655066 active treatment arm starting at Week 16 after adalimumab pre-treatment. BI 655066 active treatment always starts with a loading dose 4 weeks after the first injection.

Patients starting with active adalimumab and switching to active BI 655066 at Week 16 will receive 2 syringes active adalimumab at randomization (2 x 40mg) followed by 1 syringe active adalimumab (40mg) at Weeks 1, 3, 5, 7, 9, 11, 13, 15; and 1 placebo adalimumab syringe at Weeks 17, 19, 21, etc. up to Week 41 to maintain blinding. These patients also receive 2 syringes of BI 655066 placebo at randomization and Week 4 followed by two active BI 655066 injections (2 x 75mg) at Weeks 16, 20 and 32 as well as 2 placebo BI 655066 injections at Week 28.

Patients starting and continuing with adalimumab active drug will receive 2 syringes active adalimumab at randomization (2 x 40mg) followed by 1 syringe active adalimumab (40mg) at Weeks 1, 3, 5, 7, 9, etc. up to Week 41. These patients also receive 2 syringes of placebo BI 655066 at randomization and at Weeks 4, 16, 20, 28 and 32.

Individual patient participation is concluded when the patient has completed the last planned visit. The “last-patient-last-visit-primary-endpoint” is the last scheduled primary endpoint visit at Week 16 completed by the last patient. The end of the trial is defined as “last patient out”, i.e. last scheduled visit completed by last patient.

Patients will be offered to roll over into an open label extension (OLE) trial if they have completed the study 1311.30 and meet the inclusion criteria for the OLE trial.

Patients who terminate the study drug early in study 1311.30, will complete EOT Visit procedures instead of the planned treatment period visit and return 16 (± 1) weeks after the last BI 655066 (active or placebo) administration for EOO Visit. Discontinuation of study medication should not necessarily lead to withdrawal from the study. If possible, the patient should be further followed up and complete all study visits and procedures until EOO.

Patients who complete the randomized treatment period of study 1311.30, but will not be included in the OLE study will have their EOO Visit 4 (± 1) weeks after their EOT Visit at Week 44 (which is at Week 48 ± 1 week).

3.1.1 Administrative structure of the trial

The trial is sponsored by AbbVie in the USA and Boehringer Ingelheim (BI) ex-US. Boehringer Ingelheim has appointed a Trial Clinical Monitor (TCM), responsible for coordinating all required activities, in order to:

- manage the trial in accordance with applicable regulations and internal Standard Operating Procedures (SOPs),

- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and investigators of participating countries.

A Coordinating Investigator will be responsible to coordinate activities of investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating investigators and other important participants, including their curricula vitae, will be filed in the ISF

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

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

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

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 last study visit. 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

This is a randomized double blind, double dummy and active controlled parallel design study. This design is appropriate for assessing the safety and efficacy of BI 655066 compared to adalimumab in patients with moderate to severe chronic plaque psoriasis. Patients will be followed up for a total of 44 weeks plus a residual effect period in order to assess the safety and maintenance of efficacy of BI 655066 compared to adalimumab.

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

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 600 patients will be randomized in the current trial. A sufficient number of patients will be screened to meet this randomization goal. Patients will be recruited at multiple investigative sites in multiple countries. Approximately 70 sites are planned with approximately 4 – 10 patients to be randomized per site. Recruitment will be competitive.

3.3.1 Main diagnosis for trial entry

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

Please refer to [section 8.3.1](#) (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

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

*Women of childbearing potential are defined as:

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

2. Age ≥ 18 years at screening
3. Have a diagnosis of chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug. Duration of diagnosis may be reported by the patient.

4. Have stable moderate to severe chronic plaque psoriasis with or without psoriatic arthritis at both Screening and Baseline (Randomization):
 - a. Have an involved body surface area (BSA) $\geq 10\%$ and
 - b. Have a Psoriasis Area and Severity Index (PASI) score ≥ 12 and
 - c. Have a static Physician Global Assessment (sPGA) score of ≥ 3 .
5. Must be candidates for systemic therapy or phototherapy for psoriasis treatment, as assessed by the investigator
6. Must be candidates for treatment with adalimumab (Humira[®]) according to local label as confirmed by the investigator.
7. Signed and dated written informed consent prior to admission to the study in accordance with GCP and local legislation
8. Patient must be able and willing to self-administer the study medication

3.3.3 Exclusion criteria

1. Patients with
 - a. non-plaque forms of psoriasis (including guttate, erythrodermic, or pustular)
 - b. current drug-induced psoriasis (including an exacerbation of psoriasis from beta blockers, calcium channel blockers, or lithium)
 - c. active ongoing inflammatory diseases other than psoriasis that might confound trial evaluations according to investigator's judgment
2. Previous exposure to BI 655066
3. Previous exposure to adalimumab (Humira[®])
4. Currently enrolled in another investigational study or less than 30 days (check also with restricted medication [table 4.2.2.1: 1](#)) (from screening) since completing another investigational drug or device study.
5. Use of any restricted medication as specified in [Table 4.2.2.1: 1](#) or any drug considered likely to interfere with the safe conduct of the study.
6. Major surgery performed within 12 weeks prior to randomization or planned within 12 months after screening (e.g. hip replacement, removal aneurysm, stomach ligation).
7. Known chronic or relevant acute infections, such as active tuberculosis, HIV or viral hepatitis. Confirmation of these diseases testing is required at screening. QuantiFERON[®] TB test or PPD skin test will be performed according to local labelling for Humira[®]. If the result is positive, patients may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If presence of latent tuberculosis is

established, then treatment should have been initiated and maintained according to local country guidelines.

8. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell or squamous cell carcinoma of the skin or in situ carcinoma of uterine cervix.
9. Evidence of a current or previous disease, medical condition (including chronic alcohol or drug abuse) other than psoriasis, surgical procedure (i.e., organ transplant), medical examination finding (including vital signs and ECG), or laboratory value at the Screening Visit outside the reference range that in the opinion of the investigator is clinically significant and would make the study participant unreliable to adhere to the protocol or to complete the trial, compromise the safety of the patient, or compromise the quality of the data.
10. History of allergy/hypersensitivity to a systemically administered biologic agent or its excipients
11. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
12. Previous enrolment in this trial

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

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

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

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy)
- Development of a toxicity or adverse event which warrants BI 655066 discontinuation including but not limited to SAEs or SUSARs
- If prohibited treatment is used during the study for any indication, the subject must discontinue use of the prohibited treatment if he/she wishes to continue in the study. In case of undue safety risk for the subject, the subject should discontinue study treatment at the discretion of the investigator. If the subject received a live virus vaccination during the study, the subject must discontinue study treatment.

- If the patient experiences an intolerable increase of psoriasis during the course of the trial the patient will be discontinued from the trial to receive 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 be further followed up and complete all study visits and procedures as initially planned.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the [flow chart](#) and [section 6.2.3](#).

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

For randomised patients leaving the study before the planned EOO, vital status should be collected at the date of the planned EOO Visit for a completed patient not going into the OLE study. Vital status assessment for discontinued patients should occur at 48 (± 1) weeks after randomisation.

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

3.3.4.2 Discontinuation of the trial by the sponsor

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

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

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

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

Multiple doses of BI 655066, comparator drug adalimumab and matching placebos to both BI 655066 and adalimumab will be administered subcutaneously. All products will be supplied by Boehringer Ingelheim.

4.1.1 Identity of BI investigational product and comparator product

Table 4.1.1: 1 Description of test product BI 655066

Substance:	BI 655066: Anti-human IL-23p19 mAb
Pharmaceutical form:	Injection solution of BI 655066, presented in a pre-filled syringe
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Anti-human IL-23p19 mAb
Molecular weight	Approximately 148 kDa
Unit Strength:	75 mg BI 655066 in pre-filled syringe
Route of administration:	Subcutaneous injection
Posology:	2 injections à 75mg at randomization, at Weeks 4, 16 and 28 for patients initially randomized to BI 655066 and who continue on BI 655066; 2 injections à 75mg at Weeks 16, 20 and 32 for patients crossing over from adalimumab to BI 655066 at Week 16
Duration of use:	28 weeks (from first to last administration) for BI 655066 arm 16 weeks (from first to last administration) for patients crossing over from adalimumab arm to BI 655066

Table 4.1.1: 2 Description of BI 655066 placebo

Substance:	Placebo to match BI 655066
Pharmaceutical form:	0.9% sodium chloride solution presented in a pre-filled syringe
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Not applicable
Molecular weight	Not applicable

Table 4.1.1: 2 Description of BI 655066 placebo (cont'd)

Unit Strength:	Not applicable
Route of administration:	Subcutaneous injection
Posology:	a) 2 injections at Week 20 and 32 for patients who start with BI 655066 and continue on BI 655066 b) 2 injections at randomization, Weeks 4 and 28 for patients switching from adalimumab to BI 655066 at Week 16 c) 2 injections at randomization, Weeks 4, 16, 20, 28, and 32 for patients who start with adalimumab and continue on adalimumab
Duration of use:	12 weeks or 28 weeks or 32 weeks from first to last administration for treatment arms a), b) and c), respectively

Table 4.1.1: 3 Description of test product adalimumab

Substance:	Adalimumab (Brand Name Humira®)
Pharmaceutical form:	Injection solution of adalimumab, presented in a pre-filled syringe
Source:	AbbVie Inc.
Chemical form:	recombinant human IgG1 monoclonal antibody specific for human tumor necrosis factor
Molecular weight	Approximately 148 kDa
Unit Strength:	40 mg adalimumab in a pre-filled syringe
Route of administration:	Subcutaneous injection
Posology:	2 injections à 40mg at randomization (80 mg loading dose), then 1 injection à 40mg at Weeks 1, 3, 5, 7, etc., every other week until Week 41 for patients who start with and continue on adalimumab; or only up to Week 15 for patients who switch from adalimumab to BI 655066 at Week 16.
Duration of use:	41 weeks (from first to last administration) for patients who start and continue on adalimumab, or 15 weeks for patients who cross-over to BI 655066 at Week 16

Table 4.1.1: 4 Description of adalimumab placebo

Substance:	Placebo to match Adalimumab
Pharmaceutical form:	0.9% sodium chloride solution presented in a pre-filled syringe
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Chemical form:	Not applicable
Molecular weight	Not applicable
Unit Strength:	Not applicable
Route of administration:	Subcutaneous injection
Posology:	2 injections at randomization, followed by 1 injection at Weeks 1, 3, 5, 7 etc., every other week
Duration of use:	41 weeks (from first administration at randomisation to last administration at Week 41) for patients who start with and continue on BI 655066; 24 weeks (from first administration at Week 17 to last administration at Week 41) for patients who cross-over from active adalimumab to BI 655066 at Week 16

4.1.2 Method of assigning patients to treatment groups

Through the utilization of Interactive Response Technology/Tool (IRT), patients will be initially randomized to receive BI 655066 or adalimumab in a ratio of 1:1.

After the eligibility criteria are confirmed, the patient will be randomized 1:1 to either BI 655066 or adalimumab on Day 1 (Visit 2) through IRT call or website entry. At visits where study medication is to be administered or dispensed to the patient, study sites will be required to complete the medication resupply module in the IRT.

Patients initially randomized to adalimumab and with a PASI response of \geq PASI 50 and $<$ PASI 90 at Week 16 will be re-randomised 1:1 to receive either BI 655066 or adalimumab (refer to [Section 3.1](#)). Patients initially randomized to BI 655066 will stay on BI 655066. Patients initially randomized to adalimumab and \geq PASI 90 at Week 16 will continue on adalimumab. Allocation of patients to the three treatments (who continue on BI 655066 / who will be switched from adalimumab to BI 655066 / who will continue on adalimumab) from Week 16 onwards through EOT will be realized by the IRT. The study personnel will enter the PASI score into the IRT system at Visit 2 and at Visit 8 (Week 16).

Details regarding the use of the IRT are described in the site-user manual available in the ISF.

4.1.3 Selection of doses in the trial

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

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

[REDACTED]

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 [REDACTED] 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 [REDACTED]

The current PK-PD modelling results [REDACTED]

[REDACTED]

The PK-PD modelling confirmed the conclusions of the clinical data that [REDACTED] mg provided optimal efficacy, defined at least [REDACTED] % of patients achieving PASI 90. Doses above [REDACTED] mg were also modelled and these results indicated [REDACTED] in the proportion of patients achieving PASI 90. [REDACTED]

[REDACTED]

The model was also used to examine alternative dosing regimens, [REDACTED]

[REDACTED]

[REDACTED]

Final Phase III Dose Selection

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.

[REDACTED]

Given that administration involving more than one injection on an ongoing basis could limit patient acceptability, modelling was used to predict PASI responses for a 150 mg dose administered at Weeks 0, 4 and every 12 weeks thereafter.

PK-PD analyses indicated no relevant reduction in efficacy when the dose was changed from 180 mg to 150 mg (based on interpolation). In summary, taking into consideration expert advisor recommendation and prescriber preferences, the proposed dosing for BI 650666 in the 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 150mg dose will be administered as two pre-filled syringes of 75 mg active drug each [REDACTED]

4.1.4 Drug assignment and administration of doses for each patient

An IRT will be used to allocate medication to patients through medication numbers. At visits where study medication is to be administered or to be dispensed to patients, study sites will be required to complete the medication resupply module in the IRT. These visits are specified in the [Flow Chart](#), see also [Fig. 3.1: 1](#))

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

Study drugs will be administered subcutaneously. Injections will be given in a double blind/dummy fashion with each patient receiving 2 injections of BI 655066 or matching placebo and 1 injection (2 injections only at randomisation) of comparator drug adalimumab or matching placebo. Adalimumab will be dosed and administered according to the prescribing information with a loading dose of 80mg at randomisation followed by a dose of 40mg at Week 1 and a dose of 40mg at every other week.

At Visit 2 (randomisation) study medication (2 injections BI 655066 or placebo and 2 injections adalimumab or placebo) will be administered by the investigator or authorized study personnel. It does not matter whether BI 655066 or adalimumab (active or placebo) will be administered first at Visit 2. The four injections should be administered within approximately 5 minutes.

At Visits 3 and 4 (Weeks 1 and 3) study medication (1 injection adalimumab or placebo) will be self-administered by the patient at the study site under supervision of study personnel. All

following adalimumab (active or placebo) injections (at weeks 5, 7, 9, 11, etc. with a time window of ± 3 days) will be self-administered by the patient at home. The study site should remind the patient by phone when each home administration is due. The patient is asked to record date and time of each home administration of adalimumab (active or placebo) in a paper diary.

At Visit 5 (Week 4), Visit 8 (Week 16), Visit 9 (Week 20), Visit 11 (Week 28) and Visit 12 (Week 32) the patient self-administers BI 655066 (active or placebo) at the study site under supervision of study personnel. The two injections at these dosing visits should be administered within approximately 5 minutes. The study personnel will complete a study drug self-administration questionnaire for the BI 655066 (active or placebo) self-administrations by patients (refer to [Section 5.6.2](#) and [Appendix 10.8](#)).

BI 655066 (active and matching placebo) as well as adalimumab (active or matching placebo) will be administered as a subcutaneous injection in the abdomen (preferably lower abdomen) or thigh. The two BI 655066 (active or matching placebo) injections done subsequently within approximately 5 minutes 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. Further information regarding injection details will be provided in the ISF. The dosing time to be entered in the eCRF is always the time of administration of the first syringe.

For study site visits, investigators and patients are instructed to adhere to the regular allowed time window according to the [Flow Chart](#) (i.e. ± 1 day at Visit 3; ± 3 days at Visits 4 to 14 and at EOT Visit; ± 7 days at EOO Visit). In the rare event that a patient comes too late to a scheduled visit it must be decided whether the delayed visit should still be performed or should be skipped. [Table 4.1.4: 1](#) shows the upper limits for extended time windows up to which study visits can still be performed

Table 4.1.4: 1 Upper Limits for extended time windows for study visits

Visit	Week	Scheduled Visit Day	Upper limit of delay (Days)	Upper limit (Day)
V3	Week 1	Day 8	+ 6	Day 14
V4	Week 3	Day 22	+ 6	Day 28
V5	Week 4	Day 29	+ 27	Day 56
V6	Week 8	Day 57	+ 27	Day 84
V7	Week 12	Day 85	+ 27	Day 112

Table 4.1.4: 1 Upper Limits for extended time windows for study visits (cont'd)

Visit	Week	Scheduled Visit Day	Upper limit of delay (Days)	Upper limit (Day)
V8*	Week 16	Day 113	+ 13	Day 126*
V9	Week 20	Day 141	+ 27	Day 168
V10	Week 24	Day 169	+ 27	Day 196
V11	Week 28	Day 197	+ 27	Day 224
V12	Week 32	Day 225	+ 27	Day 252
V13	Week 36	Day 253	+ 27	Day 280
V14	Week 40	Day 281	+ 27	Day 308

*if Day 126 is exceeded, Visit 8 (Week 16) will be performed, but patient will continue their previous treatment

There is an exception for Visit 8 (Week 16). This visit will not be skipped. If the upper limit of 126 days for Visit 8 (Week 16) is exceeded, Visit 8 will be performed, but the patient will continue with their previous treatment, irrespective of PASI score.

Adalimumab (active or placebo) home administrations should occur with a time window of ± 3 days. The distance between two adalimumab (active or placebo) administrations should not be less than 11 days. The time window of ± 3 days can be utilized for planning of home administrations. If the minimum distance of 11 days cannot be adhered to, the respective administration should be skipped and the next scheduled dose should be administered.

The injections at each visit, including dummy injections of placebo necessary in order to assure blinding are presented in [Table 4.1.4: 2](#).

Table 4.1.4: 2 Dosing Schedule

Dosing	Patients only on BI 655066**	Patients starting with adalimumab and switching to BI 655066** at Week 16	Patients only on Adalimumab
Randomisation (Visit 2)	Active BI 655066 and Placebo adalimumab*	Placebo 655066 and Active adalimumab*	Placebo 655066 and Active adalimumab*
Week 1 (Visit 3)	Placebo adalimumab	Active adalimumab	Active adalimumab

Table 4.1.4: 2 Dosing Schedule (cont'd)

Dosing	Patients only on BI 655066**	Patients starting with adalimumab and switching to BI 655066** at Week 16	Patients only on Adalimumab
Week 3 (Visit 4)	Placebo adalimumab	Active adalimumab	Active adalimumab
Week 4 (Visit 5)	Active BI 655066	Placebo 655066	Placebo 655066
Week 5	Placebo adalimumab	Active adalimumab	Active adalimumab
Week 7	Placebo adalimumab	Active adalimumab	Active adalimumab
Week 9	Placebo adalimumab	Active adalimumab	Active adalimumab
Week 11	Placebo adalimumab	Active adalimumab	Active adalimumab
Week 13	Placebo adalimumab	Active adalimumab	Active adalimumab
Week 15	Placebo adalimumab	Active adalimumab	Active adalimumab
Week 16 (Visit 8)	Active BI 655066	Active BI 655066	Placebo 655066
Week 17	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 19	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 20 (Visit 9)	Placebo 655066	Active BI 655066	Placebo 655066
Week 21	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 23	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 25	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 27	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 28 (Visit 11)	Active BI 655066	Placebo 655066	Placebo 655066
Week 29	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 31	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 32 (Visit 12)	Placebo 655066	Active BI 655066	Placebo 655066
Week 33	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 35	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 37	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 39	Placebo adalimumab	Placebo adalimumab	Active adalimumab
Week 41	Placebo adalimumab	Placebo adalimumab	Active adalimumab

- * Two injections adalimumab (active or placebo) only at Visit 2 (adalimumab loading dose is 80mg); one injection adalimumab (active or placebo) at Visits 3 and 4 and at all home administrations
- ** BI 655066 (active or placebo) always two injections (two injections à 75mg for active drug)

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after database lock.

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

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

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's drug safety group to access the randomisation code for individual patients during study conduct via the IRT system. In such cases, access to the code will only be permitted by authorised drug safety representatives. Refer to [Section 4.1.5.2](#) for rules of breaking the blinding code for an individual or for all patients in emergency situations

4.1.5.2 Unblinding and breaking the code

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

4.1.6 Packaging, labelling, and re-supply

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

For details of packaging and the description of the label, refer to the ISF.

4.1.7 Storage conditions

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

If the storage conditions are found to be outside the specified range, the sponsor must be contacted immediately. Refer to the ISF.

Trial medication must be securely stored, e.g. in a locked refrigerator or at a pharmacy. The medication may only be dispensed to trial patients according to the CTP by authorized personnel as documented in the trial staff list.

4.1.8 Drug accountability

Drug supplies will be provided by the sponsor.

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

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

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 have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

4.2.1 Rescue medication, emergency procedures, and additional treatments

There are no special emergency procedures to be followed.

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

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

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

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

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

Table 4.2.2.1: 1 Restricted medications

Medication or class of medications	Restriction duration (through EOO Visit)
Guselkumab, tildrakizumab	Not allowed neither before nor during trial participation
Briakinumab, secukinumab (Cosentyx®), ustekinumab (Stelara®)	6 months prior to randomisation
Brodalumab, ixekizumab	4 months prior to randomisation
Infliximab (Remicade®) Investigational products for psoriasis (non biologics)	12 weeks prior to randomisation
Etanercept (Enbrel®) Live virus vaccinations	6 weeks prior to randomization

Table 4.2.2.1: 1 Restricted medications (cont'd)

Medication or class of medications	Restriction duration (through EOO Visit)
Any investigational device or product (excludes psoriasis products) Other systemic immunomodulating treatments, e.g. methotrexate, cyclosporine A, corticosteroids ¹ , cyclophosphamide, tofacitinib (Xeljanz [®]), apremilast (Otezla [®]) Other systemic psoriasis treatments (e.g. retinoids, fumarates, any other drug known to possibly benefit psoriasis) Photochemotherapy (e.g., PUVA)	30 days prior to randomisation
Phototherapy (e.g., UVA, UVB) Topical treatment for psoriasis or any other skin condition (e.g. corticosteroids ² , vitamin D analogues, vitamin A analogues, pimecrolimus, retinoids, salicylvaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, andanthralin, α -hydroxy, fruit acids)	14 days prior to randomisation

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

² Exception: Topical steroids of US class 6 (mild, such as desonide) or US class 7 (least potent, such as hydrocortisone) for use on the face, axilla, and/or genitalia with a restriction of use within 24 hours prior to trial visit in which PASI is assessed.

4.2.2.2 Restrictions on diet and life style

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

4.2.2.3 Restrictions regarding women of childbearing potential

Female patients of childbearing potential should use the contraception methods described in [Section 3.3.2](#) and the patient information.

4.3 TREATMENT COMPLIANCE

Study medication will be administered in accordance with the protocol. At Visit 2 (randomisation) the study drugs will be administered by authorized study personnel (e.g. study nurse). At Visits 3 and 4 the adalimumab (active or placebo) injections will be self-administered by the patient under supervision of study personnel. Any further adalimumab administrations (active or placebo) will be self-administered by the patient at home. BI 655066 (active or placebo) will be self-administered by the patient under supervision of the

study personnel at Visit 5 (Week 4) and at any later visit with BI 655066 (active or placebo) administration.

The measured plasma concentrations will provide additional information about compliance. Any missed dose has to be documented. The study site should remind the patient by phone about the adalimumab (active or placebo) injections to be self-administered by the patient at home. The patient will record date and time of each home administration in a paper diary.

5. VARIABLES AND THEIR ASSESSMENT

5.1 TRIAL ENDPOINTS

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

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 chronic plaque psoriasis. These are as follows:

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

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

5.1.2 Secondary Endpoint(s)

Key Secondary Endpoints:

The key secondary endpoints are as follows:

- Achievement of $\geq 75\%$ 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 $\geq 90\%$ reduction from baseline PASI score (PASI 90) at Week 44 for those patients who are re-randomized at Week 16

Other Secondary Endpoints:

The other secondary endpoints are as follows:

- Achievement of an sPGA score of clear or almost clear (0 or 1) at Week 44
- Achievement of sPGA score of clear (0) at Week 44

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, PASI 100 and sPGA 0 or 1
- Time until loss of PASI 75, PASI 90, PASI 100 and sPGA 0 or 1 response

- Change and percent change from baseline in PASI at all visits collected
- Absolute PASI score 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
- 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 WLQ at all visits collected
- 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
- Response to individual questions on the self-administration questionnaire at each visit where BI 655066 active or placebo is self-administered
- Change of metabolic risk factors from baseline (waist circumference, body weight, HOMA-index)

5.2 ASSESSMENT OF EFFICACY

- The skin condition will be assessed by using the PASI, sPGA, and other relevant scores as described in [section 5.1.1](#) and the ISF.
- Symptoms, quality of life, and physical function will be assessed by the DLQI and the WLQ.

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 assessed by Rheumatology Common Toxicity Criteria (RCTC) version 2.0 (refer to ISF for details).
- Physical examination
- Vital signs
- 12-lead ECG
- Local tolerability

5.3.1 Physical examination

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

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

5.3.1.1 Waist circumference

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

5.3.1.2 Body weight

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

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

5.3.2 Vital Signs

Vital signs evaluations will be performed at visits as shown in the [flow chart](#). This includes temperature, pulse rate, systolic/diastolic blood pressure and respiratory rate. Respiratory rate, pulse rate, and blood pressure will be measured after patients have been sitting comfortably for at least five minutes. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements. At dosing visits vital signs evaluations will be performed pre-dose and at Visit 2 and Visit 5 additional measurements will be performed approximately 5 minutes post-dose (5 min. after last injection) and approximately 60 minutes post-dose (60 min. after last injection).

Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at the Randomization Visit and for approximately 1 hour after the last injection at all other visits with drug administration. Hypersensitivity reactions should be treated according to medical standards. Pre-medications for further injections might be considered and will be agreed on between investigator and BI clinical monitor.

5.3.3 Safety laboratory parameters

The laboratory tests listed in [Table 5.3.3: 1](#) will be performed at the central laboratory service provider. Local laboratory may be used for selected tests in exceptional cases. Patients should be fasting for at least 8 hours prior to the blood sample being taken (except Screening Visit).

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF. For time points of laboratory sampling, see [Flow Chart](#).

Laboratory results (i.e. all safety laboratory and clinical laboratory data relevant for current clinical practice) of the patients will be available in real time to the respective investigator (via laboratory reports) and to the sponsor (via the central laboratory website) and selected abnormal laboratory alerts will be flagged to the site and sent to sponsor in real time.

Clinically relevant abnormal findings will be reported as baseline conditions or AEs. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be confirmed using an unscheduled visit laboratory kit and should be repeated until normalization or stabilization or until an alternative explanation has been found. Abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria ([R13-3515](#)).

Table 5.3.3: 1 Laboratory tests

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

Table 5.3.3: 1 Laboratory tests (cont'd)

Category	Test name
Enzymes	AST(GOT) ALT(GPT) Alkaline Phosphatase (AP) Creatine Kinase (CK) CK-MB, only if CK is elevated Gamma-Glutamyl Transferase (GGT/ γ -GT) Lactic Dehydrogenase (LDH) Amylase Lipase
Electrolytes	Calcium Sodium Potassium Chloride Bicarbonate
Substrates	Glucose BUN (blood urea nitrogen) Uric acid Creatinine eGFR (estimated by CKD-EPI formula) Bilirubin Total Bilirubin Direct (if total is elevated) Bilirubin Indirect (if total is elevated) Troponin I (reflex when CK is elevated) Albumin C-Reactive Protein (high sensitive) Cholesterol, total Triglycerides LDL-Cholesterol (calculated by Friedewald formula) HDL-Cholesterol HOMA-IR (only at Visit 2, Visit 8, and EOT Visit)
Urine Pregnancy test (only for female patients of childbearing potential) at randomization and continued as indicated in the Flow Chart (including EOT and EOO Visit) (test done in clinic)	Human Chorionic Gonadotropin in the urine (Dipstick not performed at central lab)
Serum Pregnancy test (only for female patients of childbearing potential) at screening and if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin (quantitative)
Hormones (only at screening)	TSH, (free T3 and free T4 in case of abnormal TSH results)

Table 5.3.3: 1 Laboratory tests (cont'd)

Category	Test name
Autoantibodies (only at screening)	Rheumatoid Factor
Urinalysis (dipstick)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH
Urine-Sediment (microscopic examination, only if urine analysis abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epithelial Cells Urine Sed. Crys., Unspecified Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes
Urine	Albumin (quantitative) Creatinine Albumin/creatinine ratio
Infections screening (only at screening and EOT Visit)	Hepatitis B Surface Antigen (qualitative) Hepatitis C Antibodies (qualitative) HIV-1, and HIV-2 Antibody (qualitative) QuantiFERON®-TB ¹

¹ There is the trial 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](#).

ECGs will be recorded after the patients have rested for at least 5 minutes in a supine position and will always precede blood sampling. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six pre-cordial leads (V1–V6), according to Wilson, will be used.

ECGs may be repeated for quality reasons and the repeat used for analysis. Additional ECGs may be collected for safety reasons. Clinically relevant, abnormal findings will be reported as AEs.

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

ECGs will be read and evaluated by a central vendor. The study site will be informed about the results of the assessment of the ECG obtained at screening and if there are findings that would exclude the patient from study participation according to exclusion criterion #9.

The electronic version of the ECG is regarded as source data. Dated and signed printouts will be stored in the patient's medical file.

5.3.5 Other safety parameters

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

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

Adverse event

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

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

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.

Every new occurrence of cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be

considered to be “serious” even though they may not have met the criteria of an SAE as given above.

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

Adverse events of special interest (AESIs)

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESI need to be reported to the Sponsor’s Pharmacovigilance Department within the same timeframe that applies to SAE, see [Section 5.3.7](#).

The following are considered as AESIs:

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

- an elevation of AST and/or ALT ≥ 3 fold ULN combined with an elevation of total bilirubin ≥ 2 fold ULN measured in the same blood draw sample, and/or
- marked peak aminotransferase (ALT, and/or AST) elevations ≥ 10 fold ULN

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the “DILI checklist” provided in the ISF and the RDC-system.

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

Intensity of AEs

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

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

Causal relationship of AEs

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

Yes: There is a reasonable causal relationship between the trial medication administered and the AE.

No: There is no reasonable causal relationship between the trial medication administered and the AE.

5.3.7 Adverse event collection and reporting

AE Collection

The following must be collected and documented on the eCRF by the Investigator (see [Figure 5.3.7: 1](#))

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

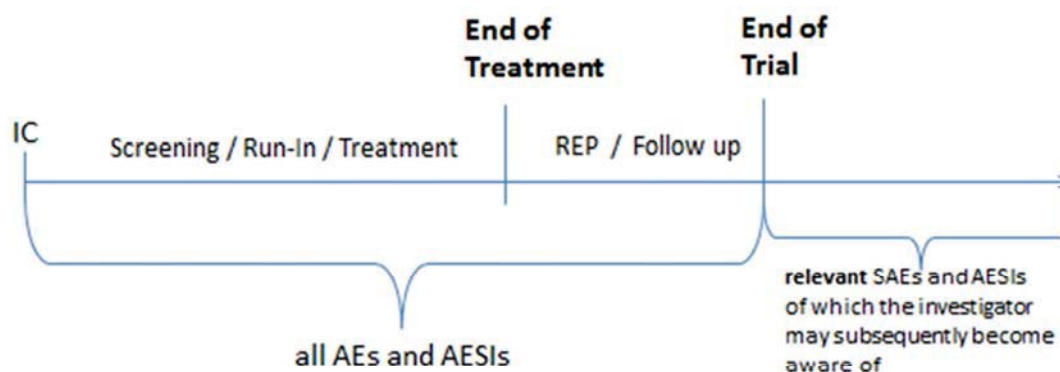


Figure: 5.3.7: 1 Adverse Events Collection

The REP is defined as 15 weeks after the last administration of BI 655066 (active or placebo). All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see [Section 7.3.4](#). Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines

The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the Sponsor's unique entry point (country specific contact details will be provided in the ISF).

The same timeline applies if follow-up information becomes available. In specific occasions the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

Information required

For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, e.g. onset, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug(s). The Investigator should determine the causal relationship to the trial medication.

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

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

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

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

Pregnancy

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

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

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

If a patient becomes pregnant during a trial, the study medication needs to be discontinued, and the patient will complete end of treatment as well as follow-up procedures.

The 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 [Flow Chart](#) for the time points of PK and ADA sample collection. Date and exact time of drug administration and PK and ADA sampling will be recorded on eCRFs. These actual administration and sampling times will be used for determination of PK parameters. On visits with study medication dosing, PK and ADA sampling should be collected prior to administration of study drug.

After completion of the study (i.e., clinical trial report archived), PK and ADA plasma samples may be used for further methodological investigations (e.g., stability testing).

5.4.2 Methods of sample collection

5.4.2.1 Plasma sampling for pharmacokinetic analysis

For quantification of BI 655066 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 assessment.

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.

5.5 ASSESSMENT OF EXPLORATORY BIOMARKERS

5.5.1 Skin biopsy assessment

Skin biopsies will be collected in a subset of patients at selected study sites to assess changes in gene and protein expression levels over time by treatment group. Biopsies are planned to be collected from approximately 75 patients. The biomarkers planned to be assessed by immunohistochemistry may include but not be limited to K16, Ki67 (on keratinocytes), S100 A7 (on keratinocytes), lipocalin-2 (NGAL), β -defensin 2, CD3+ T lymphocytes, CD11+ and DC lamp (Dendritic Cells). Dermal and epidermal tissue will be evaluated. In addition, in situ hybridization analyses to identify changes in the proportion of select T cell sub-populations will be determined using expression of specific biomarkers (ie IL-23R on T17 cells and Fox P3 on T reg cells). RNA sequencing profiling of the skin biopsies will also be assessed to link changes in select pathways associated with IL-23 blockade and changes in the T cell sub-populations.

5.5.1.1 Methods of sample collection

Skin biopsies will be performed at time points outlined in the [Flow Chart](#) and should be collected prior to administration of study drug at dosing visits. Participation of patients in skin biopsies requires their separate informed consent. At Visit 2 both non-lesional and lesional skin biopsies will be collected and at Visit 7 only lesional skin biopsies will be collected. Refer to ISF (Laboratory Manual) for biopsy, sample preparation and shipment instructions.

5.5.1.2 Analytical determinations

Immunohistochemistry will be performed as described in [Section 5.5.1](#). RNA will be extracted from skin biopsies according to standard molecular genetics methods and analysed by RNA sequencing, TaqMan[®] or other standard gene expression technologies.

5.5.2 Assessment of soluble protein biomarkers

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 over time by treatment group. Additionally, changes in levels of biomarkers related to metabolic syndrome such as leptin, resistin, TNF α , IL-6 and VEGF will be explored.

5.5.2.1 Methods of sample collection

Approximately 12.5 ml of blood will be collected at time points indicated in the [Flow Chart](#). Samples should be collected prior to administration of study drug at dosing visits. For details on sample handling and logistics refer to the ISF (Laboratory Manual).

5.5.2.2 Analytical determinations

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

5.5.3 Biomarker sample banking

After completion of the study any unused serum and tissue samples collected for biomarker sampling as listed in [Section 5.5.1](#) and [5.5.2](#) may be used for further investigations (e.g. additional biomarkers for immunological & inflammatory diseases), if participation and the informed consent for biomarker sample banking is agreed upon by the patient.

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

5.5.4 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.

5.5.4.1 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).

5.5.4.2 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 Strasse 65, in 88397 Biberach, Germany). The stored DNA may be retrospectively analysed, e.g. to identify whether there are other genetic factors that could contribute to a better therapeutic outcome or a higher risk of developing treatment-related adverse drug reactions.

5.6 OTHER ASSESSMENTS

5.6.1 Quality of Life Questionnaires DLQI and WLQ

Dermatology Life Quality Index (DLQI) and Work Limitations Questionnaire (WLQ) are questionnaires self-administered by patients at Visits 2, 8 and EOT. DLQI and WLQ will be used to assess quality of life, overall health and disability status, as well as work limitations (see [Appendix 10.6](#) and [10.7](#)).

5.6.2 Study drug self-administration questionnaire

At study visits with self-administration of BI 655066 drug (active or placebo) by patients the trial site completes a questionnaire. This occurs at Visits 5, 8, 9, 11 and 12. The questionnaire captures information whether the patient did the injections of BI 655066 drug (active or placebo) correctly or not (see [Appendix 10.8](#)).

5.6.3 Health Care Resource Utilization (HCRU) Questionnaire

For the purpose of a separate health economic analysis (such as cost-utility analysis), HCRU data will be collected at visits shown in the [Flow Chart](#). Resource use data collected for calculating direct costs will include hospitalisations, unscheduled outpatient or home visits and emergency room visits. The economic evaluation of the HCRU data will not be part of the Clinical Trial Report, but reported separately.

5.7 APPROPRIATENESS OF MEASUREMENTS

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

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

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the [Flow Chart](#) and the respective protocol sections. Refer to [Section 5](#) and the [Appendix Section 10](#) for explanations of procedures. Additional details on procedures at selected visits are provided below.

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

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

The quality of life questionnaires (DLQI and WLQ) are self-administered by the patient using an electronic device. Also the Questionnaires to be completed by study site personnel (PASI, sPGA, NAPSI, PPASI, PSSI, HCRU, and the BI 655066 (active or placebo) self-administration questionnaire) will be completed using an electronic device, after the DLQI and WLQ have been completed by the patient. All questionnaires are detailed in [Appendix 10](#).

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. A separate informed consent is required for optional study procedures which are DNA banking from blood samples, biomarker serum sample banking, skin biopsies and biomarker tissue sample banking from skin biopsies.

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 the eCRF pages.

Screening (Visit 1) should normally take place no more than 42 days before Visit 2 and be completed no less than 7 days prior to Visit 2. Screening procedures may be extended to more than 1 physical visit, if needed.

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

For the comprehensive list of the trial procedures required at the Screening Visit (Visit 1) please refer to [flow chart](#).

Infection screening

[See table 5.3.3: 1](#) for the list of infection screening tests that will be performed to verify exclusion criteria. Instructions regarding sample collection, sample handling/processing and sample shipping are provided in the Laboratory Manual in the ISF. See exclusion criteria [Section 3.3.3](#) with study participation directive for patients with a positive QuantiFERON® or PPD skin test for TB.

Demographics

Informed consent date, HIPAA status (US patients only), sex, ethnicity and race (if allowed by local law) will be collected and reported in the eCRF. The patient's smoking and alcohol history will also be assessed.

Medical History

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

Baseline Conditions

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

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 is from Visit 2 to End of Treatment (EOT) Visit.

Safety laboratory testing

Visits 2, 5, 8, 11, EOT and EOO should be performed in fasted state (8 hours no food and only water). This is not necessary at the Screening Visit. 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 child-bearing potential will be conducted on-site approximately every four weeks and must be negative to further treat the patient. The pregnancy testing should be done prior to administration of study drug. A positive urine test must be confirmed with a serum pregnancy test.

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

Skin biopsies should be collected prior to administration of study drug at dosing visits.

Venipuncture (i.e. safety laboratories, PK, ADA, biomarkers) should be the last procedure prior to any study drug administration. On dosing visits PK and ADA samples should be taken approximately within 1 hour prior to administration of study drug.

Patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 2 hours after the last injection at the Randomization Visit (Visit 2) and approximately 1 hour after the last injection at all other drug administration.

6.2.3 Follow Up Period and Trial Completion

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

6.2.3.1 Early treatment and trial termination

If study medication is discontinued prior to the planned [Flow Chart](#) visit EOT, every effort should be made to have the patient continue in the trial and complete all of the remaining trial visits and procedures including EOT and EOO Visit; with the EOO Visit to be performed 4 weeks after the EOT Visit.

If a patient cannot or will not continue in the trial, the patient should complete EOT Visit procedures instead of the next planned treatment period visit. These patients should be registered as prematurely discontinued in IRT and return to the clinic for End of Observation Visit 16 (± 1) weeks after their last administered dose of BI 655066 (active or placebo). Patients who discontinue from the trial prematurely will not have the option to participate in the open label extension (OLE) study.

6.2.3.2 Trial completion

Patients who complete the randomized treatment period and who qualify for the open-label extension (OLE) study will continue treatment with active BI 655066 and therefore will not have a Follow-up Visit in study 1311.30.

6.2.3.3 Vital Status

Randomised patients who do not participate in the OLE study and who withdraw from the study prior to their planned EOO Visit will be contacted for their vital status assessment

(alive / dead / lost to follow-up). In case the patient died, an SAE form should be completed by the site and forwarded immediately to the sponsor. Vital status assessment should occur at 48 (\pm 1) weeks after randomisation.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a confirmatory, multicenter, randomized, double-blind and active comparator controlled 44 week study evaluating the efficacy and safety of BI 655066 in patients with moderate to severe chronic plaque psoriasis. The primary objective of this trial is to assess the safety and efficacy of BI 655066 in comparison to adalimumab in patients with moderate to severe chronic plaque psoriasis. The primary efficacy evaluation will be assessed at 16 weeks comparing treatment with BI 655066 to adalimumab. The study will also evaluate the efficacy of treatment with BI 655066 following insufficient or only partial response with adalimumab.

Baseline refers to the measurement recorded at randomisation (Visit 2); if data at Visit 2 is missing, then data from Visit 1 will be considered baseline. The percent reduction from baseline is calculated by % PASI reduction from baseline = $((\text{PASI at baseline} - \text{PASI at Visit X}) / \text{PASI at baseline}) * 100$, at all follow up visits. Achieving an x% or larger reduction from baseline PASI score is denoted as PASI X.

Randomization 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.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary hypotheses are that BI 655066 is different than adalimumab in achieving $\geq 90\%$ reduction from baseline in the Psoriasis Area and Severity Index score (PASI 90) and sPGA score of clear(0) or almost clear(1) at Week 16 in participants with moderate to severe chronic plaque psoriasis. For the primary analyses, this study has 2 treatment arms (BI 655066 and adalimumab [refer to [Figure 3.1: 1](#)]).

- Arm 1 – Patients randomised at Visit 2 to receive 150mg BI 655066 at Randomisation (Visit 2), Week 4 and then q12 weeks
- Arm 2 – Patients randomised at Visit 2 to receive 80mg adalimumab at Randomisation (Visit 2) and then 40mg adalimumab at Week 1 and then every other week

For the second part of the trial, patients randomised to receive adalimumab at Visit 2 and achieve a PASI 50 response but not PASI 90 at Week 16 will be re-randomised to one of the following treatment arms:

Arm A – Patients re-randomised to receive BI 655066 during the remaining treatment period of the trial

Arm B – Patients re-randomised to continue to receive adalimumab during the remaining treatment period of the trial

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

1. BI 655066 arm (Arm 1) is not different from adalimumab (Arm 2) with respect to PASI 90 or sPGA score of clear or almost clear (0 or 1) response at Week 16
2. BI 655066 arm (Arm 1) is not different from adalimumab (Arm 2) with respect to PASI 75 response at Week 16
3. BI 655066 arm (Arm 1) is not different from adalimumab (Arm 2) with respect to PASI 100 response at Week 16

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

- BI 655066 arm (Arm A) is not different from adalimumab (Arm B) with respect to PASI 90 response at Week 44 for patients who are re-randomized at Week 16.

7.3 PLANNED ANALYSES

The efficacy analyses will be based on the intent-to-treat principle, comprising all participants who were randomised and received at least one dose during the trial. 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 randomization); this set of patients is called the Full Analysis Set (FAS). Safety analyses will be based on the actual treatment received at the Randomization Visit; this set of patients is called the Safety Set (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 the patients included in the Week 44 assessment of re-randomization. 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 PASI 90 at Week 16 is the first co-primary endpoint and is a binary variable with values of 0 or 1. The difference in proportion responding between the BI 655066 arm and the adalimumab 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:

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

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

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

x_i denotes the number of patients with event in treatment₁ in stratum $i, i = 1, \dots, u$

y_i denotes the number of patients with event in treatment₂ in stratum $i, i = 1, \dots, u$

n_i denotes the number of patients on treatment₁ in stratum $i, i = 1, \dots, u$

m_i denotes the number of patients on treatment₂ in stratum $i, i = 1, \dots, u$

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

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

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

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:

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

If there is a stratum for a treatment group that has 0 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. Comparisons of the BI 655066 arm and adalimumab arm will include both a p-value and 95% confidence interval.

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

7.3.2 Secondary endpoint analyses

Key secondary endpoints:

The achievement of PASI 75 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 PASI 90 co-primary endpoint detailed in the [Section 7.3.1](#).

The achievement of PASI 100 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 PASI 90 co-primary endpoint detailed in the [Section 7.3.1](#).

The achievement of PASI 90 at Week 44 is a binary variable with values of 0 or 1. The analysis of this endpoint will be identical to that of the PASI 90 co-primary endpoint detailed in the [Section 7.3.1](#). Note that this endpoint will only be analysed for patients who are re-randomized at Week 16 (i.e., only for Arm A and Arm B defined in [Section 7.2](#)).

Other secondary endpoints:

Other secondary endpoints will be summarized descriptively.

7.3.3 Further endpoint analyses

Further endpoints will be summarized descriptively, with number and proportion of responders for dichotomous endpoints and mean, median, SD and IQR presented for continuous variables.

Time to onset of *Endpoint*. The time to event will be calculated as:

- Time to first onset (with observed event) = [date of first onset] – [date of first active treatment] + 1
- If a patient never attains *Endpoint* (e.g. PASI 75 or PASI 90), then that patient's time to first onset will be censored at the last visit where the *Endpoint* was measured (e.g. PASI).

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

- a) Never attains *Endpoint* (Failure at time 0)
- b) After achieving *Endpoint*, patient will be a failure if they subsequently do not achieve *Endpoint* and either discontinue from the study or switch therapy while still not achieving *Endpoint*. Time to failure will be calculated using date of first failure to achieve *Endpoint*.
- c) Patients that take prohibited meds to treat Psoriasis will be counted as failures at the time when they add the prohibited med.
- d) Patients that switch therapy while maintaining response will be censored at their last measurement prior to switching 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. If needed, further information will be provided in the TSAP.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard AbbVie summary tables and listings will be produced. All adverse events with an onset between start of treatment and end of the residual effect period (REP), a period of 15 weeks after the last administration of BI 655066 (active or placebo), will be assigned to the treatment period for evaluation.

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

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 15 weeks. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

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

7.3.5 Pharmacokinetic analyses

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

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

7.3.6 Pharmacodynamic analyses

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

7.3.7 Biomarker analyses

Changes in serum protein, tissue protein and RNA biomarker levels over time will be described by treatment group. The details of these analyses will be included in the TSAP.

7.4 INTERIM ANALYSES

No interim analysis is planned for this study.

7.5 HANDLING OF MISSING DATA

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

The following rules will be used to impute for missing data:

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

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

Missing items from the Quality of Life questionnaires will be handled according to the measure instructions (cf. [Appendix 10.6](#) and [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:

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

7.6 RANDOMISATION

At Visit 2, patients will be randomized in blocks to double-blind treatments, stratified by weight (≤ 100 kg vs. >100 kg) and prior exposure to TNF antagonists (0 vs. ≥ 1). Patients will be randomized to BI 655066 or adalimumab in a ratio of 1:1 within each level of stratification.

Patients originally randomized to BI 655066 150mg will stay on BI 655066 150mg. Patients who are originally randomized to adalimumab will be separated into three groups at Week 16 depending on their Week 16 PASI score. Patients will be switched to BI 655066 if they don't achieve PASI 50 at Week 16. Patients will continue on adalimumab if they achieve PASI 90 at Week 16. Patients will be re-randomized in a 1:1 ratio to either BI 655066 or adalimumab in a second double-blinded portion of the trial if they achieve PASI 50 but not PASI 90 at Week 16.

BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization lists will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block sizes will be documented in the CTR. Access to the codes will be controlled and documented.

7.7 DETERMINATION OF SAMPLE SIZE

This study is designed to show a benefit of BI 655066 over adalimumab in terms of PASI 90 response and sPGA scores of clear or almost clear at Week 16. This study is also powered to show a benefit in PASI 90 response at Week 44 between the patients randomized to continue on adalimumab vs patients randomized to BI 655066 at Week 16.

Based on the assumption that the Week 44 PASI 90 rate will be approximate 40% for adalimumab and 70% for BI 655066 for the patients who are re-randomized at Week 16, a total of 120 patients will result in $>90\%$ power for the key secondary objective of the trial using a type-I error rate at 5%. See [Table 7.7: 1](#) sample size calculations for different scenarios. Assuming for those patients originally randomized to adalimumab the response rate at Week 16 for PASI 90 and PASI 50 are 45% and 85%, respectively, then this leaves approximately 40% of patients expected to fall in the more than or equal to PASI 50 and less than PASI 90 range and thus be eligible for re-randomisation. This requires that 300 (40% of 300 = 120) patients be randomized to adalimumab at Randomisation.

Based on the outcome from the trials 1311.1 and 1311.2, the PASI 90 response rate at Week 16 is assumed to be at least 65% in the BI 655066 arm. For the primary analysis comparing BI 655066 to adalimumab, sample sizes of 300 per arm will allow for $> 90\%$ power assuming 70% and 50% PASI 90 response rates for BI 655066 and adalimumab, respectively. See [Table 7.7: 2](#) for more sample size calculations.

Table 7.7: 1 Sample sizes for 90% power for testing against adalimumab using PASI 90 at re-randomization

BI 655066 rate	adalimumab rate	Delta	Re-randomisation ratio BI 655066: adalimumab = Total N
65%	40%	25%	82:82 = 164
70%	45%	25%	80:80 = 160
70%	40%	30%	56:56 = 112
75%	45%	30%	54:54 = 108
80%	50%	30%	51:51 = 102

Table 7.7: 2 Sample sizes for 90% power for testing against adalimumab using PASI 90

BI 655066 rate	adalimumab rate	Delta	Randomisation ratio BI 655066: adalimumab = Total N
65%	50%	15%	226:226 = 452
70%	55%	15%	217:217 = 434
70%	50%	20%	124:124 = 248
75%	55%	20%	118:118 = 236
70%	45%	25%	80:80 = 160
75%	50%	25%	77:77 = 154

Based on the outcome from the trials 1311.1 and 1311.2, the achievement of sPGA clear or almost clear rate at Week 16 is assumed to be at least 85% in the BI 655066 arm. Assuming 70% rate for the adalimumab arm, by using the PASI 90 required sample sizes, 300 patients per treatment arm will provide at least 90% power for sPGA endpoint. See [Table 7.7. 3](#) for more sample size calculation.

As PASI 90 and sPGA are highly correlated, this trial will have >90% power for comparing BI 655066 arm to adalimumab arm on both of these endpoints.

Table 7.7. 3 Sample sizes for 90% power for testing against adalimumab using sPGA clear or almost clear

BI 655066 rate	adalimumab rate	Delta	Randomisation ratio BI 655066: adalimumab = Total N
85%	72.5%	12.5%	223:223 = 446
85%	70%	15%	161:161 = 322
87.5%	72.5%	15%	148:148 = 296
87.5%	70%	17.5%	113:113 = 226

Calculations were performed using ADDPLAN Version 6.0.4.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), and relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The Investigator will inform the Sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

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

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

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

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

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

Re-consenting may become necessary when new relevant information becomes available and should be conducted according 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

Electronic Case Report Forms (eCRF) for individual patients will be provided by the Sponsor. See [Section 4.1.5.2](#) for rules about emergency code breaks. For drug accountability, refer to [Section 4.1.8](#).

8.3.1 Source documents

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

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

For eCRFs all data must be derived from source documents.

8.3.2 Direct access to source data and documents

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

An adaptive approach to clinical trial monitoring will be 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 subject safety and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any monitoring adaptations.

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 BI 655066 this is the current version of the Investigator's Brochure ([c02161217-10](#)). For adalimumab this is the United States Product Information (US PI).

The current versions of these reference documents are provided in the ISF.

8.4.2 Expedited reporting of Adverse Events

BI is responsible to fulfil their legal regulatory reporting obligation and in accordance to the requirements defined in this CTP.

8.5 STATEMENT OF CONFIDENTIALITY

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 detailed 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.

9. REFERENCES

9.1 PUBLISHED REFERENCES

- R02-0127 Zigmund AS, Snaith RP. The Hospital Anxiety and Depression scale. *Acta Psychiatr Scand* 1983. 67:361-370.
- R05-2548 Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) - a simple practical measure for routine clinical use. Joint Ann Mtg of the British Association of Dermatologists and the Canadian Dermatology Association, Oxford, 6 - 10 Jul 1993 *Clin Exp Dermatol* 1994. 19:210-216.
- R07-1226 Herrmann C. International experiences with the Hospital Anxiety and Depression Scale - a review of validation data and clinical results. *J Psychosom Res* 1997. 42(1):17-41.
- R08-1089 Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature* 2007; 445(7130):866-873.
- R11-1257 Nestle FO, Kaplan DH, Barker J. Mechanisms of disease: psoriasis. *N Engl J Med* 2009; 361(5):496-509.
- R11-1259 Menter A, Griffiths CEM. Psoriasis 2: current and future management of psoriasis. *Lancet* 2007; 370:272-284.
- R11-1547 Smith RLI, Warren RB, Eyre S, Ho P, Ke X, Young HS, Griffiths CEM, Worthington J. Polymorphisms in the IL-12beta and IL-23R genes are associated with psoriasis of early onset in a UK cohort. *J Invest Dermatol* 2008. 128:1325-1327.
- R13-3515 Woodworth T, Furst DE, Alten R, Bingham C, Yocum D, Sloan V, Tsuji W, Stevens R, Fries J, Witter J, Johnson K, Lassere M, Brooks P. Standardizing assessment and reporting of adverse effects in rheumatology clinical trials II: the Rheumatology Common Toxicity Criteria v.2.0. *J Rheumatol* 2007. 34(6):1401-1414.
- R14-3559 Revicki DA, Jin Y, Wilson HD, Chau D, Viswanathan HN. Reliability and validity of the psoriasis symptom inventory in patients with moderate-to-severe psoriasis. *J Dermatol Treat* 2014. 25(1):8-14.
- R14-3562 Bushnell DM, Martin ML, McCarrier K, Gordon K, Chiou CF, Huang X, Ortmeier B, Kricorian G. Validation of the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure to assess psoriasis symptom severity. *J Dermatol Treat* 2013. 24(5):356-360.

- R14-5159 Reich K, Puig L, Paul C, Kragballe K, Luger T, Lambert J, Chimenti S, Girolomoni G, Nicolas JF, Rizova E, Brunori M, Mistry S, Bergmans P, Barker J, TRANSIT Investigators. One-year safety and efficacy of ustekinumab and results of dose adjustment after switching from inadequate methotrexate treatment: the TRANSIT randomized trial in moderate-to-severe plaque psoriasis. *Br J Dermatol* 2014. 170(2):435-444.
- R15-1219 Martin ML, McCarrier KP, Chiou CF, Gordon K, Kimball AB, Voorhees AS van, Gottlieb AB, Huang X, Globe D, Chau D, Viswanathan HN, Kricorian G. Early development and qualitative evidence of content validity for the Psoriasis Symptom Inventory (PSI), a patient-reported outcome measure of psoriasis symptom severity. *J Dermatol Treat* 2013. 24(4):255-260.
- R15-1393 Davidovici BB, Sattar N, Joerg PC, Puig L, Emery P, Barker JN, Kerkhof P van de, Stahle M, Nestle FO, Girolomoni G, Krueger JG, Psoriasis Education and Learning Syllabus (PEARLS). Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. *J Invest Dermatol* 2010. 130(7):1785-1796.
- R15-3846 Bruce B, Fries JF. The Stanford Health Assessment Questionnaire: a review of its history, issues, progress, and documentation. *J Rheumatol* 2003. 30(1):167-178.
- R15-3848 Lerner D, Amick BC, Rogers WH, Malspeis S, Bungay K, Cynn D. The work limitations questionnaire. *Med Care* 2001. 39(1):72-85.
- R15-3849 The Health Assessment Questionnaire (HAQ) and the improved HAQ (formerly called the PROMIS HAQ) (revised June 2009). [http://aramis.stanford.edu/downloads/HAQ%20Instructions%20\(ARAMIS\)%2006-30-09.pdf](http://aramis.stanford.edu/downloads/HAQ%20Instructions%20(ARAMIS)%2006-30-09.pdf) (access date: 15 July 2015) ; Stanford: Stanford University School of Medicine, Division of Immunology & Rheumatology 2009.
- R15-3850 Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *J Psychosom Res* 2002. 52(2):69-77.
- R15-3862 Langley RG, Feldman SR, Han C, Schenkel B, Szapary P, Hsu MC, Ortonne JP, Gordon KB, Kimball AB. Ustekinumab significantly improves symptoms of anxiety, depression, and skin-related quality of life in patients with moderate-to-severe psoriasis: results from a randomized, double-blind, placebo-controlled phase III trial. *J Am Acad Dermatol* 2010. 63(3):457-465.
- R15-5200 Langley RGB, Feldman SR, Nyirady J, Kerkhof P van de, Papavassilis C. The 5-point Investigator's Global Assessment (IGA) scale: a modified tool for evaluating plaque psoriasis severity in clinical trials. *J Dermatol Treat* 2015. 26(1):23-31.

- R16-2653 Tuong W, Armstrong AW. Scalp Psoriasis: Clinical Features and Assessment, In: Adebajo A, Boehncke WH, Gladman DD, Mease PJ, editors. Psoriatic Arthritis and Psoriasis: Pathology and Clinical Aspects. Cham: Springer, 139 – 141 (2016)
- R16-2654 Rich P, Scher RK. Nail Psoriasis Severity Index: A useful tool evaluation of nail psoriasis. J AM Acad Dermatol 49 (2), 206 – 212 (2003)
- R96-3541 Fredriksson T, Pettersson U. Severe psoriasis - oral therapy with a new retinoid. Dermatologica 1978; 157:238-244.

9.2 UNPUBLISHED REFERENCES

- c02161217-10 Investigator's Brochure BI 655066, Psoriasis, Crohn's Disease, Ankylosing Spondylitis, Asthma, Psoriatic Arthritis
1311.P1/1311.P2/1311.P3/1311.P4/1311.P5.
- c02434648 Summary report of analysis, Trial 1311.1. 26 Mar 2015.
- c03272682-01 Summary report of interim analysis at Week 48, Trial 1311.2. 05 May 2015.

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

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

To calculate the PASI, 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:

$$\text{PASI} = 0.1(\text{Eh}+\text{Ih}+\text{Dh})\text{Ah} + 0.3(\text{Et}+\text{It}+\text{Dt})\text{At} + 0.2(\text{Eu}+\text{Iu}+\text{Du})\text{Au} + 0.4(\text{El}+\text{Il}+\text{Dl})\text{Al}$$

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 patient's disease state at the time of the assessments, without comparison to any of the subject's previous disease states, whether at Baseline or at a previous visit. A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

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

Erythema

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

Induration (plaque elevation)

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

Scaling

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

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

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

Table 10.2: 1 sPGA Rating Scale for Overall Psoriatic Disease

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

10.3 NAIL PSORIASIS SEVERITY INDEX (NAPSI)

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 PALMOPLANTAR PSORIASIS SEVERITY INDEX (PPASI)

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 DERMATOLOGY LIFE QUALITY INDEX (DLQI)

The DLQI is a subject-administered, ten-question, quality of life questionnaire that covers six domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment ([R05-2548](#)). The DLQI has a one-week recall period. 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

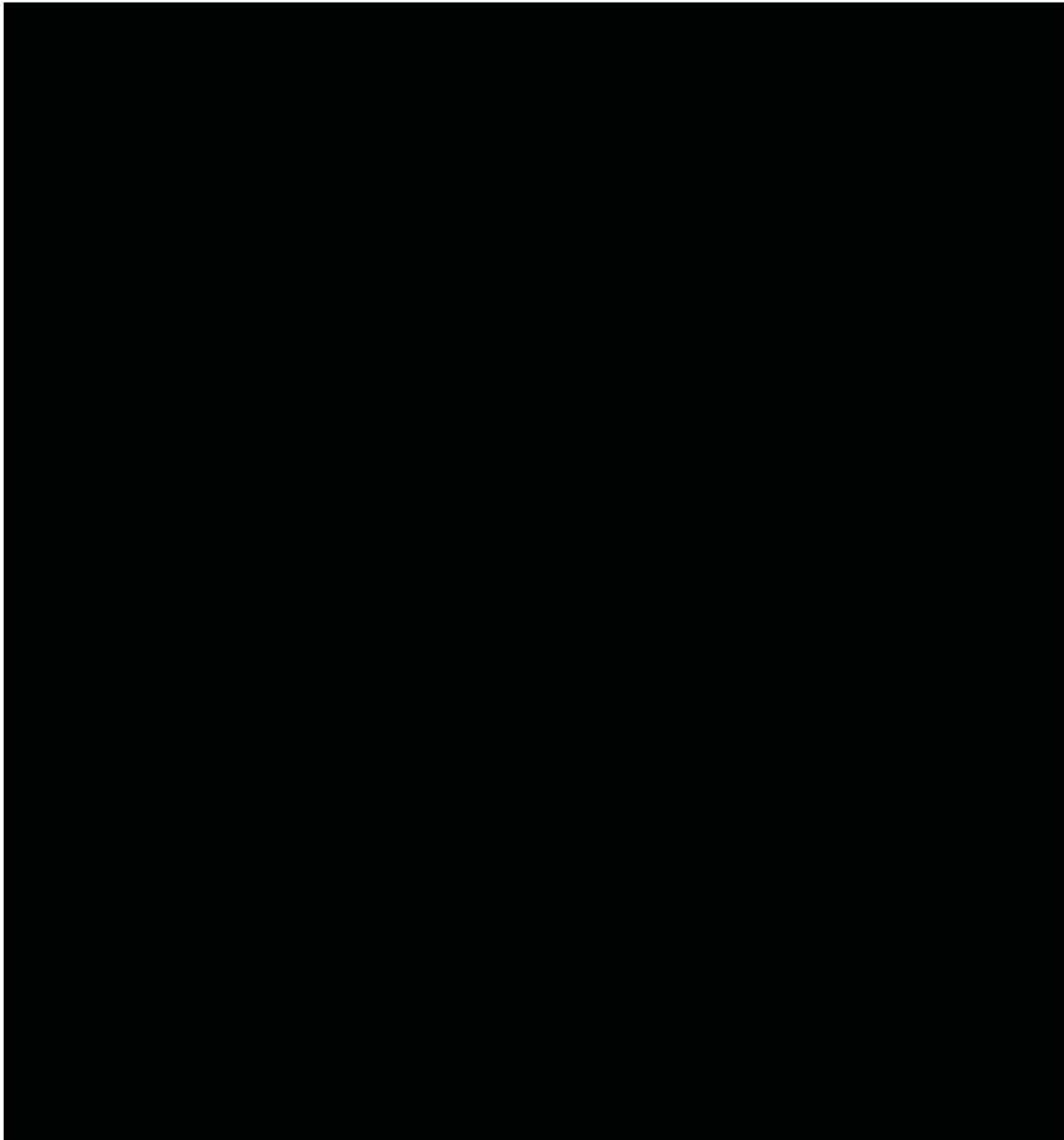
DLQI total score is calculated by summing the scores of each question resulting in a range of 0 to 30 where 0-1 = no effect on subject’s life, 2-5 = small effect, 6-10 = moderate effect, 11-20 = very large effect, and 21-30 = extremely large effect on subject’s life. The higher the score, the more the quality of life is impaired. 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.



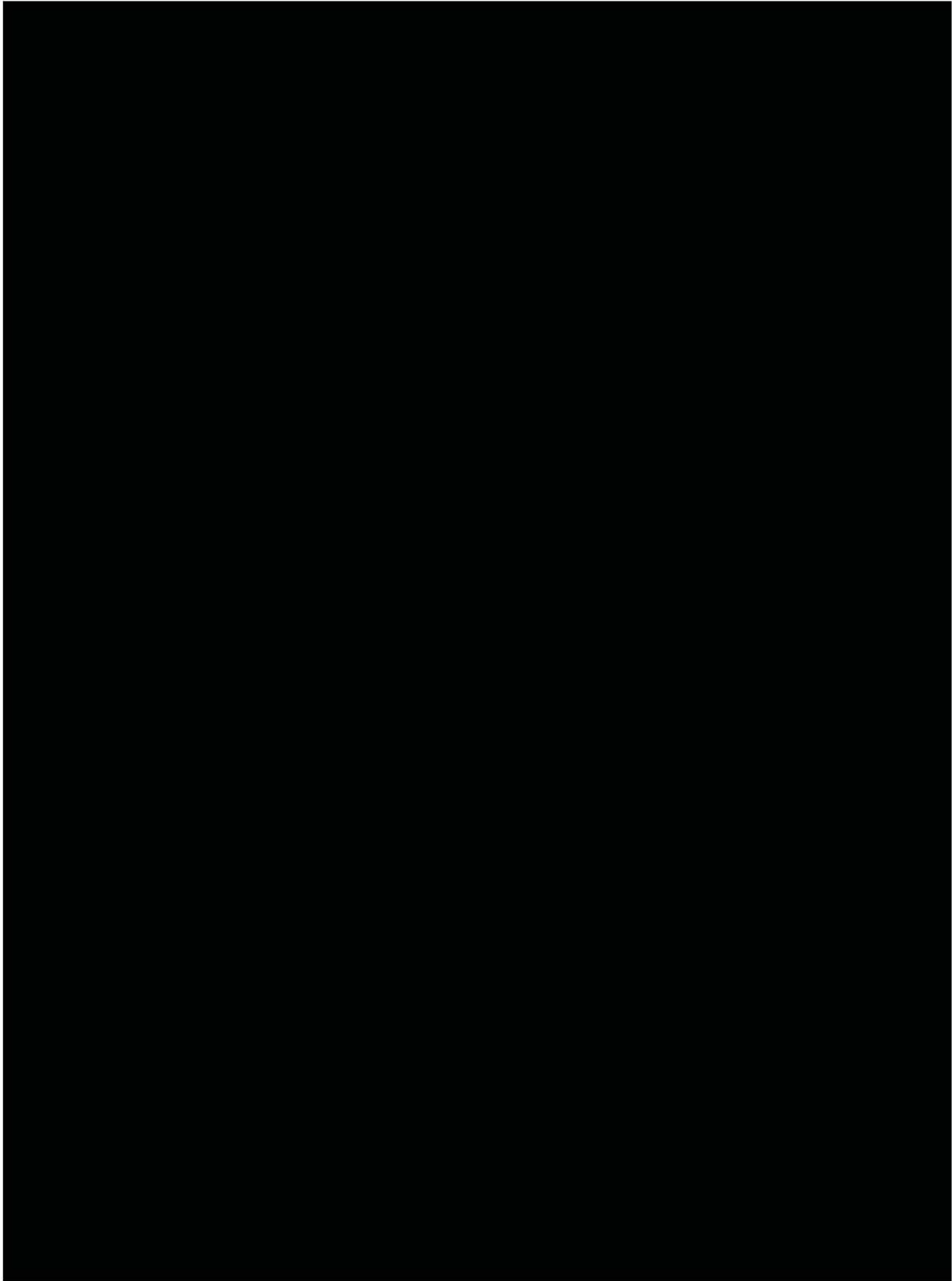
10.7 WORK LIMITATIONS QUESTIONNAIRE (WLQ)

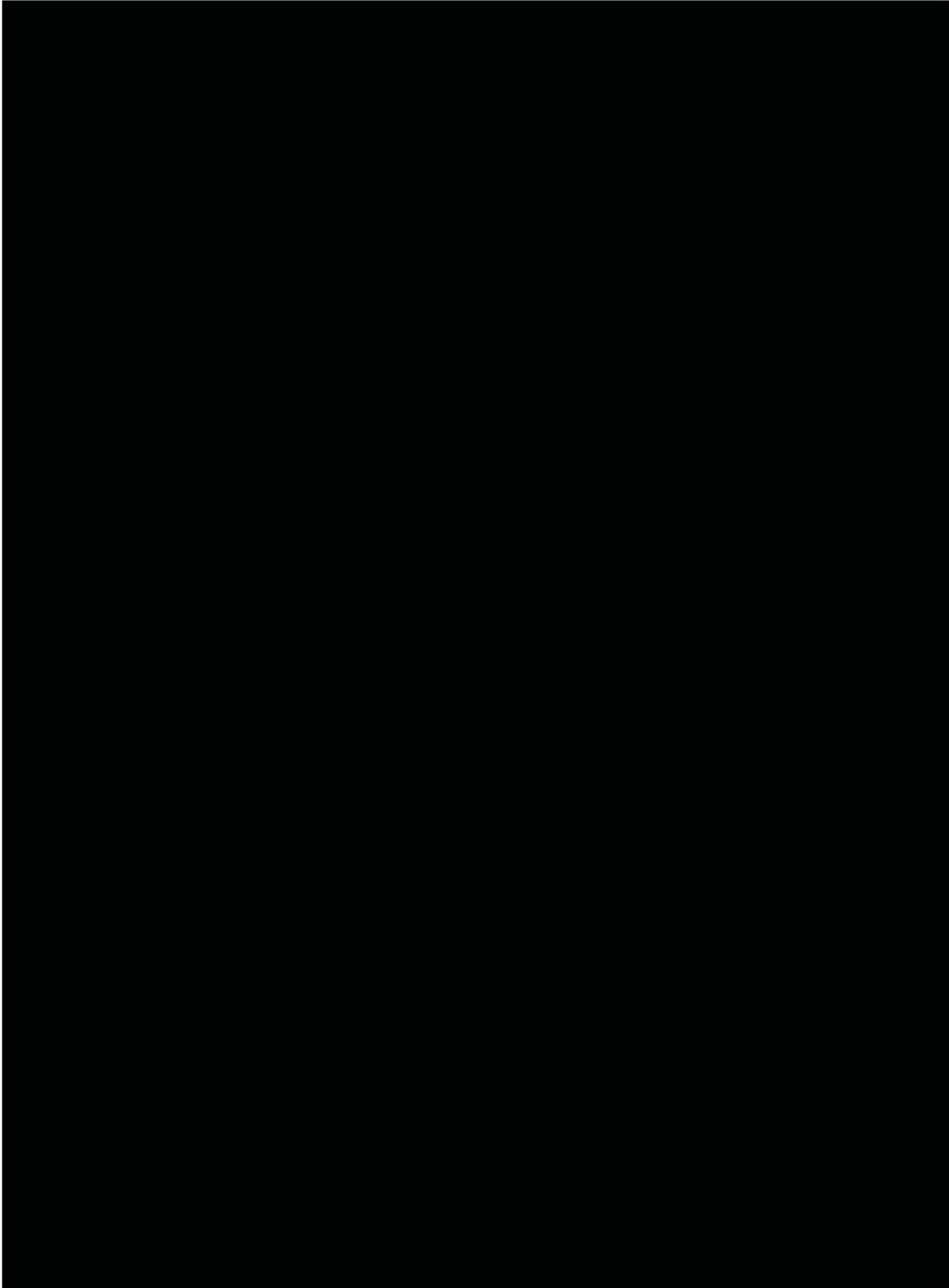
The WLQ is a 25-item questionnaire that measures the degree to which health problems interfere with specific aspects of job performance and the associated health-related productivity loss ([R15-3848](#)). Respondents rate their level of difficulty or ability to perform specific job demands during the previous two weeks. The WLQ has four scales: time management, physical demands, mental-interpersonal demands and output demands. Item scores range from 0 (limited none of the time) to 4 (limited all of the time). Each scale is scored separately and scale scores are converted mathematically to 0 (no limitations) and 100 (most limitations). Additionally, using an algorithm, WLQ scale scores can be converted into an estimate of productivity loss. The WLQ has been used in clinical trials in psoriasis ([R15-3862](#)). The WLQ is not applicable to patients who are unemployed and have no paid job.

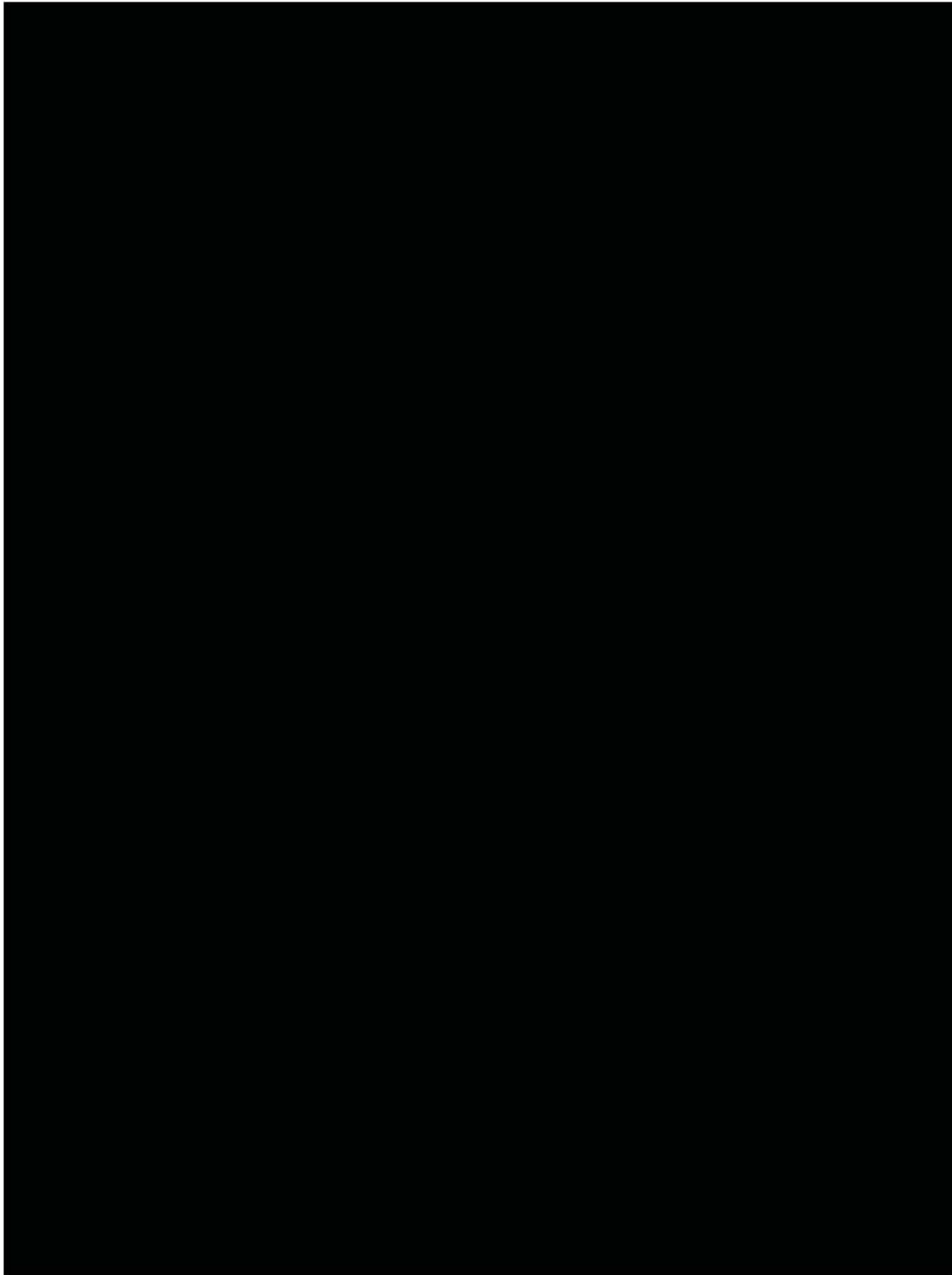
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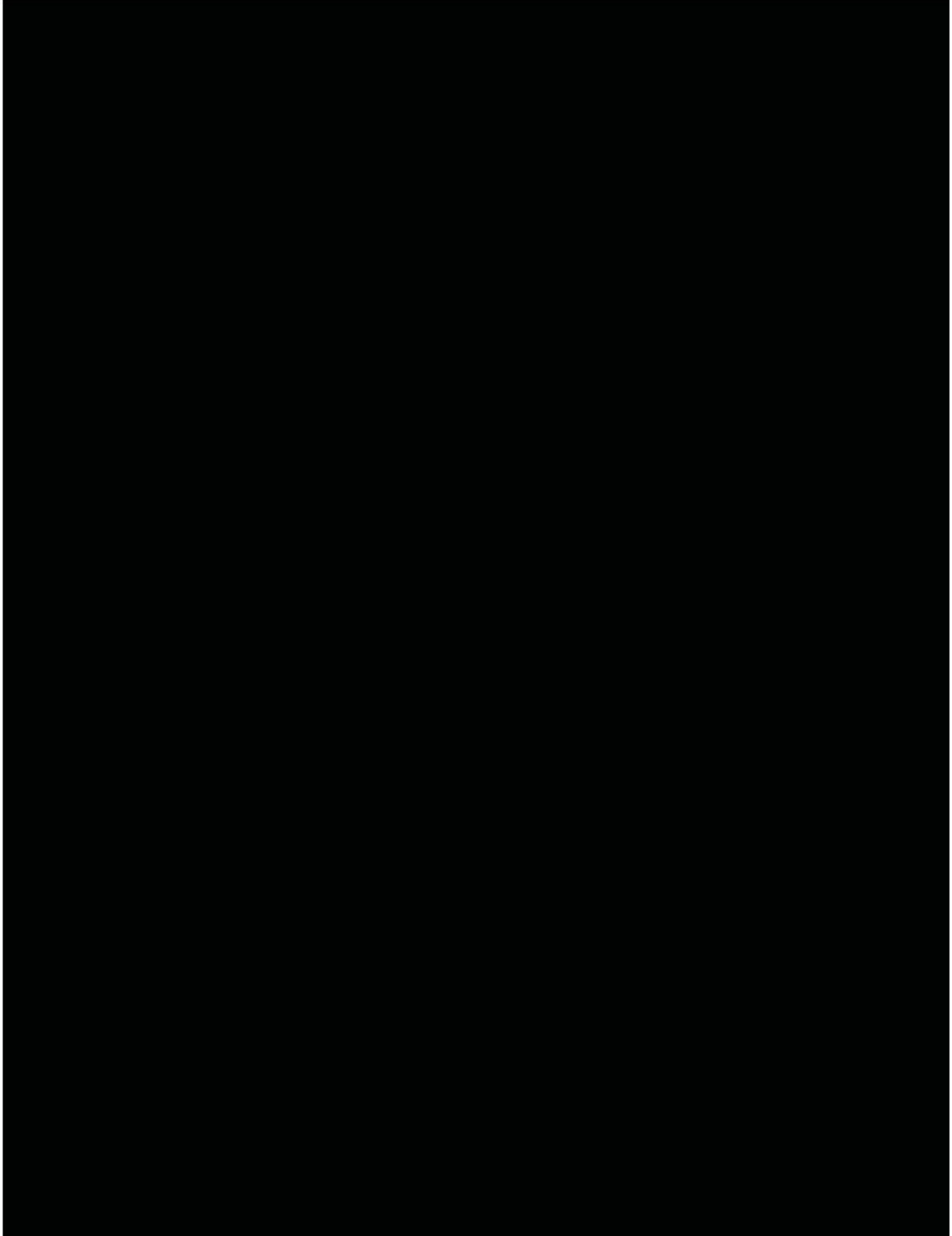


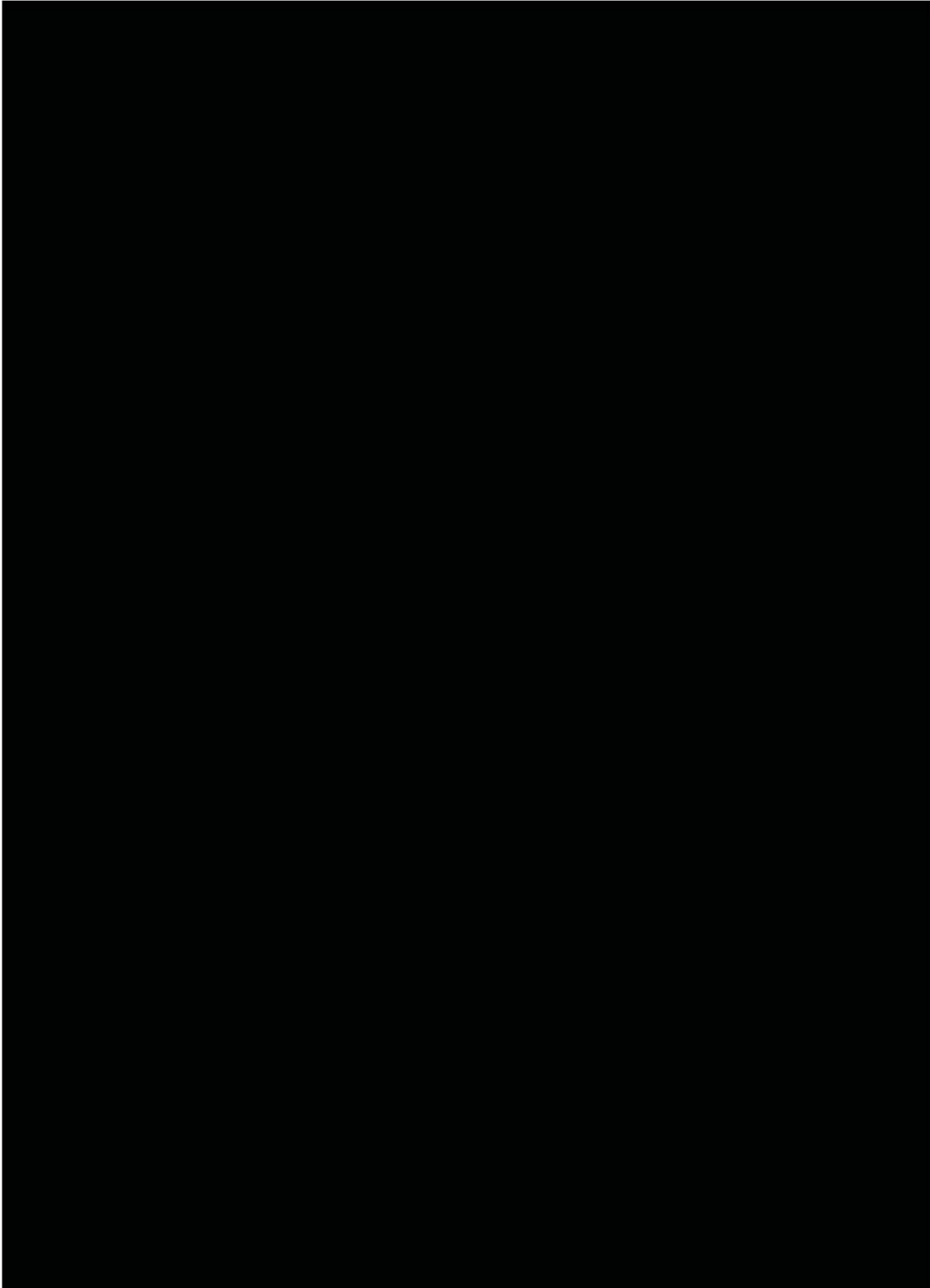
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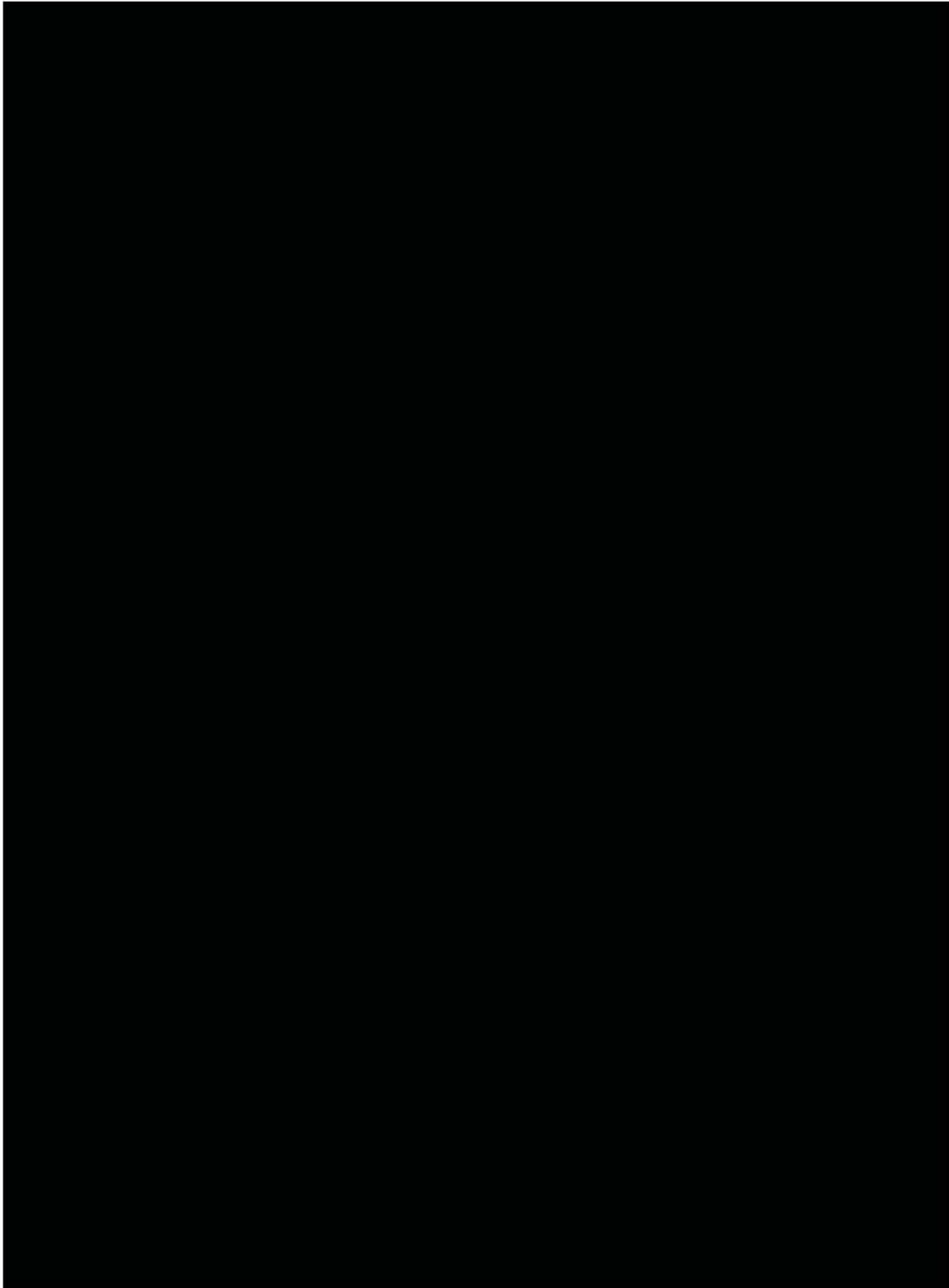


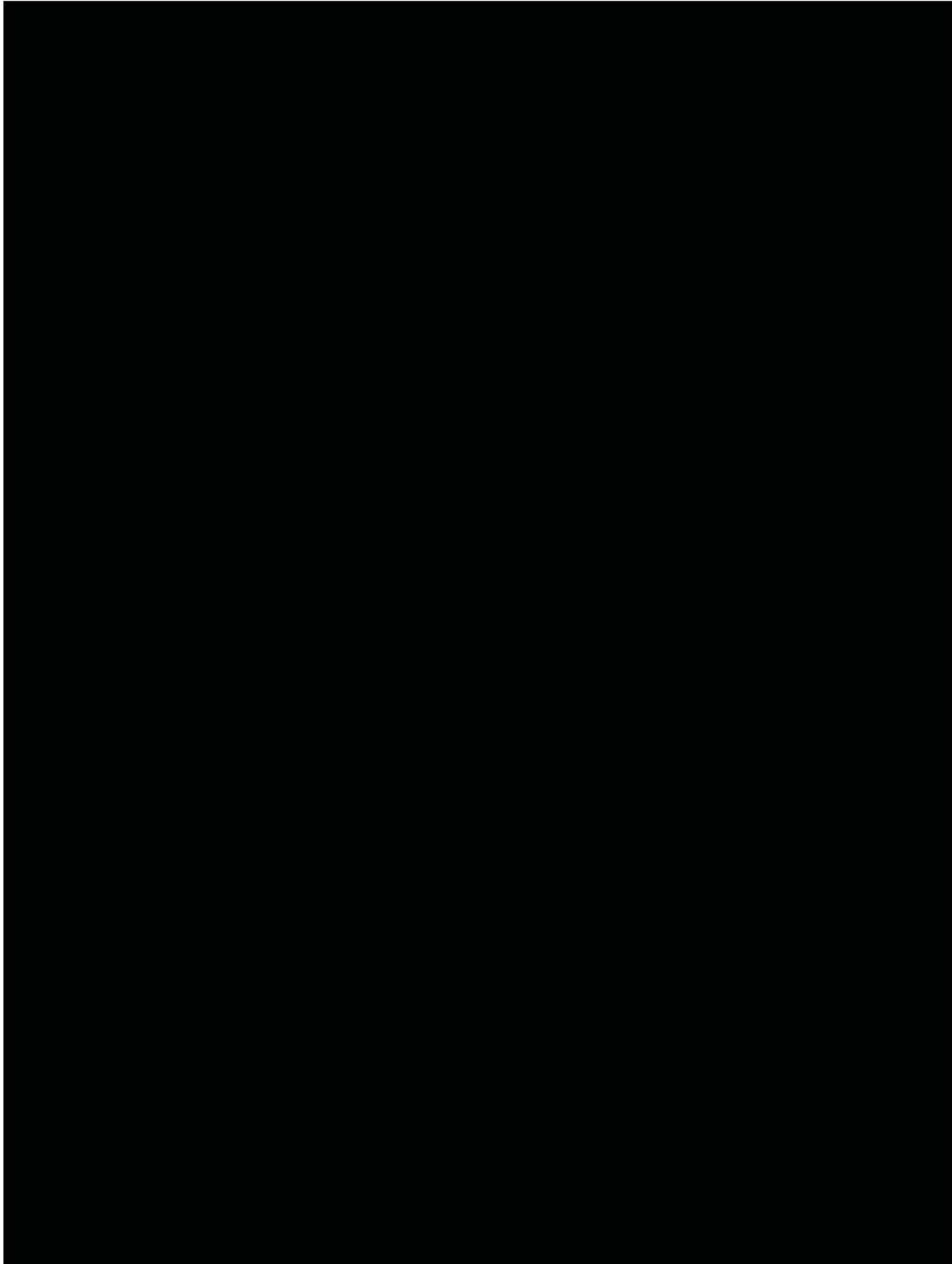


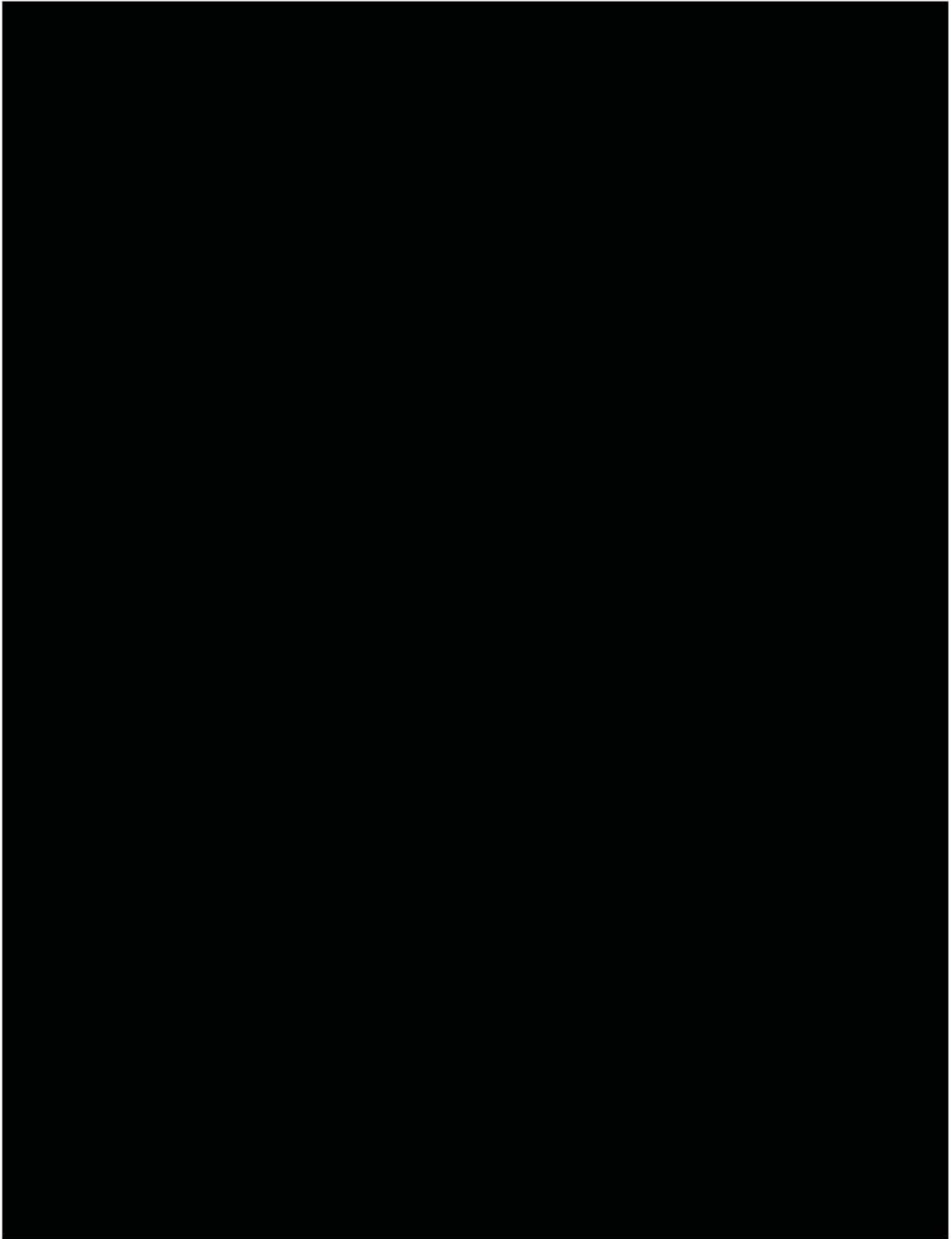


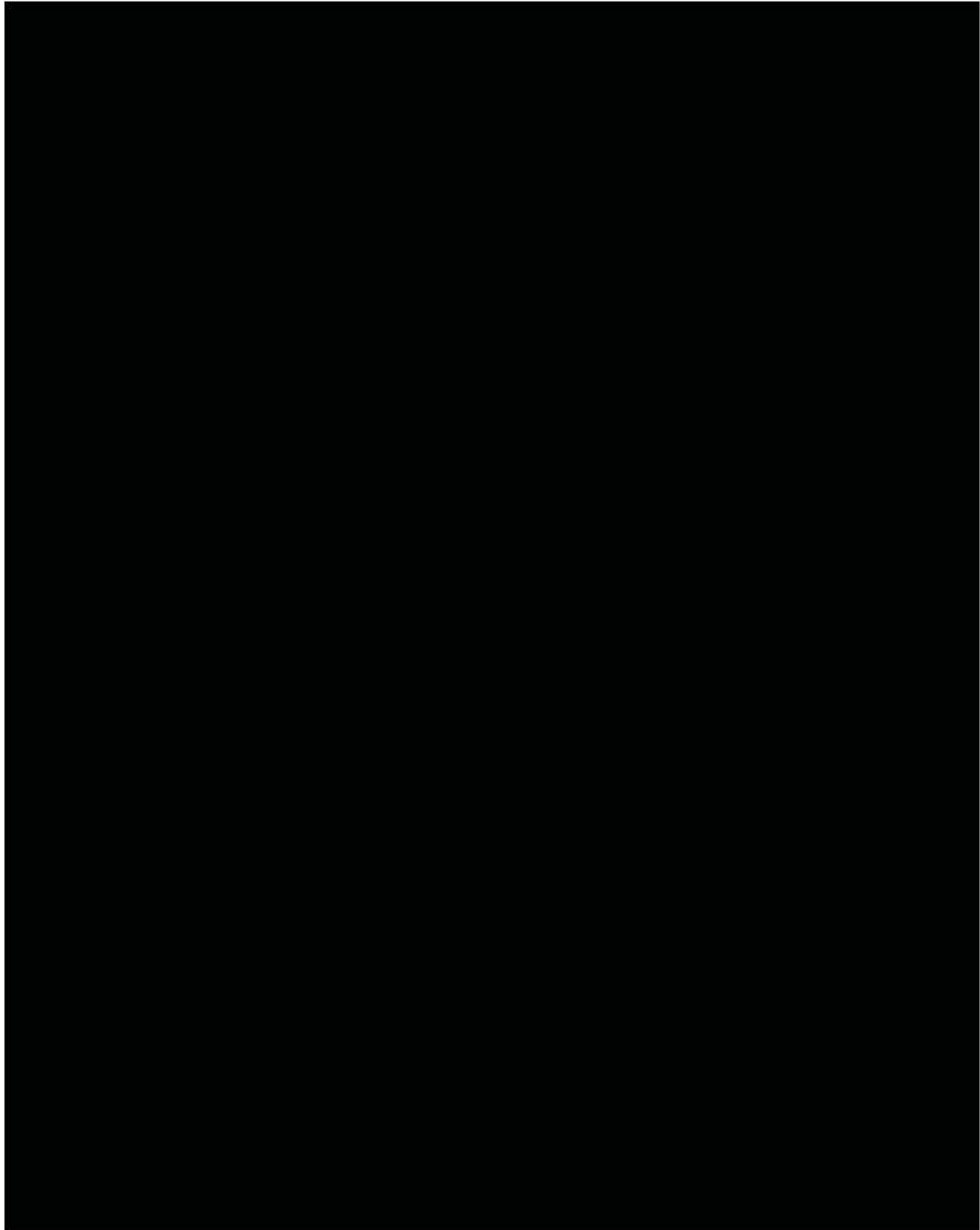












**10.8 SUPERVISING NURSE/HEALTH CARE PROFESSIONAL
QUESTIONNAIRE – SELF-ADMINISTRATION OF BI 655066 ACTIVE OR
PLACEBO**

The following questions ask about whether the patient was able to successfully inject the BI 655066 (active or placebo) medication. Please complete this questionnaire after the patient has self-injected both syringes.

First syringe BI 655066 active or placebo medication	
Question 1: Was the patient able to inject all of the liquid from the syringe into their body?	YES <input type="checkbox"/> /NO <input type="checkbox"/>
If “Yes”, proceed directly to Question 3.	
If “No”, continue with Question 2 below:	
Question 2: Why was the patient unable to inject all of the liquid from the syringe into their body? (please check all that apply):	
They were not able to remove the needle cap	<input type="checkbox"/>
They were not able to fully push down the plunger	<input type="checkbox"/>
They were not able to empty the syringe	<input type="checkbox"/>
More than a drop of medication remained on their skin after they had completed the injection	<input type="checkbox"/>
The patient had some other problem injecting all of the liquid from the syringe. Please describe below:	<input type="checkbox"/>
Question 3: Which injection site was selected (check only one):	
Left lower abdomen	<input type="checkbox"/>
Right lower abdomen	<input type="checkbox"/>
Left thigh	<input type="checkbox"/>
Right thigh	<input type="checkbox"/>
Question 4: Did you help the patient to administer the injection?	YES <input type="checkbox"/> /NO <input type="checkbox"/>

Second syringe BI 655066 active or placebo medication	
Question 5: Was the patient able to inject all of the liquid from the syringe into their body?	YES <input type="checkbox"/> /NO <input type="checkbox"/>
If “Yes”, proceed directly to Question 7.	

If "No", continue with Question 6 below:	
Question 6: Why was the patient unable to inject all of the liquid from the syringe into their body? (please check all that apply):	
They were not able to remove the needle cap	<input type="checkbox"/>
They were not able to fully push down the plunger	<input type="checkbox"/>
They were not able to empty the syringe	<input type="checkbox"/>
More than a drop of medication remained on their skin after they had completed the injection	<input type="checkbox"/>
The patient had some other problem injecting all of the liquid from the syringe. Please describe below:	<input type="checkbox"/>
Question 7: Which injection site was selected (check only one):	
Left lower abdomen	<input type="checkbox"/>
Right lower abdomen	<input type="checkbox"/>
Left thigh	<input type="checkbox"/>
Right thigh	<input type="checkbox"/>
Question 8: Did you help the patient to administer the injection?	YES <input type="checkbox"/> /NO <input type="checkbox"/>

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1.0
Date of CTP revision		17 June 2016
EudraCT number		2015-003623-65
BI Trial number		1311.30
BI Investigational Product(s)		BI 655066 (risankizumab)
Title of protocol		BI 655066 (risankizumab) versus adalimumab in a randomised, double blind, parallel group trial in Moderate to severe plaque psoriasis to assess safety and efficacy after 16 weeks of treatment and after inadequate adalimumab treatment response (IMMvent)
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Title page and synopsis
Description of change		Added risankizumab after BI 655066
Rationale for change		New name added for completeness
Section to be changed		Synopsis
Description of change		1. New further endpoint added: Absolute PASI score of <3 at all visits collected. 2. Abbreviation for HOMA and ECG explained
Rationale for change		1. new further endpoint (update to original CTP). 2. explanation
Section to be changed		Flow Chart
Description of change		1. “Biologic therapy history” changed to “Psoriasis therapy history” 2. %BSA involvement at Visit 1 and 2 added as line item 3. ADA sampling at Week 4 added 4. Randomisation, Re-Randomisation at Visit 8: it should read footer 14 (not footer 13)

		<p>5. Footer 4: Revised text to specify timing of vital sign measurements and hypersensitivity monitoring at dosing visits</p> <p>6. Footer 15: It should read: At Visit 2 all study drugs will be administered by study personnel</p> <p>7. New footer 20 to specify that patients who discontinue treatment should complete remaining study visits</p>
Rationale for change		<p>1. and 2. Clarification</p> <p>3. Request from Health Authorities</p> <p>4. Correction</p> <p>5. Clarification</p> <p>6. Clarification</p> <p>7. Update to original CTP</p>
Section to be changed		Abbreviations
Description of change		Several new abbreviations explained
Rationale for change		Clarification
Section to be changed		1.2 Drug Profile
Description of change		Second sentence should read: The antibody has been engineered to reduce Fcγ receptor and complement binding and potential charge heterogeneity.
Rationale for change		Correction
Section to be changed		2.3 Benefit – Risk Assessment
Description of change		The third paragraph should read: There is not enough information at this time to rule out a risk of cancer with BI 655066, but this risk is considered small with this type of compound as experience with the anti-IL 12/23 mAb ustekinumab has not suggested significant risk for cancer/serious infection.
Rationale for change		To correct a typo (anti-IL12/23 mAb)
Section to be changed		2.3 Benefit – Risk Assessment
Description of change		The second to last paragraph should read: In order to recognize any safety signals as early as possible, an independent Data Monitoring Committee (DMC) will monitor this study and all studies where patients are receiving BI 655066.
Rationale for change		Clarification
Section to be changed		3.1 Overall Trial Design and Plan
Description of change		<p>1. Several text changes to better understand the treatment arms and blinding of the study</p> <p>2. Discontinuation from Study medication should not necessarily lead to withdrawal from the study</p>
Rationale for change		<p>1. Correction and Clarifications</p> <p>2. Update original CTP</p>

Section to be changed		3.1.1 Administrative structure of the trial
Description of change		Abbreviations TCM and SOP explained
Rationale for change		Clarification
Section to be changed		3.1.2 Data Monitoring Committee (DMC)
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		3.3 Selection of Trial Population
Description of change		Update on the approximate number of participating sites and number of patients per site
Rationale for change		Update to original CTP
Section to be changed		3.3.2 Inclusion criteria
Description of change		New inclusion criterion added: Patient must be able and willing to self-administer the study medication
Rationale for change		Update to original CTP
Section to be changed		3.3.3 Exclusion criteria
Description of change		Exclusion criteria number 4 and 7 slightly changed for better understanding and clarification
Rationale for change		Clarification
Section to be changed		3.3.4.1 Removal of individual patients
Description of change		Patients that discontinue study medication should complete all study visits and procedures as initially planned, if possible
Rationale for change		Update to original CTP
Section to be changed		4.1.2 Method of assigning patients to treatment groups
Description of change		Section revised to better understand assigning patients to the respective treatments
Rationale for change		Clarification
Section to be changed		4.1.3 Selection of doses in the trial
Description of change		Correction in the second to last paragraph
Rationale for change		Correction
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Revised text to specify timing of vital sign measurements and hypersensitivity monitoring at dosing visits; further information regarding drug injection details; additional description on what has to be done if the patient accidentally comes too late to a visit.
Rationale for change		Clarification

Section to be changed		4.2.2.1: 1 Restrictions regarding concomitant treatment
Description of change		1. Added tofacitinib (Xeljanz®) and apremilast (Otezla®) 2. Removed efalizumab (Raptiva®)
Rationale for change		1. Additional medication requiring washout 2. Medication not available
Section to be changed		5.1.3 Further endpoints
Description of change		Added: “Absolute PASI score of <3 at all visits collected”
Rationale for change		Update to CTP
Section to be changed		5.3.2 Vital Signs
Description of change		Revised text to specify timing of vital sign measurements and hypersensitivity monitoring at dosing visits
Rationale for change		Clarification
Section to be changed		5.3.3 Safety laboratory parameters
Description of change		Some laboratory parameters are better specified. Added Albumin/creatinine ratio in urine
Rationale for change		Clarification and Update to CTP
Section to be changed		5.3.4 Electrocardiogram
Description of change		Correction of wording in second to last paragraph
Rationale for change		Clarification
Section to be changed		5.6.1 Quality of Life Questionnaires DLQI and WLQ
Description of change		Abbreviations given
Rationale for change		Clarification
Section to be changed		6.2 Details of trial procedures at selected visits
Description of change		Removed: “At Visit 2 these questionnaires should be obtained after having the patient randomised”
Rationale for change		To match order of administration of patient reported outcome questionnaires DLQI and WLQ which should always come first (before any interaction with the investigator or other site personnel)
Section to be changed		6.2.1 Screening period
Description of change		1. New sentence: “Screening procedures may be extended to more than 1 physical visit, if needed.” 2. Removed: “or local tolerability” from baseline conditions
Rationale for change		1. Patients may require more than 2 visits for screening procedures. 2. Correction to original CTP
Section to be changed		6.2.2 Treatment period
Description of change		Last paragraph: Revised text to specify timing of

		hypersensitivity monitoring at dosing visits
Rationale for change		Clarification
Section to be changed		6.2.3.1 Early treatment and trial termination
Description of change		Patients that discontinue study medication should complete all study visits and procedures as initially planned, if possible
Rationale for change		Update to original CTP
Section to be changed		7.2 Null and alternative hypotheses
Description of change		Treatment arms better described
Rationale for change		Clarification
Section to be changed		7.3 Planned analyses
Description of change		Clarifying the important protocol violations (IPVs), the intent-to-treat population, the per-protocol set (PPS) and the Re-randomised per-protocol set (RR-PPS). Hypothesis tests as described in Section 7.2 will be repeated on the PPS or RRS-PPS populations, as appropriate.
Rationale for change		Response from Health Authorities
Section to be changed		7.3.3 Further endpoint analyses
Description of change		Added "Time to onset of Endpoint" definition.
Rationale for change		Update to CTP
Section to be changed		7.3.4 Safety analyses
Description of change		Clarification of Residual Effect Period (REP)
Rationale for change		Clarification
Section to be changed		7.4 Interim analyses
Description of change		No interim analysis is planned for the study
Rationale for change		Clarification
Section to be changed		7.5 Handling of missing data
Description of change		Explanations on sensitivity analyses
Rationale for change		Update to CTP
Section to be changed		9.2 Unpublished references
Description of change		The reference for the Investigator's Brochure listed twice was deleted once
Rationale for change		Correction
Section to be changed		10.3 Nail Psoriasis Severity Index (NAPSI)
Description of change		Addition of Reference number
Rationale for change		Update to CTP
Section to be changed		10.4 Palmoplantar psoriasis severity index (PPASI)
Description of change		Correction of wording
Rationale for change		Correction

Section to be changed		10.5 psoriasis scalp severity index (PSSI)
Description of change		Addition of Reference number

Rationale for change		Update to CTP
Section to be changed		10.6 Dermatology life quality index (DLQI)
Description of change		Correction of response categories
Rationale for change		Correction
Section to be changed		10.7 Work Limitations Questionnaire (WLQ)
Description of change		The WLQ is not applicable to unemployed patients
Rationale for change		Clarification
Section to be changed		10.8 Supervising nurse/health care professional questionnaire – self-administration of BI 655066 active or placebo
Description of change		Update of the lay-out
Rationale for change		Correction

Number of global amendment		2.0
Date of CTP revision		05 July 2016
EudraCT number		2015-003623-65
BI Trial number		1311.30
BI Investigational Product(s)		BI 655066 (risankizumab)
Title of protocol		BI 655066 (risankizumab) versus adalimumab in a randoMized, double blind, parallel group trial in Moderate to severe plaque psoriasis to assess safety and efficacy after 16 weeks of treatment and after inadequate adalimumab treatment response (IMMvent)
To be implemented only after approval of the IRB / IEC / Competent Authorities		<input checked="" type="checkbox"/>
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		
		Section 11
Description of change		
		Ticked “To be implemented only after approval of the IRB / IEC / Competent Authorities”
Rationale for change		
		Clarification


Number of global amendment		3.0
Date of CTP revision		17 Oct 2016
EudraCT number		2015-003623-65
BI Trial number		1311.30
BI Investigational Product(s)		BI 655066 (risankizumab)
Title of protocol		BI 655066 (risankizumab) versus adalimumab in a randomized, double blind, parallel group trial in Moderate to severe plaque psoriasis to assess safety and efficacy after 16 weeks of treatment and after inadequate adalimumab treatment response (IMMvent)
To be implemented only after approval of the IRB / IEC / Competent Authorities		<input type="checkbox"/>
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		<input type="checkbox"/>
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		<input checked="" type="checkbox"/>
Section to be changed		
Description of change		Title page, Synopsis
Rationale for change		Changed BI drug or BI 655066 to refer to either names for this compound: BI 655066/ABBV-066 (risankizumab)
Section to be changed		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 USA, as well as the modifications to certain study conduct responsibilities as a result of that license agreement are listed as separate changes below.
Description of change		Section 3.1.1
Description of change		1. Changed sponsor from Boehringer Ingelheim (BI) to AbbVie in the USA; BI remains the sponsor for all other participating countries. 2. Changed text to specify Statistical Evaluation

		will be done by AbbVie according to their SOPs.
Rationale for change		Refer to rational for first change listed
Section to be changed		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 5.5.4.2
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 Strasse 65, 88397 Biberach, Germany)
Rationale for change		Refer to rational for first change listed
Section to be changed		Section 5.5.1.1
Description of change		Skin biopsies will be collected only at Visit 2 (lesional and non-lesional) and at Visit 7 (only lesional) as shown in the Flow Chart
Rationale for change		Correction
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 are based on AbbVie standards
Rationale for change		Refer to rational for first change listed

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Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
		17 Oct 2016 15:23 CEST
		17 Oct 2016 15:44 CEST
		17 Oct 2016 15:58 CEST
		17 Oct 2016 23:09 CEST
		18 Oct 2016 10:21 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
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