Clinical Trial Protocol

Doc. No.: c02318676-08

EudraCT No.:	2014-001687-36
BI Trial No.:	1311.13
BI Investigational Product(s):	BI 655066
Title:	An open label extension trial assessing the safety and Efficacy of BI 655066/ ABBV-066/risankizumab administered subcutaneously in patients with moderate to severe chronic plaque psoriasis.
Clinical Phase:	IIb
Trial Clinical Monitor:	[redacted]
Co-ordinating Investigator:	[redacted]
Status:	Final Protocol (Revised Protocol (based on global amendment 5)
Version and Date:	**Version: 6.0** **Date: 30-Jan-2018**

TITLE PAGE

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company: Boehringer Ingelheim		**Tabulated Trial Protocol**	
Name of finished product: NA			
Name of active ingredient: BI 655066			
Protocol date: 13 June 2014	**Trial number:** 1311.13		**Revision date:** 30-Jan-2018
Title of trial:	An open label extension trial assessing the safety and efficacy of BI 655066/ ABBV-066/risankizumab administered subcutaneously in patients with moderate to severe chronic plaque psoriasis.		
Co-ordinating Investigator:	[redacted]		
Trial site(s):	Multicenter, multinational		
Clinical phase:	IIb		
Objective(s):	Long term safety and efficacy of BI 655066/ ABBV-066/risankizumab during open-label treatment in patients with moderate to severe chronic plaque psoriasis.		
Methodology:	Open label extension.		
No. of patients:	100 (estimated)		
total entered:	100 (estimated)		
each treatment:	All patients will receive 90 mg BI 655066/ ABBV-066/risankizumab for 12 weeks, followed by 90 or 180 mg every 12 weeks depending on efficacy		
Diagnosis :	Moderate to severe chronic plaque psoriasis.		
Main criteria for inclusion:	Patients with moderate to severe chronic plaque psoriasis, who have successfully completed the preceding trial 1311.2. Successful completion of preceding trial is defined as either of the following: a. Completion of the entire follow up period, thus reaching EOS visit. b. Loss of response, defined as decrease in response to <PASI50 at any time from week 24.		
Test product(s):	BI 655066		
dose:	90 mg every 12 weeks, or 180 mg every 12 weeks		
mode of admin.:	Subcutaneous injection		
Comparator products:	NA		
dose:	NA		

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mode of admin.:	NA
Duration of treatment:	Approximately four years of administration to patient after receiving first BI 655066/ ABBV-066/risankizumab dose in either trial 1311.2 or trial 1311.13
Criteria for efficacy:	The achievement of $PASI_{90}$ at week 48 in the Extended dosing period (i.e. a $\geq$ 90% reduction in PASI score from baseline), is the primary efficacy endpoint.
Criteria for safety:	Occurrence of AEs, drug related AEs and SAEs are primary endpoints of safety. Safety analyses will focus on adverse events related to early discontinuation, immune suppression and injection site reactions. Analysis of laboratory measures will similarly focus on hematologic measures of immune suppression. Safety will also be assessed by evaluation of vital signs (BP, PR, RR, oral or tympanic body temperature) and local tolerability. Additionally, time to antibody development formation will be examined using Kaplan Meier empirical survival curves.
Statistical methods:	There is no statistical model; the analyses are descriptive. Statistical analyses will include a responder analysis, time to loss of response, and time to AESI. The analyses will be based on proportions of patients achieving a response, Kaplan Meier empirical survival curves to describe patterns of event incidence, and as well as cumulative event rates at critical time-points.

FLOW CHART – EXTENDED DOSING PERIOD

Trial periods			**Extended Dosing Period**						**Extended FU period[3]**
Visit	**Extended Visit 1[1, 2, 3]**	**Extended Visit 2[3]**	**Extended Visit 3**	**Extended Visit 4**	**Extended Visit 5**	**Extended Visit 6-17[23]**	**Extended Visit 18 →**	**Extended EOT[4]**	**Extended EOS visit [18,23]**
Day	**1**	**84**	**168**	**252**	**336**	**420-1344**	**1428 →**	X	**Extended EOT +84**
Week	**0**	**12**	**24**	**36**	**48**	**60-192**	**204 →**	X	**Extended EOT + 12**
Visit window (days)		**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**+7**
Informed Consent	x								
Demographics[20]	x								
Consent for vital status follow up[20]	x [19]								
Med. history, smoking and alcohol use[20]	x								
Psoriatic arthritis assessment /PASE[5]	x				x	x [5]		x	x
Weight, waist circum[22]	x				x	x[22]		x	x
Physical exam [6,7]	x [C]	x [T]	x [C]	x [T]	x[C]	x [T/C]	x [T]	x [C]	x [T]
Vital signs [8]	x	x	x	x	x	x	x	x	x
12-Lead ECG[9]	x		x		x	x[9]	x	x	x
In/Ex eligibility[20]	x								
Administer BI 655066 [3]	x	x	x	x	x	x	x	x[10]	
Adverse event [11]	x	x	x	x	x	x	x	x	x
Conc. Therapy	x	x	x	x	x	x	x	x	x
PASI[5,21]	[PreD] x	[PreD] x	[PreD] x	[PreD] x	[PreD] x	[PreD] x	[PreD] x	[PreD] x	x

Trial periods			**Extended Dosing Period**						**Extended FU period[3]**
Visit	**Extended Visit 1[1, 2, 3]**	**Extended Visit 2[3]**	**Extended Visit 3**	**Extended Visit 4**	**Extended Visit 5**	**Extended Visit 6-17[23]**	**Extended Visit 18 →**	**Extended EOT[4]**	**Extended EOS visit [18,23]**
Day	**1**	**84**	**168**	**252**	**336**	**420-1344**	**1428 →**	X	**Extended EOT +84**
Week	**0**	**12**	**24**	**36**	**48**	**60-192**	**204 →**	X	**Extended EOT + 12**
Visit window (days)		±7	±7	±7	±7	±7	±7	±7	+7
sPGA[21]	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	X
Pain VAS [12,21]	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	X
DLQI[21]	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	X
Local tolerability test		PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	
Safety Lab [13, 14]	X	X	X	X	X	X	X	X	X
Serum pregnancy test [13, 15, 20, 24]	X							X	X[24]
TB screening [13, 20, 24]	X							X	X[24]
Urine Pregnancy test[16]	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	PreD X	X
PK[17]	PreD X		PreD X		PreD X	PreD X[17]	PreD X	PreD X	X
Anti-drug Ab (ADA)[17]	PreD X		PreD X		PreD X	PreD X[17]	PreD X	PreD X	X
Protein biomarker in plasma /serum[17]	PreD X		PreD X		PreD X	PreD X[17]	PreD X	PreD X	X
M15-997 Open label extension study[23]									X
Conclusion of patient Participation									X

Footnotes:

1. Extended Visit 1 of this OLE study should preferably be performed in one visit combined with EOS visit in preceding trial 1311.2, or within an interim period of maximum 6 weeks thereafter. If not performed as combined visits, informed consent must be signed before the roll-over visit due to lab sampling fasting at EV1 in trial 1311.13. Informed consent must not be signed before the 1311.2 date of last visit.
2. Assessments performed at EOS in the previous trial do not have to be repeated at EV1 in this trial, if performed as combined visits. If EV1 is performed as a separate visit to 1311.2 EOS, all EV1 assessments should be performed.
3. After the approval of this protocol amendment in each respective country, all patients will follow Flow Chart (Extended dosing period) and receive 90mg BI 655066 subcutaneously at their EV1. After 12 weeks, at EV2, the dose can be increased to 180 mg BI 655066 based on evaluation of the PASI90 achievement (see section 4.1.2 and 6.2.2). For ongoing patients under the previous protocol amendment, EV1 should be conducted at the following time points:
    a. For ongoing patients with ≥12 weeks since the EOT visit: Conduct EV1 as soon as possible
    b. For ongoing patients still undergoing treatment or with <12 weeks since the EOT visit: Conduct EV1 at the time of the next scheduled treatment or follow up visit (note: EV1 should not be conducted at the time point of Visit 2 under the previous protocol, patients with Visit 2 as their next scheduled visit should have their EV1 replacing their Visit 3 instead)
4. For patients who prematurely discontinue the treatment period before study end (for any reason), an early Extended EOT visit is required. If the decision to discontinue study participation is taken at a regular study visit, the visit should be turned into an Extended EOT visit, i.e. an Extended EOT visit is to be performed instead of the scheduled visit. If the decision to discontinue study participation is taken in between study visits, an Extended EOT visit is to be scheduled at the earliest convenience and by the latest at the next upcoming visit according to the Flow Chart. This early Extended EOT visit will include the same procedures as the normal Extended EOT visit and the patient will subsequently enter a follow up period of 12 weeks, until a final Extended EOS is performed.
5. The Psoriatic Arthritis status assessment (PSOA: Psoriatic arthritis diagnosed, suspected, or not present) will be performed at roll-over visit only. Psoriatic arthritis screening and evaluation tool (PASE) to be completed by the patient if psoriatic arthritis is suspected or confirmed. To be repeated once per year until study end, i.e at EV1, EV5, EV10…
6. "xC" is a complete physical examination including assessment of vital sign measurements, general appearance, and evaluation of all organ systems
7. "xT" is a targeted physical examination including assessment of vital sign measurements, and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.
8. Measured after 5 minutes of rest in the supine position. Measurements of vital signs should, if possible, always precede blood sampling.
    a. Extended visit 1: Vital signs will be taken ~ 30 min predose, 5 minutes, and 1 hour after the dose is administered
    b. Following dosing visits: Vital signs will be taken ~ 30 min predose, 5 minutes and 30 minutes after the dose is administered
    c. Non-dosing visit (Extended EOS): Vital signs will be measured once per visit
9. ECG to be performed after 5 minutes of rest in the supine position, at every 24 weeks, starting from EV1 (EV1, EV3, EV5…). Should, if possible, be performed prior to blood sampling.
10. Not to be performed for patients who prematurely discontinue the treatment period.
11. All new AEs as well as unresolved AE from the preceding trial 1311.2 should be followed up within this study.
12. Only for patients with psoriatic arthritis.
13. For details of laboratory tests cf. Section5.2.3, Table 5.2.3:1 and 5.2.3:2
14. Patients must be fasting for at least 8 hours prior to collection of the safety laboratory samples.
15. Only applicable for women of childbearing potential.
16. In women of childbearing potential urine pregnancy test has to be performed before each administration of study drug.
17. Blood samples for protein biomarker, PK and ADA will be drawn ~ 30 min before the subcutaneous injection (PreD) at every 24 weeks, starting from EV1 (EV1, EV3, EV5…).
18. For patients who prematurely discontinue the follow up period before study end (for any reason), an early Extended EOS visit is required. This early Extended EOS visit will include the same procedures as the normal Extended EOS visit.
19. Patients will be asked to give consent to be contacted (or for their primary care physician to be contacted) by the study team to obtain vital status information preferably at the time of study entry
20. Only required at EV1 for patients who are having EV1 as their first 1311.13 visit
21. All efficacy assessments should be performed pre-dose (PreD)
22. To be repeated once per year until study end (EV1, EV5, EV10…)

23. After 01-May-2018 and approval of this protocol amendment in each respective country patients who have completed the study without early treatment discontinuation will be offered to roll over to M15-997 open label extension (OLE) trial if they fulfill the in- and exclusion criteria for the M15-997 trial. Refer to section 6.2.3.
    The next visit and also the last visit after 1st May and approval of this amendment will be Extended EOS visit. Termination of trial medication page should be completed in the eCRF and treatment completed registered in IRT.
24. For patients not prematurely discontinued.

Abbreviations: PreD = Prior to dose

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ABBREVIATIONS

ADA	Anti-drug antibodies
ADL	Activities of daily living
AE(s)	Adverse event(s)
AESI	Adverse event of special interest
ALT [U/L]	Alanine transaminase (SGPT)
aPTT	Partial Thromboplastin Time
AP/ALP	Alkaline Phosphatase
AST [U/L]	Aspartate transaminase (SGOT)
β	Slope parameter associated with the power model used to evaluate dose proportionality
BCG	Bacille Calmette-Guérin vaccine
BI	Boehringer Ingelheim
BP [mmHg]	Blood pressure
BSA	Body surface area
CA	Competent Authority
Cf.	Confer (compare)
CHF	Congestive heart failure
CML	Local clinical monitor
CRA	Clinical research associate
CRO	Clinical research organisation
CRF(s)	Case report form(s)
CRP	C-reactive protein
CTP	Clinical Trial Protocol
DILI	Drug-induced liver injury
DLQI	Dermatology Life Quality Index
DMC	Data monitoring committee
e.g.	Example given
ECG	Electrocardiogram
eCRF(s)	Electronic case report form(s)
EDTA	Ethylendiaminetetraacetic acid
ELISA	Enzyme-linked immunosorbent assay
EOS	End of study
EOT	End of treatment
Etc.	Etcetera
EV	Extended Visit
FDA	Food and drug administration
FVC	Forced vital capacity
g	gram(s) (for description of mass); gravity (description of centrifugation)
GCP	Good clinical practice

Hb	Haemoglobin
HbA1c	Haemoglobin (glycated Hb of A1c subtype)
HCG	Human chorionic gonadotropin
Hct	Haematocrit
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
i.e.	Id est, that is
ICH	International conference on harmonisation
IEC	Independent ethics committee
IFN	Interferon
IgG	Immuneglobuline
IGRA	Interferon gamma release assay
IL	Interleukin
INR	International normalised ratio
IRB	Institutional review board
IRT	Interactive Response Technology
ISF	Investigator site file
i.v.	Intravenous
LLN	Lower limit of normal
mAb	Monoclonal antibody
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical dictionary for drug regulatory affairs
mg	Milligrams
ml	Millilitre
mM	Millimole/Millimolar
MRI	Magnetic resonance imaging
NGAL	Neutrophil gelatinase associated lipocalin
nM	Nanomole/nanomolar
NPFPS	National Psoriasis Foundation Psoriasis Score
OLE	Open label extension
OPU	Operation Unit
OTC	Over the counter medication
PASE	Psoriatric Arthritis Screening and Evaluation Tool
PASI	Psoriasis Area and Severity Index
PD	Pharmacodynamic(s)
pH	Power of hydrogen
PK	Pharmacokinetic(s)
PMN	Polymorphonuclear
PR [1/min]	Pulse rate
PT	Prothrombin time
PUVA	Psoralen + UVA
RBC	Red blood cell count
RCTC	Rheumatology Common Toxicity Criteria
RDC	Remote data capture

REP	Residual effect period
RR	Respiratory rate
SAE	Serious adverse event
s.c.	Subcutaneous
SOP	Standard operating procedure
sPGA	Static Physician Global Assessment
SUSARs	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TCM	Trial Clinical Monitor
Th	T helper (cell)
TMF	Trial Master File
TNF	Tumor necrosis factor
ULN	Upper limit of normal
US	United States
UVA	Ultraviolet-A rays
UVB	Ultraviolet-B rays
VAS	Visual Analogue Scale
WBC	White blood cells

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Psoriasis is a common skin disease characterized by raised, well-demarcated erythematous oval plaques with adherent silvery scales (R11-1257). It affects approximately 2% of the world population including 25 million people in North America and Europe making it the most prevalent immune mediated skin disease (R08-1089). It usually begins in late adolescence and early adulthood and then usually persists for life with remissions and relapses. The latter can be triggered by infections, medications and stress.

Disease severity can be characterized by body surface area (BSA) involvement with <5% being considered mild, 5-10% moderate and >10% severe (R11-1259). Disease status has been measured using the Psoriasis Area and Severity Index (PASI), a composite measure of erythema, induration, desquamation and BSA affected by psoriasis with a range of scores from 0 to 72 (R96-3541). The percentage of patients reaching PASI75, a 75% reduction in score from baseline to 12 or 16 weeks is traditionally used as a primary endpoint in psoriasis treatment trials.

Topical agents, including corticosteroids, are the mainstay for mild disease. Treatments for more advanced conditions can be classified into phototherapy, immunosuppressants, other systemic agents, and more recently, biologics (R11-1261).

Many of the agents may be used in combination or on a rotational basis to limit toxicity. Phototherapy may be used alone or with topical tar and dithranol products or with systemic and biologic agents. Although effective, the frequency and nature of this treatment reduces adherence. Adverse events (AEs) of phototoxicity, skin aging and concerns of development of skin cancers, also reduce acceptance of this therapy (R11-1261). Immunosuppressants, such as methotrexate or cyclosporine, are also effective for the management of moderate to severe psoriasis and relapses, but cumulative hepatotoxicity, bone marrow suppression and rarely pulmonary toxicity with methotrexate and nephrotoxicity with cyclosporine, requires careful monitoring and prevents the use of these agents long term.

Biologic agents such as tumor necrosis factor (TNF) blockers were first found efficacious in Crohn's disease, ulcerative colitis and rheumatoid arthritis prior to their use in psoriasis. Although not studied in head-to-head comparisons, different agents in this class have varying efficacy in psoriasis: infliximab and adalimumab are more efficacious especially in short term with PASI75 of 70-87% vs. etanercept (PASI75 of 50%) (R11-1261). These agents have been used for treating relapses and maintenance as well as the management of psoriatic arthritis, which occurs in approximately a third of all patients with psoriasis. However, TNF has myriad effects on immune function and TNF blockers have been associated with an increased risk of serious infections, in particular, tuberculosis and other opportunistic infections, cancers, including lymphomas, and demyelinating disorders.

BI 655066 is a humanized antagonistic monoclonal antibody (mAb) directed against the p19 subunit of the human cytokine interleukin-23 (IL-23). IL-23 plays a critical role in the

differentiation and function of Th17 cells, which have emerged as an important T-cell subpopulation involved in the pathogenesis of immune mediated disorders (R12-1008)

The therapeutic rationale for an IL-23 antagonist in inflammatory diseases such as psoriasis, Crohn's disease, and ankylosing spondylitis, is supported by several lines of evidence including mouse models, genome-wide association studies and histological findings in humans.

Although previous experience with selective IL-23 antagonists is limited, a mAb targeting the common p40 subunit of the IL-12 and IL-23 cytokines, ustekinumab (Stelara®), has been approved for the treatment of psoriasis, and a second (briakinumab) reached Phase III clinical trials before development was stopped. Both ustekinumab and briakinumab showed efficacy in the treatment of psoriasis.

The critical role of IL-12 in adaptive immunity raised concerns that mAbs directed against the IL-12 p40 subunit could increase the risk of infections or cancer, due to inhibition of IL-12-dependent immune surveillance mechanisms (P06-11555, R11-1236). Indeed, higher rates of these events were noted in pivotal Phase III randomised controlled trials of briakinumab (R11-1529, R12-1010), although not in trials of ustekinumab. However, complete IL-23 deficiency is not associated with a predisposition to mycobacterial infections (R12-1011) although it is associated with significant defects in humoral and delayed-type hypersensitivity responses in mice (R11-1204).

Observations of Major Adverse Cardiovascular Events (MACE) during the clinical development of both briakinumab and ustekinumab raised concerns that inhibition of either IL-12, IL-23, or both could pose cardiovascular safety risks (R11-4193). However, such a risk has not been confirmed among patients receiving ustekinumab for up to five years (R13-3518). No additional data has emerged to suggest a specific cardiovascular risk associated with inhibition of IL-23; nevertheless, particular attention will be given to cardiovascular AEs in clinical trials of BI 655066.

1.2 DRUG PROFILE

BI 655066 is a humanized monoclonal antibody (mAb) of the IgG1 subclass that is directed towards IL-23p19. The framework of the antibody has been engineered with two mutations in the Fc region to reduce Fcγ receptor and complement binding. The C-terminal lysine of the heavy chain has also been deleted to reduce potential charge heterogeneity.

In Study 1311.1, a Phase I single rising dose trial in psoriasis patients, administration of BI 655066 either intravenously or subcutaneously appeared to be well tolerated. A total of 39 patients received a single dose of either BI 655066 i.v. (n=18), s.c. (n= 13), or placebo (n=8). All patients who received 0·01, 0·25, 3, or 5 mg/kg i.v., or 0·25 or 1 mg/kg s.c. doses of BI 655066 (n=27) achieved $PASI_{75}$ responses by Week 12 *vs.* 33% (1/3) and 67% (2/3) in 0·05 and 1 mg/kg i.v. dose groups, respectively *vs.* 13% (1/8) in the combined placebo group. $PASI_{90}$ rates by Week 12 were up to 100% (0·01 mg/kg i.v. group [3/3] and in both s.c. dose groups [13/13]) *vs.* 0% (0/8) in placebo group. Efficacy was well maintained at Week 24 and beyond. Treatment with BI 655066 resulted in significant changes in select psoriasis related

biomarkers in the skin and plasma through Week 12 and correlated with improvement in PASI scores. There were no clear relationships between the overall frequency of AEs and treatment; nor were there clear relationships between the occurrence of AEs in specific organ classes, individual AEs, their severity or relatedness, and treatment. Exposure increased in an approximately dose-proportional manner, with absolute bioavailability of 59%, providing a rationale for conducting further clinical studies of BI 655066 in patients with psoriasis. (M14-0004)

2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The phase I, single rising dose study (1311.1) has shown proof of concept and proof of efficacy for BI 655066 in patients with moderate to severe psoriasis.

The preceding phase II study (1311.2) will allow for the evaluation of the efficacy, safety, tolerability, pharmacokinetics and pharmacodynamics of three different dose regimens (18 mg, 90 mg and 180 mg) of BI 655066, as well as dose-finding of BI 655066 for further studies. In addition the 1311.2 trial will compare the efficacy of BI 655066 with Stelara®, an approved therapy for patients with moderate to severe psoriasis.

The data generated from this extension study is anticipated to provide additional safety data of up to approximately four years treatment in approximately 100 patients treated with BI 655066. Furthermore the study is being performed in order to allow extended access to a potential beneficial intervention, according to the principles laid down in the Declaration of Helsinki.

2.2 TRIAL OBJECTIVES

The overall purpose of this open label extension (OLE) trial is to assess long-term safety and efficacy (durability of response) of BI 655066 in patients with moderate to severe chronic plaque psoriasis. In addition, this study will provide an opportunity for subjects to have extended access to a proven active therapy for approximately four years administration.

The primary objective of the study is to investigate safety of BI 655066, in patients with moderate to severe chronic plaque psoriasis, receiving long-term treatment.

Additional objectives of this study are to further investigate long-term efficacy, tolerability, pharmacokinetics, pharmacodynamics and immunogenicity of BI 655066.

Study endpoints are listed in Section 5.

2.3 BENEFIT - RISK ASSESSMENT

Results of the Phase I study with BI 655066 (study 1311.1) suggest that a single injection intravenously or subcutaneously (i.v. or s.c.) of BI 655066 is associated with substantial and durable improvements in the cutaneous manifestations of psoriasis. At doses of 0.25 mg/kg intravenously and above, all active dose groups showed improvement in mean PASI scores of at least 75% from baseline by week 12, which lasted at least until week 24. Similar improvements were observed in both of the active BI 655066 subcutaneous dose groups (M14-0004).

Patients rolling over in this OLE will have completed the single blind 1311.2 study where 75% of all patients will have received BI 655066 at different dose levels. Based on the preliminary data from study 1311.1 described in Section 1.2, where good tolerability was

shown, and no drug related serious adverse events (SAE), patients are likely to benefit from participation in this study.

Risks of participating in this study include risks related to the trial specific procedures such as blood sampling, subcutaneous injection of study medication. Blood sampling and subcutaneous injections can cause local bruising, inflammation, and pain.

As with any immune modulating agent, BI 655066 has the potential to impair immune function resulting in a risk of infection. This will be addressed by clinical monitoring for AEs during the treatment and follow up periods. Interferon gamma (IFN-γ) release assay to *M. tuberculosis* will be obtained at the initial roll-over visit, in order to exclude or discontinue documented untreated patients with active or latent tuberculosis infection (TB). All patients will be re-tested at the Extended end of treatment visit in order to assess long-term impact of BI 655066 on *M. tuberculosis* exposure. Patients having current signs or symptoms of infection or history of serious infection will not be included in the study.

The role of IL-23 in tumour immunity is not well established at this time, but an increased risk of cancer from an IL-23 antagonist, though considered small, cannot be excluded.

Major adverse cardiovascular events (MACE), including myocardial infarction, cerebrovascular accident, and cardiovascular death, have been initially reported in association with the anti-IL-12/23 agents, ustekinumab and briakinumab, in patients with psoriasis. However, such a risk has not been confirmed among patients receiving ustekinumab for up to five years (R13-3518). The overall risk of MACE in the present study is considered to be low.

Local reactions to i.v. and s.c. administered biologic agents are uncommon, and are usually limited to redness, swelling or induration at the injection site. Manifestations of systemic hypersensitivity reactions include anaphylaxis, pruritus, hypotension, and respiratory distress. Both local and systemic hypersensitivity reactions are readily detectable, transient in nature, and manageable with standard medical treatment. No systemic hypersensitivity reactions have been reported with BI 655066 to date. Patients will be closely monitored 30 minutes to 1 hour after drug administration for signs of redness, swelling or hardness at the injection site or generalized itching, dizziness or difficulty breathing.

Although rare, a potential for drug-induced liver injury is under constant surveillance by sponsors and regulators. Therefore, this study requires timely detection, evaluation, and follow-up of laboratory alterations of selected liver laboratory parameters to ensure patients´ safety (cf. section 10.4).

The study has been designed, and will be conducted in such a manner as to limit these risks as much as possible. In order to mitigate any safety signals as early as possible, an independent Data Monitoring Committee (DMC) will oversee this study. Since all patients will receive active treatment at a dose of, or greater than the projected marketed dose, most patients will likely have a benefit from participating in this study. Therefore, the benefit-risk assessment is considered appropriate for a clinical trial of an experimental therapy at this stage of development.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This open label extension trial (OLE), investigates the additional safety and efficacy of the 90 mg dose of BI 655066. Approximately 100 patients who meet the entry criteria are planned for inclusion in this trial, rolling over from the preceding 1311.2 trial. The treatment will be open label.

The treatment period will be approximately four years of administration starting with first administration of BI 655066 in either trial 1311.2 or 1311.13, followed by a 12 week follow up period. After 01-May-2018 and approval of this protocol amendment in each respective country, the next study visit will be the Extended EOS visit and therewith the last visit in this study. Patients who have completed the study without early treatment discontinuation will be offered to roll over to M15-997 open label extension (OLE) trial if they fulfill the in- and exclusion criteria for the M15-997 trial. Refer to section 6.2.3.

Patients rolling over from the preceding trial 1311.2 will have to complete the treatment period in that trial, or complete the entire trial including the follow up period, reaching end of study. If, during the follow up period of the preceding trial (at any visit from week 24 and onwards in trial 1311.2) loss of response is detected, the patient can roll over in this extension trial. For this, loss of response is defined as < $PASI_{50}$.
Extended visit 1of this trial should preferably be performed as a combined visit the same day as End of Study visit of 1311.2, or within an interim period of maximum 6 weeks thereafter.

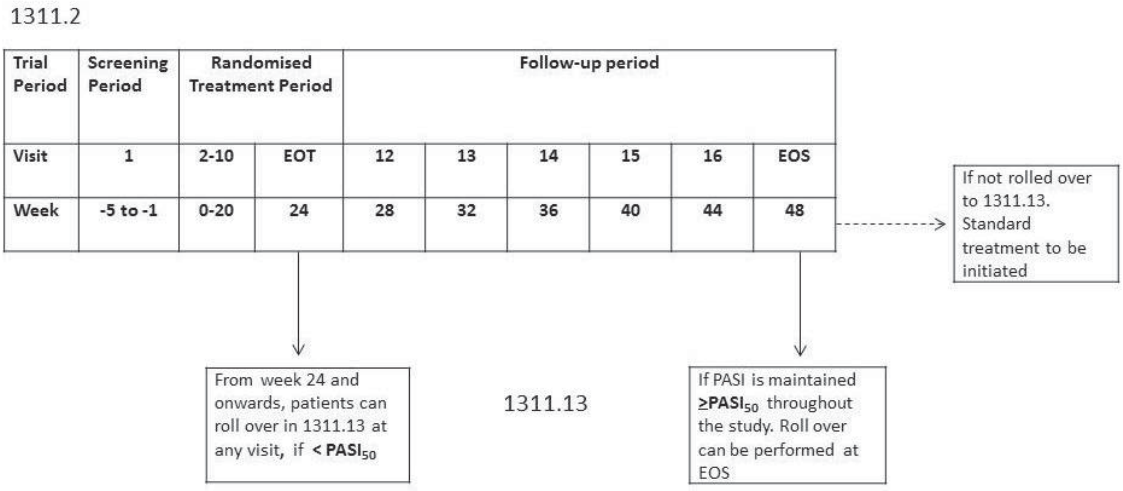
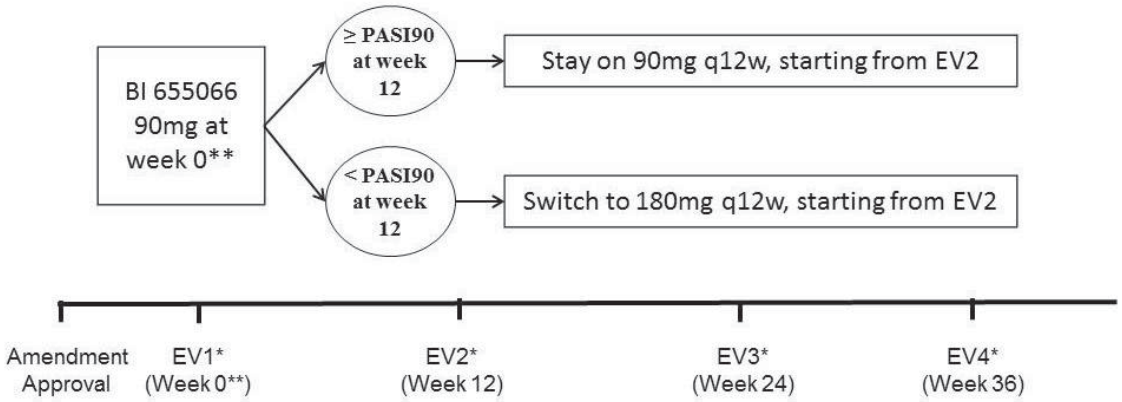


Figure 3.1:1 Guideline for roll over of patients from 1311.2 to OLE study 1311.13

After the approval of this protocol amendment in each respective country, all patients will follow Flow Chart (Extended Dosing Period) and receive 90mg BI 655066 subcutaneously at their Extended visit 1 (EV1). From EV1 onwards, BI655066 will be administered subcutaneously every 12 weeks during the trial. At EV2, if there is a lack of response, defined as <PASI90, the dose should be increased to 180mg for the remainder of the trial (see Fig 3.1.2).

For ongoing patients under the previous protocol amendment (Pre-Extended Dosing Period, see Fig 3.1.3), EV1 should be conducted at the following time points:

1. For ongoing patients with ≥12 weeks since the EOT visit: Conduct EV1 as soon as possible
2. For ongoing patients still undergoing treatment or with <12 weeks since the EOT visit: Conduct EV1 at the time of the next scheduled treatment or follow up visit (note: EV1 should not be conducted at the time point of Visit 2 under the previous protocol, patients with Visit 2 as their next scheduled visit should have their EV1 replacing their Visit 3 instead)



* EV stands for extended visit
** Week 0 is the first scheduled visit after amendment approval.

Figure 3.1:2 Guideline for assessment of dose adjustment

Trial periods	Treatment period							Follow Up period			
Visit	1[1]	2	3	Interim Contact	4	5	EOT	FU 1	FU 2	FU 3	EOS visit
Day	1	42	84	126, 210, 294, etc…	168	252	336		EOT +168	EOT +252	EOT +336
Week	0	6	12	18, 30, 42, etc…	24	36	48	EOT +12	EOT +24	EOT +36	EOT +48
Visit window (days)	+7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7

Figure 3.1:3 Visit schedule Pre-Extended Dosing Period

If there are any tolerability issues, as assessed by the investigator, the patient will be discontinued.

The plaque psoriasis will be evaluated by PASI score at each visit. The standard clinical endpoints of PASI50, PASI75, PASI90 and PASI100 will be assessed at each visit based on the baseline PASI from 1311.2.

The end of study is defined as the date the last subject completes the Extended End-of-study visit.

3.1.1 Administrative structure of the trial

The trial is sponsored by AbbVie in the US and Boehringer Ingelheim (BI) ex-US.

The trial is planned to be conducted at sites participating in the 1311.2 trial, i.e. it will be conducted at approximately 24 sites in 4 different countries.

Boehringer Ingelheim has appointed a Trial Clinical Monitor (TCM), responsible for coordinating the activities required in order to manage the trial in accordance with applicable regulations and internal standard operating procedures (SOPs), directing the clinical trial team in the preparation, conduct and reporting of the trial and ensuring appropriate training and information for Local Clinical Monitors (CML), Clinical Research Associates (CRAs) and investigators of participating countries.

Data management will be done by BI according to BI SOPs and the Statistical Evaluation will be done by AbbVie according to their SOPs. For these activities a Trial Data Manager and a Trial Statistician have been appointed. A list of responsible persons will be available in the Trial Master File (TMF).

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 have been agreed and a written contract filed before initiation of the clinical trial. In each OPU participating in this study, a CML will be appointed responsible for coordinating the activities required, in order to manage the trial in accordance with applicable regulations and internal SOPs in the countries covered by the respective BI OPU.

A Co-ordinating Investigator has been nominated to coordinate investigators at different sites participating in this multicentre, multinational trial. Tasks and responsibilities for the Coordinating Investigator will be defined in a written contract filed before initiation of the trial.

Details of the trial supplies including responsible institutions are given in Section 4 of this protocol.

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

A central laboratory service and an Interactive Response Technology (IRT) vendor will be used in this trial. Details will be provided in IRT Manual and Central Laboratory Manual, available in ISF.

Safety will be monitored by an independent Data Monitoring Committee (DMC).

3.1.2 Data Monitoring Committee (DMC)

The trial will include the review of data by an external, independent DMC, including an independent statistician. The purpose of the DMC is to ensure the welfare of subjects participating in this trial is maintained by monitoring the trial for possible, untoward harmful effects or inappropriate frequency of adverse events for this class of medication. The DMC will evaluate and analyse accrued, unblinded safety and efficacy data in order to recommend whether the trial should continue, be modified or stopped due to safety or lack of efficacy concerns. For details regarding DMC structure and scheduled meetings, please consult the DMC charter.

Sponsor will agree with the DMC a set of strictly defined stopping criteria for the study level, to be included into the DMC Charter.

The final DMC Charter will be available before study initiation.

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

Study 1311.13 is designed as an open label extension clinical trial, and is expected to generate additional safety information to support the registration submission. As noted in section 4.1.3 below, the intermediate dose (90 mg) from the 1311.2 study will be used, with the option of moving to a higher dose (180 mg) if inadequate clinical activity is noted. Our goal in this study is to obtain safety and efficacy data following long-term drug administration. As an open-label study, we realize that no powered or controlled analysis can be obtained. However, we will be able to evaluate initial tendencies and at the same time permit our early study participants an opportunity to maintain access to a therapy that initially has shown the potential to have significant clinical benefit.

3.3 SELECTION OF TRIAL POPULATION

Eligible patients from trial 1311.2 will be offered participation in this OLE trial. The check for patient eligibility will be based upon a successful completion (cf. Section 3.3.2) of the previous trial and on signing the Informed Consent for the OLE.

A 40 % dropout rate from preceding trial is expected, leaving approximately 100 patients to be entered in this trial.

A log of all patients included into the study (i.e. having given informed consent) will be maintained in the ISF at the investigational site.

3.3.1 Main diagnosis for study entry

Moderate to severe chronic plaque psoriasis.

3.3.2 Inclusion criteria

1. Patients with moderate to severe chronic plaque psoriasis, who have successfully completed the preceding trial, 1311.2. Successful completion of preceding trial is defined as either of the following:
    a. Completion of the entire follow up period, thus reaching End-of-study (EOS) visit.
    b. Loss of response, defined as decrease in response to <$PASI_{50}$ at any time from week 24.
2. Patient must give informed consent and sign an approved consent form prior to any study procedures in accordance with Good Clinical Practice (GCP) and local legislation
3. Applicable only for female patients:

    Negative urine pregnancy dip stick test at the roll-over visit, and if available at roll-over visit, negative

    Serum ß-Human Chorionic Gonadotropin (ß-HCG) test (cf.Section3.3.4.1).

    In addition:

    Women of childbearing potential (not surgically sterilized and between menarche and

    1 year postmenopausal), that, if sexually active agree to use one of the appropriate medically accepted methods of birth control in addition to the consistent and correct use of a condom from date of the roll-over visit until 12 weeks after last treatment in this trial. Medically accepted methods of contraception's are: ethinyl estradiol containing contraceptives, diaphragm with spermicide substance, and intra-uterine-device.

    OR

Female patients which have vasectomized sexual partner(s) (vasectomy at least 1 year prior to enrolment).

OR

Surgically sterilized female patients with documentation of prior hysterectomy, tubal ligation or complete bilateral oophorectomy.

OR

Postmenopausal women with postmenopausal is defined as permanent cessation ≥ 1 year of previously occurring menses.

3.3.3 Exclusion criteria

1. Patients who experienced any drug related Serious Adverse Event in the preceding trial

2. Patients who have developed guttate, erythrodermic or pustular psoriasis or drug-induced psoriasis (as diagnosed by the investigator), during the preceding trial 1311.2.

3. Evidence of current or previous clinically significant disease, medical condition other than psoriasis, or finding of the medical examination (including vital signs and (electrocardiography (ECG)), that in the opinion of the investigator, would compromise the safety of the patient or the quality of the data.

4. Known clinically important acute or chronic infections including hepatitis, HIV. In regards to Tuberculosis the following applies:
    - Signs or symptoms suggestive of current active or latent tuberculosis upon medical history, physical examination and/or a chest radiograph (both posterior-anterior and lateral views, taken within 3 months prior to the first administration of study drug and read by a qualified radiologist).
    - History of latent or active TB prior to screening, except for patients with documented completion of an adequate treatment regimen, at least 6 months prior to the first administration of study agent.
    - Positive QuantiFERON-TB Gold In-Tube test (IGRA) within 2 months prior to the roll-over visit (if available) (cf. Section 3.3.4.1), in which active tuberculosis has not been ruled out. This does not apply to patients with history of latent tuberculosis with documented completion of an adequate treatment regimen, at least 6 months prior to the first administration of study agent.

5. Patients who have developed malignancy, or suspicion of active malignant disease during the preceding trial 1311.2 (except treated cutaneous squamous cell or basal cell carcinoma or carcinoma in situ of the cervix that have been adequately treated).

6. Intake of restricted medications (cf. Section 4.2.2.1) or other drugs considered likely to interfere with the safe conduct of the study, as assessed by the investigator.

7. Alcohol or drug abuse within 3 months prior to the roll-over visit that would interfere with trial participation or any ongoing condition leading to a decreased compliance to study procedures in the opinion of the investigator.

8. Any clinically significant laboratory abnormalities based on the last available lab results received during the preceding trial (according to the investigator's medical assessment) (cf. Section 6.2.2.1).

9. Pre-menopausal woman who is pregnant or nursing

Note:

As there might be other medical and social issues, not covered by the above criteria it is left to the discretion of the investigator to exclude patients based on clinical judgment, even if other eligibility criteria are satisfied.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

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

- The patient withdraws consent, without the need to justify the decision.
- Clinically important acute or chronic infections including hepatitis, HIV and tuberculosis (including latent tuberculosis), or a positive interferon gamma release assay (IGRA) testing for tuberculosis (cf. Table 5.2.3: 1) according to test at the roll-over visit.
- The patient is no longer able to participate for other medical reasons (e.g. pregnancy, surgery, AEs or other diseases).

A patient can be withdrawn after discussion between sponsor and investigator if eligibility criteria are being violated or if the patient fails to comply with the protocol (e.g. non-attendance at study assessments). Note: Patients using restricted medications (cf. Section 4.2.2), will continue to be followed up to collect safety data but their efficacy and PD endpoints assessed after administration of restricted medications will not be considered for analysis.

If a patient withdraws from the study after informed consent, this will be documented and the reason for withdrawal will be recorded in the case report form (CRF). This data will be included in the trial database and will be reported. At the time of discontinuation a complete end of treatment (Extended EOT) evaluation should be performed according to Flow Chart and the patient will subsequently enter a follow up period of 12 weeks, until a final Extended EOS visit is performed. If the decision to discontinue study participation is taken in between study visits in the treatment period, an Extended EOT visit is to be scheduled at the earliest convenience and by the latest at the next upcoming visit according to Flow Chart and the information will be recorded in the CRFs.

If the decision to discontinue is taken in the 12 week follow up period, an early Extended EOS visit is to be scheduled at the earliest convenience. The procedures described at Extended EOS will be performed and the information will be recorded in the CRFs. The withdrawals will be discussed in the final report of the study.

If a patient becomes pregnant during the trial, the investigational product needs to be stopped. The patient will be followed up until birth or otherwise termination of the pregnancy. The data of the patient will be collected and reported in the clinical trial report until last patient last visit and any events thereafter will be reported in the BI 655066 safety database.

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:

a. Emergence of any efficacy/safety information that could significantly affect continuation of the trial or any other administrative reasons.
b. Violation of GCP, the clinical trial protocol (CTP), or the contract by a trial site or investigator, disturbing the appropriate conduct of the trial.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination according to option a.

4. TREATMENTS

4.1 TREATMENTS TO BE ADMINISTERED

BI 655066 is supplied by Boehringer Ingelheim, and will be administered subcutaneously.

4.1.1 Identity of BI 655066 and comparator product(s)

The characteristics of the test product for s.c. administration are below.

Substance:	BI 655066: Anti-human IL23p19 mAb
Pharmaceutical formulation:	[redacted]
Chemical name:	Anti-human IL-23p19 mAb
Molecular weight:	Approximately 148 kDa
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	90 mg BI 655066 in a pre-filled syringe with 1 ml (concentration 90 mg/ml)
Posology	Multiple doses
Route of administration:	s.c.

4.1.2 Method of assigning patients to treatment groups

Patients will receive a single dose of open label BI 655066 every 12 weeks. The initial dose for all patients moving into the open label extension study will be 90 mg.

If response is maintained, i.e. achievement of $PASI_{90}$ at Extended visit 2, 90 mg dosing will occur every 12 weeks until Extended EOT.

If there is a lack of response, defined as response below $PASI_{90}$ at Extended visit 2, the dose should be increased to 180 mg, and the 180 mg dosing will occur every 12 weeks until Extended EOT.

Detailed instructions for preparation of BI 655066 for administration of each dose will be given in the ISF.

4.1.3 Selection of doses in the trial

The treatment is derived from the treatment groups in the preceding phase II trial, where the dose selection is based on the completed phase I trial in which clinical improvement in patients with psoriasis was observed across a wide dose range (~18 mg -375 mg).

The choice of the “90 mg/dose” was based on several pieces of data obtained in the initial 1311.1 single-dose, dose-escalation study: an analysis of dose given (and the subsequent “area under the curve” exposure data) plotted against the clinical response based on the PASI

score noted that the stable effective dose was likely to be greater than 1.0 mg/kg (approximately 90 mg)

Subsequent to selection of the starting dose for 1311.13, an interim analysis of 1311.2 indicated that the 180 mg dose resulted in a numerically higher proportion of patients who achieved PASI90. Since the higher dose was not associated with a higher incidence of any specific adverse events, patients who do not achieve PASI90 on the 90 mg dose are eligible to receive the higher dose of 180 mg. This dose is also consistent with the objective of obtaining safety data on a dose equal to or greater than the proposed "to be marketed" dose of 150 mg, allowing us to obtain additional safety information appropriate for inclusion in future discussion with health authorities.

4.1.4 Drug assignment and administration of doses for each patient

The study drug will be administered by the physician investigator or by authorised study personnel (e.g. study nurse). The study drug will be administered as a subcutaneous injection in the abdomen, thighs, gluteal regions, or upper arms. Injections being given in the same area should be at least 2 cm apart and should not be close to a vein. The injection site 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 technique of injection and injection materials (syringes, needles) will be provided in the ISF. For 180 mg doses, two syringes of 1 ml BI 655066, each of 90 mg, will be allocated and injected. Dilution of the study medication is not allowed and no dose modification, apart from the protocol specified doses, is permitted.

Administration of biologic agents involves the risk of local (injection site) or systemic hypersensitivity reactions. Therefore the patients should be closely monitored for signs and symptoms of hypersensitivity reactions for approximately 1 hour after the first dose administered, and 30 minutes following all other doses of study drug. Study personnel should observe the injection site for signs of redness, swelling or hardness. They should also ask subjects about itching, dizziness or shortness of breath. Patients should be advised that if they experience redness, swelling or other changes at the injection site, they should notify site personnel. They should further be advised that if they experience itching all over or a feeling of being swollen, dizzy or short of breath, they should notify site personnel or their own healthcare provider immediately.

Vital signs will be taken pre-dose, 5 minutes, and 1 hour (at roll-over visit) or 30 minutes (at following visits) after the dose is administered (cf. Flow Chart). 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.

4.1.5 Blinding and procedures for unblinding

Not applicable.

In this open-label trial, treatment allocation will not be concealed throughout the study. The CRF will contain information on treatment.

4.1.6 Packaging, labelling, and re-supply

BI 655066 supplies will be provided by Boehringer Ingelheim (cf. Section 4.1.1 for more details regarding the supplies). 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

The trial medication must be stored securely, e.g. in a locked refrigerator or at a pharmacy, in their original packaging. It may only be dispensed to trial patients according to the clinical trial protocol, by authorised personnel as documented in "Trial Staff List".

Drug supplies should be stored as indicated on the country specific booklet page. A temperature log must be maintained. If the storage conditions are found to be outside the specified range, immediately contact the local clinical monitor as provided in the lists of contacts.

Further details are provided in the Investigator´s Brochure and on the country specific labels of which a sample will be maintained in the ISF.

4.1.8 Drug accountability

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

- approval of the study protocol by the Institutional Review Board (IRB) / ethics committee,
- availability of a signed and dated clinical trial contract between the sponsor and the Head of Trial Centre,
- 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 or immediately imminent signing of the clinical trial protocol,
- availability of the proof of a medical licence for the principal investigator,
- availability of the Form 1572 (only applicable for (United States (US)).

The investigator/ pharmacist/ investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or alternative disposition of unused product(s), on the respective forms in the ISF.

These records will include dates, quantities, batch/serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product(s) 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 product(s) received from the sponsor. At the time of return to the sponsor or designee, the investigator / pharmacist / investigational drug storage manager must verify that all unused or partially used drug supplies have been returned and that no remaining supplies are in the investigator's possession. Account must be given for any discrepancies.

4.2 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

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

In principle, any additional concomitant therapy considered necessary for the patient's welfare may be given at the discretion of the investigator. 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 3.3.3), are permissible. However, all concomitant medications being taken by eligible patients must be carefully evaluated, and questions on the use of concomitant medications should be discussed with the BI clinical monitor.

In the event that a patient experiences an intolerable increase of psoriasis during the course of the trial, topical steroids of US class 6 (mild, such as desonide) or US class 7 (least potent, such as hydrocortisone) will be permitted for use limited to the face, axilla, and/or genitalia. Details of the drug used and the reason must be recorded in the electronic case report forms (eCRF). These topical medications should not be used within approximately 24 hours prior to visits requiring the PASI.

Investigational products are not allowed during the course of the trial.

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

There are no special emergency procedures to be followed.

Patients with a positive IGRA testing (Tb screening) at the roll-over visit should be followed-up according to local guidelines.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

The medications (or classes of medication) listed in Table 4.2.2.1:1 must not be taken for the specified times before the roll-over l visit and for the whole duration of the study including the Extended Follow-up Period.

Table 4.2.2.1: 1 Restricted medications

Investigational products not otherwise described below (except 1311.2 study drug)	Throughout the duration of preceding trial 1311.2, and for the whole duration of this trial, including any interim period between the trials and the Extended Follow-up Period.
Any biological agents, including but not limited to infliximab, etanercept, adalimumab	Throughout the duration of preceding trial 1311.2, and for the whole duration of this trial, including any interim period between the trials and the Extended Follow-up Period
Oral or injectable psoriasis medications (not biologicals) including but not limited to retinoids, methotrexate, cyclosporine, fumarates, or any other drugs known to possibly benefit psoriasis. Systemic corticosteroids in any dosage form. Any drug known to interfere with or to aggravate psoriasis including but not limited to lithium and interferons, or Phototherapy (UVB, PUVA, UVA).	Throughout the duration of preceding trial 1311.2, and for the whole duration of this trial, including any interim period between the trials and the Extended Follow-up Period
Steroids, retinoids, vitamin D analogs, vitamin A analogs and anthralin in any formulation (i.v., s.c., topicals, oral).	Throughout the duration of preceding trial 1311.2, and for the whole duration of this trial, including any interim period between the trials and the Extended Follow-up Period. (for exceptions cf. Section 4.2.1)

4.2.2.2 Restrictions regarding vaccination

Live vaccinations during the study are not allowed. Bacille Calmette-Guérin vaccines (BCG) are not allowed throughout the duration of preceding trial 1311.2, and for the whole duration of this trial, including any interim period between the trials. It is recommended that patients are advised not to take any live vaccines or BCG vaccines for up to 1 year after the last administration of study drug.

4.2.2.3 Restrictions on diet and life style

Patients must be fasted for at least 8 hours prior to collection of the safety laboratory samples, starting from the initial roll-over visit.

Patients should refrain from excessive physical activity at least 24 hours prior to study visits, during the course of the study (competitive sport etc.).

Use of tanning beds is not allowed during the course of the study.

4.3 TREATMENT COMPLIANCE

Dose administration compliance will be assured by administration of all study medication under supervision of the investigating physician or a designee at the research site. The measured plasma concentrations will provide additional information about compliance.

5. VARIABLES AND THEIR ASSESSMENT

5.1 EFFICACY - PHARMACODYNAMICS

5.1.1 Endpoints of efficacy

5.1.1.1 Primary endpoint of efficacy

The primary efficacy endpoint is achievement of a ≥ 90% reduction in PASI score from baseline (i.e., achieving $PASI_{90}$) at week 48 in the Extended dosing period. Baseline PASI for this study is defined as the baseline PASI for the 1311.2 study.

5.1.1.2 Secondary endpoints of efficacy

The following secondary endpoints will all be evaluated at week 48in the Extended dosing period:

- achievement of $PASI_{50}$
- achievement of $PASI_{75}$
- achievement of $PASI_{100}$
- achievement of sPGA of clear or almost clear

5.1.1.3 Further endpoints of efficacy

Additional efficacy analyses will include, but are not limited to, the following:

- achievement of $PASI_{50}$ at all Extended dosing period visits where PASI is collected
- achievement of $PASI_{75}$ at all Extended dosing period visits where PASI is collected
- achievement of $PASI_{90}$ at all Extended dosing period visits where PASI is collected
- achievement of $PASI_{100}$ at all Extended dosing period visits where PASI is collected
- achievement of sPGA of clear or almost clear at all visits where sPGA is collected
- time to loss of $PASI_{50}$, which is a time to failure endpoint. This will be repeated using $PASI_{75}$, $PASI_{90}$, and $PASI_{100}$ as the endpoint.
- sPGA will be evaluated in terms of time to loss of response which is defined as a score exceeding 1, and will be evaluated as a time to failure endpoint
- change from baseline in Pain-VAS (in subgroup of patients with psoriatic arthritis only where baseline VAS is from 1311.2)
- mean DLQI scores at all Extended dosing period visits where PASI is collected

5.1.2 Assessment of efficacy

The PASI measures the severity of a patient's psoriasis and the percent of the patient's skin that is affected. See Section 10.1 for a detailed description of the PASI.

The Static Physician Global Assessment (sPGA) is a 6 point scale used by physicians to describe the severity of a patient's psoriasis. See Section 10.2 for a detailed description of the sPGA.

The Pain-VAS is a Visual Analogue Scale used to assess a patient's psoriatic arthritis. See Section 10.3 for a detailed description of the Pain-VAS.

Immunogenicity testing (Anti-Drug Antibodies (ADA)) will be performed at the visits specified in the Flow Chart in order to detect the emergence of antibodies.

The Dermatology Life Quality Index (DLQI) is a questionnaire that determines a patient's quality of life. See Section 10.4 for a detailed description of the DLQI.

5.2 SAFETY

5.2.1 Endpoint(s) of safety

5.2.1.1 Primary endpoints of safety

The primary endpoints of safety are as follows:

- the occurrence of AEs
- the occurrence of drug related AEs
- the occurrence of SAEs

5.2.1.2 Secondary endpoints of safety

Not applicable as there are no secondary endpoints of safety.

5.2.1.3 Further endpoints of safety

Safety and tolerability will be assessed in a descriptive way based on:

- Changes in vital signs and physical examination
- Adverse events (AEs)
- The occurrence of Adverse events of special interest (AESIs)
- Discontinuation of therapy due to AEs, SAE
- Changes in safety laboratory analysis

Immunogenicity testing (ADA) will be performed at the visits specified in Flow Chart in order to detect the emergence of antibodies. Immunogenicity will be evaluated in terms of time to antibody emergence starting from the time of first exposure to BI 655066 in either 1311.2 or 1311.13.

5.2.2 Assessment of adverse events

5.2.2.1 Definitions of adverse events

Adverse event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a

pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Serious adverse event

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, 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 judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Intensity of adverse event

The intensity grading of AEs will be performed according to Rheumatology Common Toxicity Criteria (RCTC) Version 2.0 developed by Outcome Measures in Rheumatology (OMERACT) (R13-3515). Cf. Appendix 10.7 and ISF for intensity/severity classification.

Causal relationship of adverse event

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

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

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

Worsening of the underlying disease or other pre-existing conditions

Worsening of the underlying disease or of other pre-existing conditions will be recorded as an (S)AE in the (e)CRF.

Changes in vital signs, ECG, physical examination, and laboratory test results

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an (S)AE in the (e) CRF, if they are judged clinically relevant by the investigator.

Adverse Events of Special Interest (AESI)

The following are considered as Adverse events of Special Interest (AESI):

Hepatic injury defined by the following alterations of liver parameters (for patients with normal liver function at baseline): an elevation of AST and/or ALT $\geq$3 fold upper limit of normal (ULN) combined with an elevation of total bilirubin $\geq$2 fold ULN measured in the

same blood draw sample.
Patients showing these lab abnormalities need to be followed up according to section 10.6 of this clinical trial protocol and the "Drug induced liver injury (DILI) checklist" provided in ISF.

- Major adverse cardiovascular events (MACE).
  Including, but not limited to the following preferred terms: Atherosclerosis, Coronary artery disease, Myocardial infarction, Angina Pectoris, Transient ischemic attack, Cerebrovascular accident (including Stroke), Cardiac failure congestive, Peripheral arterial occlusive disease.

ASEIs are to be reported in an expedited manner similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria – for details please see section 5.2.2.2.

5.2.2.2 Adverse event and serious adverse event reporting

All adverse events, serious and non-serious, occurring during the course of the clinical trial (i.e., from signing the informed consent onwards through the Residual Effect Period (REP) /Extended follow-up period) will be collected, documented and reported to the sponsor by the investigator on the appropriate CRF(s) / eCRFs / SAE reporting forms. Reporting will be done according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Investigator Site File.

Reporting of Adverse Events in Remote Data Capture system (RDC):

AEs that are ongoing at the end of the previous trial (1311.2) will have to be re-entered, and any adverse events that have started between the two trials (in the event that the 6 weeks time-window is used), will also be entered into the 1311.13 RDC system.

Reporting of Adverse Events on the SAE form:

Specific instructions for the SAE reporting process concerning SAE forms in previous and roll-over studies will be provided in the ISF.

The REP for BI 655066 is 12 weeks. Therefore, all events reported within 12 weeks of the last trial medication will be considered on treatment. All adverse events will be reported up until the last per protocol visit (Extended EOS visit), which is 84 (+7 days) days after the last dose of trial medication.

The investigator does not need to actively monitor patients for AEs once the clinical trial has ended. However, if the investigator becomes aware of an SAE(s) that occurred after the patient has completed the clinical trial (including any protocol required REP and / or follow-up), it should be reported by the investigator to the sponsor if considered relevant by the investigator.

For each adverse event, the investigator will provide the onset date, end date, intensity, treatment required, outcome, seriousness, and action taken with the investigational drug. The

investigator will determine the relationship of the investigational drug to all AEs as defined in Section 5.2.2.1.

The investigator must report the following events using paper process SAE form via telephone/fax immediately (within 24 hours) to the sponsor: SAEs and non-serious AEs relevant to the SAE(s), and AESIs.

Boehringer Ingelheim has set up a list of AEs which are defined to be always serious. In order to support the investigator with the identification of these "always serious adverse events", if a non-serious AE is identified to be serious per Boehringer Ingelheim definition, a query will be raised. The investigator must verify the description and seriousness of the event. If the event description is correct, the item "serious" needs to be ticked and an SAE has to be reported in expedited fashion following the same procedure as above.

The list of these adverse events can be found via the RDC-system.

With receipt of any further information to these events, a follow-up SAE report has to be provided. SAEs and non-serious AEs must include a causal relationship assessment made by the investigator.

The SAE form is to be forwarded to the defined unique entry point identified for the BI OPU (country-specific contact details will be provided in the Investigator Site File) or by using the electronic submission process. This immediate report is required irrespective of whether the investigational product has been administered or not and irrespective of causal relationship. It also applies if new information to existing SAEs or AESIs becomes available.

Pregnancy

In rare cases, pregnancy might occur in clinical trials. Once a female subject has been enrolled into the clinical trial, after having taken study medication, the investigator must report immediately any drug exposure during pregnancy to the sponsor. Drug exposure during pregnancy has to be reported immediately (within 24 hours or next business day whichever is shorter) to the defined unique entry point for SAE forms of the respective BI OPU (country-specific contact details will be provided in the Investigator Site File). The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up. In the absence of an (S)AE, only the Pregnancy Monitoring Form for Clinical Trials and not the SAE form is to be completed. The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part B).

5.2.3 Assessment of safety laboratory parameters

The laboratory parameters that will be determined are listed in Tables 5.2.3: 1 and 5.2.3: 2 at the time points provided in Flow Chart. The respective reference ranges will be provided in the ISF. The laboratory tests will be performed at a designated central laboratory, and if necessary by additional specialist laboratories.

Laboratory results of the patients will be available in real time to the respective investigator and to the clinical monitor of each country (central laboratory website), and selected

abnormal laboratory alerts will be sent automatically to the sites and to the sponsor in real time. PK, PD and biomarker data will not be available to the investigators or local clinical monitors, but only to the Trial Team (sponsor) and to the DMC.

Clinically relevant laboratory values will be commented on in the eCRF. A clinically relevant value may be either in- or outside the reference range. Clinically relevant abnormal laboratory test results must be repeated using an unscheduled visit lab kit and must be repeated until normalisation or stabilisation or until an alternative explanation has been found. Clinically relevant abnormal laboratory values will be also graded for intensity by using RCTC Version 2.0 criteria.

The tests listed in Table 5.2.3: 1 constitute laboratory tests and hormones (assessed in female patients only) that will be done only at the initial roll-over visit and at Extended EOT or Extended EOS after approval of amendment # 5 and start of the rollover of patients to the M15-997 study from 01-May-2018, i.e. these tests are only required at EV1 for patients that are having EV1 as their first 1311.13 visit. The results will not be included into the report. Samples will be archived and run as clinically necessary.

Table 5.2.3: 1 Exclusionary Testing

Category	**Test name**
Tb screening	Interferon-gamma release assay (IGRA)
Serum pregnancy test (only female patients of childbearing potential)	Serum β-Human Chorionic Gonadotropin

Table 5.2.3: 2 Safety laboratory tests

Category	**Test name**
Haematology	Haematocrit (Hct) Haemoglobin (Hb) Red Blood Cell Count / Erythrocytes Reticulocyte Count White Blood Cells / Leucocytes Platelet Count / Thrombocytes HbA1c (Haemoglobin (glycated Hb of A1c subtype)) Roll-over and final visits only

Table 5.2.3: 2 Safety laboratory tests (cont'd)

Category	Test name
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	Partial Thromboplastin Time (=aPTT) Prothrombin Time (Quick and International normalised ratio (INR))
Enzymes	Aspartate Aminotransferase/ Glutamate-Oxaloacetate Transaminase (AST/GOT) Alanine transaminase(Glutamic Pyruvate Transaminase (ALT/GPT) Alkaline Phosphatase (AP/ALP) Creatine Kinase (CK) CK-MB if CK is elevated Lactic Dehydrogenase (LDH)
Substrates	Glucose Creatinine Blood urea nitrogen Bilirubin Total Bilirubin Direct Protein, Total C-Reactive Protein (CRP) Uric Acid Cholesterol, total High density lipoprotein (HDL) Cholesterol Calculated low density lipoprotein (LDL) Cholesterol Triglycerides
Electrolytes	Calcium Sodium Potassium

Table 5.2.3: 2 Safety laboratory tests (cont'd)

Category	Test name
Urinalysis (Stix)	Urine Nitrite Urine Protein Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/Erythrocyte Urine WBC/Leukocytes Urine pH Urine albumin (microalbumin urine test) (roll-over visit only)
Urine-Sediment (microscopic examination) *(if urine analysis abnormal)*	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epith Cells Urine Sediment Crystals, Unspecified Urine Sediment red blood cell count (RBC)/Erythrocytes Urine Sediment white blood cell count (WBC)/Leucocytes

5.2.4 Electrocardiogram

The 12-lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be recorded after the patients have rested for at least 5 minutes in a supine position. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven. The ECGs will be evaluated by the study physician investigator or designee. ECGs may be repeated for quality reasons and the repeat tracing may be used for analysis. Additional ECGs may be collected by the investigator for safety reasons. Abnormal ECG recordings will be noted, and clinically relevant abnormal findings will be reported as AEs by the investigator. Any ECG abnormalities will be carefully monitored and if necessary medically treated.

ECG recordings will be obtained from roll-over visit and every 24 weeks, until study end including Extended EOT visit and Extended EOS visit

ECG measurements should, if possible, always precede blood sampling to avoid impact of sampling on the ECG results.

Signed and dated printouts of either ECG tracings or electronic ECG reports will be kept in the subject's/patient's medical file.

5.2.5 Assessment of other safety parameters

Vital signs

Vital signs include blood pressure (BP), pulse rate (PR), respiratory rate (RR), and oral or tympanic body temperature.

Systolic and diastolic BP as well as PR (by palpation, counted for 1 minute) will be measured after 5 minutes of rest in the supine position. (cf. Flow Chart for time points).

Measurements of vital signs should, if possible, always precede blood sampling to avoid impact of sampling on the results of vital signs.

Medical examination

Complete physical examination will include vital sign assessment and general appearance as well as evaluation of all organ systems (eyes, ears, nose, mouth, and throat, neck, respiratory, cardiovascular, chest, gastrointestinal, lymphatic, musculoskeletal, skin, neurologic and psychiatric). Targeted physical examination will include vital sign assessment and evaluation of organ systems associated with AE(s) symptoms or laboratory abnormalities.

The medical examination carried out at the initial roll-over visit, will include documentation of patient information, informed consent, demographics including weight and waist circumference, smoking and alcohol history, relevant medical history and concomitant medication, review of inclusion/exclusion criteria, review of vital signs, 12-lead ECG and laboratory, and a complete physical examination.

Local tolerability

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”.

5.3 OTHER

5.3.1 Other endpoint(s)

Not applicable

5.3.2 Other assessment(s)

Not applicable

5.3.3 Pharmacogenomic evaluation

No pharmacogenetic samples will be collected in this study, as those samples will be available from the preceding trial.

5.4 APPROPRIATENESS OF MEASUREMENTS

The majority of measurements performed during this trial are standard measurements and will be performed in order to monitor safety aspects and to determine efficacy, PK and PD parameters in an appropriate way.

The scheduled measurements are appropriate to see drug induced changes in vital signs, standard laboratory values and ECG. These safety measurements standard and accepted for

evaluation of safety and tolerability of an s.c. drug, and they are widely used in this kind of study.

The PK parameters and measurements outlined in Section 5.5 are generally used as measurements to assess drug exposure.

The efficacy endpoints are standard for assessment of patients with moderate to severe psoriasis. In addition, a number of exploratory PD measures (biomarkers) are also incorporated in this CTP. As these biomarkers have not been validated as prognostic measures, they may be analysed selectively and may not be included in the clinical trial report.

5.5 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

Time points for dosing, PK and ADA sampling are listed in Flow Chart. Date and exact clock time of administration as well as pharmacokinetic and ADA sampling time points will be recorded. They will be documented in the CRFs by the medical personnel.

5.5.1 Pharmacokinetic endpoint(s)

PK samples will serve to determine the following endpoints:

- steady state trough concentrations of BI 655066.

Individual concentration-time data with descriptive statistics for trough concentrations will be presented in the CTR. If deemed necessary, further appropriate pharmacokinetic parameters might be calculated.

Pharmacokinetic data may additionally be analysed using population pharmacokinetic approach. For this purpose data may also be combined with data from other trials. Modelling activities will be planned and documented separately.

5.5.2 Methods of sample collection

5.5.2.1 Plasma sampling for pharmacokinetic analysis

For the quantification of analyte plasma concentrations, approximately 2.5 mL of blood will be taken from a forearm vein into a K_3EDTA (ethylendiaminetetraacetic acid) anticoagulant blood-drawing tube at the time points listed in Flow Chart under PK sampling.

Mix the K_3EDTA-anticoagulated blood samples gently and place on ice until centrifugation at approximately +4°C. The blood should be centrifuged to produce plasma as soon as possible after collection, but not later than 30 minutes after withdrawal. Centrifugation will last for approximately 10 minutes (at 2000 x g to 4000 x g) at approximately +4°C. Two aliquots of EDTA plasma samples will be obtained in two polypropylene cryotubes. The two aliquots should contain approximately 0.5 mL of plasma each. Until shipment on dry ice to the analytical laboratory, the plasma samples will be stored at -20°C or below at the clinical

site and at the analytical laboratory until analysis. Both aliquots will be shipped (in separate shipments) to the assay laboratory for the determination of BI 655066. Both aliquots will be stored until the finalization of the clinical trial report and permission for sample disposal is provided. Samples will be shipped on dry ice sufficient for 3 days transit.

5.5.2.2 Plasma sampling for assessment of anti-drug antibody

For the assessment of anti-drug antibody, approximately 2.5 mL of blood will be taken from a forearm vein into a K_3EDTA anticoagulant blood-drawing tube at the time points listed in the Flow Chart under ADA.

Mix the K_3EDTA-anticoagulated blood samples gently and place on ice until centrifugation at approximately +4°C. The blood should be centrifuged to produce plasma as soon as possible after collection, but not later than 30 minutes after withdrawal. Centrifugation will last for approximately 10 minutes (at 2000 x g to 4000 x g) at approximately +4°C. Two aliquots of EDTA plasma samples will be obtained in two polypropylene cryotubes. Both aliquots should contain approximately 0.5 mL of plasma each. Until shipment on dry ice to the analytical laboratory, the plasma samples will be stored at -20°C or below at the clinical site and at the analytical laboratory until analysis. Both aliquots will be shipped (in separate shipments) to the assay laboratory for the assessment of potential ADA to BI 655066. The ADA sample aliquots will be banked for possible/ additional ADA characterization in the future. Samples will be shipped on dry ice sufficient for 3 days transit.

5.5.3 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 will then be characterized in a validated neutralizing antibody (NAb) assay.

5.6 BIOMARKER(S)

Biomarkers associated with psoriatic disease and the IL-23 pathway will be assessed in plasma and serum from psoriasis patients, post treatment with BI 655066.

Blood samples (serum and plasma) will be collected at time points indicated in Flow Chart for the analysis of biomarkers. After completion of the study these samples may be used for not yet specified non-genetic biomarker analyses associated with autoimmune diseases as well as method development and evaluation. Samples will be stored for a maximum of 3 years (under consideration of local legislation) upon signature of the final study report.

5.6.1 Endpoints based on biomarker(s)

Serum and plasma will be collected to assess changes in protein levels of disease specific markers such as but not limited to β defensin 2, neutrophil gelatinase associated lipocalin (NGAL), and S-100 proteins (A7, A8, A12) post treatment with BI 655066. These biomarkers are considered exploratory biomarkers and respective assays will need to be qualified to meet the required performance criteria.

5.6.2 Methods of sample collection

For the assessment of soluble protein biomarkers in serum, approximately 8 ml of blood will be collected from a forearm vein in a serum separation tube at time points indicated in the Flow Chart. The blood will be thoroughly mixed with clotting activation agent by inverting the tube not less than five times and will be allowed to clot for 30 minutes with the tube standing upright. The tube is then centrifuged at 1500 to 2000 x g for 15 minutes until clot and serum are separated by a well formed barrier. The serum will then be aliquoted in at least 6 aliquots (in polypropylene tubes) of at least 500 µl and should be frozen immediately at -20°C or below until shipment on dry ice to the analytical laboratory.

For the assessment of soluble protein biomarkers in plasma, approximately 8 ml of blood will be collected from a forearm vein in a potassium -EDTA (ethylendiaminetetraacetic acid)-anticoagulant blood drawing tube at the time points indicated in the Flow Chart. Tube content will be mixed immediately by gently inverting the tube at least 8 to 10 times and tube will then be transferred into an ice bath until centrifugation. The EDTA-anticoagulated blood sample will be centrifuged within 30 minutes after collection (intermittent storage in ice water or on ice). Centrifugation will last for about 10 minutes at 2000-4000 x g at 4-8°C until cells and plasma are well separated. After centrifugation, the EDTA plasma will be aliquoted in at least 6 aliquots (in polypropylene tubes) of at least 500 µl and will be frozen immediately at -20°C or below.

5.6.3 Analytical determinations

Characteristics of the analytical methods for the analysis of serum and plasma biomarkers will be given in detail in the clinical trial report or in an accompanying technical/biomarker report.

5.7 PHARMACODYNAMICS

Serum and plasma will be collected to assess changes in the levels of disease specific markers such as but not limited to β defensin 2, neutrophil gelatinase associated lipocalin (NGAL), and S-100 proteins (A7, A8, A12).

5.7.1 Pharmacodynamic endpoints

Cf. section 5.6.1.

5.7.2 Methods of sample collection

Cf. section 5.6.2.

5.8 PHARMACOKINETIC - PHARMACODYNAMIC RELATIONSHIP

No formal analysis of pharmacokinetic/pharmacodynamic relationships is planned.

If the data suggest a pharmacokinetic/pharmacodynamic relationship of special parameters, e.g. PASI, a detailed analysis may be performed.

Correlation between drug concentration and response may be made if adequate data are available. In addition, exploratory correlations may also be made between drug concentration and AEs.

Data may also be used to develop pharmacokinetic/pharmacodynamic models using nonlinear mixed effect modelling techniques, if feasible. For this purpose data may also be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and SOP.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All subjects have to adhere to the visit schedule as specified in Flow Chart. Any missed appointments should be re-scheduled as soon as possible. If any visit has to be rescheduled, subsequent visits should follow the original visit date scheduled. The investigator/sponsor could decide to arrange an unscheduled visit if deemed necessary (e.g. for safety follow-up reasons).

For detailed description of the trial procedures, please refer to Flow Chart.

In general, if several measurements including venipuncture are scheduled for the same point of time, venipuncture should, if possible, be the last of the measurements due to its mild discomfort to the patient and possible influence on physiologic parameters.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

6.2.1 Screening and run-in period(s)

Patients in the 1311.2 trial that fulfil the criteria for roll over, either by response < $PASI_{50}$ between week 24 and week 44, or completing the entire preceding trial reaching week 48 according to protocol, will be asked to participate in this open label extension trial. Upon their agreement, they will immediately enter the treatment phase. Therefore, no screening or run-in procedures are defined in this protocol.

6.2.2 Treatment period(s)

6.2.2.1 Rollover visit - Extended visit 1

After the approval of this protocol amendment in each respective country, all patients will follow Flow Chart (Extended dosing period) and receive 90mg BI 655066 subcutaneously at their Extended visit 1 (EV1). From EV1 onwards, BI655066 will be administered subcutaneously every 12 weeks during the trial. At EV2, if there is inadequate response, defined as <$PASI_{90}$, the dose should be increased to 180mg for the remainder of the trial.

For ongoing patients from under the previous amendment (Pre-Extended Dosing Period, see Figure 3.1.3), EV1 should be conducted at the following time points:

1. For ongoing patients with ≥12 weeks since the EOT visit: Conduct EV1 as soon as possible
2. For ongoing patients still undergoing treatment or with <12 weeks since the EOT visit: Conduct EV1 at the time of the next scheduled treatment or follow up visit (note: EV1 should not be conducted at the time point of Visit 2 under the previous protocol, patients with Visit 2 as their next scheduled visit should have their EV1 replacing their Visit 3 instead)

Patients completing their EOS of 1311.2 and rolling over after approval of this protocol amendment, is immediately entering the Extended dosing period at EV1 of this trial. Eligible patients from 1311.2 who sign the informed consent for trial 1311.13, should preferably have Extended visit 1 of trial 1311.13 performed on the same day as the last visit in 1311.2, or within an interim period of up to 6 weeks thereafter.

Assessments performed at EOS in the previous trial do not have to be repeated at Extended visit 1 in this trial, if performed as combined visits. If EV1 is performed as a separate visit to 1311.2 EOS, all EV1assessments should be performed, but specific assessments are only required at EV1 for patients that are having EV1 as their first 1311.13 visit, see Flow Chart for further instructions.

Written informed consent in accordance with GCP and local legislation must be obtained prior to any study related procedure taking place. If not performed as combined visits, informed consent must therefore be signed before the roll-over visit due to lab sampling fasting at EV1 in trial 1311.13.

Review of the following inclusion/exclusion criteria will be based on the last available lab result from previous trial, at the time of roll-over, and needs to be re-assessed as soon as 1311.2 EOS/1311.13 roll-over visit results are available:

- Inclusion criteria 3 (Negative serum ß-Human Chorionic Gonadotropin (ß-HCG))
  Exclusion criteria 8 (Any clinically significant laboratory abnormalities)

Check consistency in medical history with the data obtained at visit 1 of the previous trial. All changes in medical history must be documented as adverse events and will be followed up as such during this trial.

Re-record ongoing adverse events/concomitant medications from the previous trial and record any adverse events/concomitant medications that may have started between the two trials, in the event that the 6 week time-window between trials was used.

All patients will be administered 90 mg BI 655066 s.c. at Extended visit 1.

6.2.2.2 Extended Dosing Period

After 12 weeks, if there is a lack of response, defined as response below $PASI_{90}$ at Extended visit 2, the dose should be increased to 180 mg, and 180 mg dosing will occur every 12 weeks until Extended EOT.

Self-administered patient questionnaire (DLQI) should be completed by the patient before any other visit assessments or treatments.

For detailed description of the trial procedures, please refer to Flow Chart.

6.2.3 End of trial and Extended follow-up period

Trial 1311.13 is an open label extension trial which was set up in order to assess the long term safety and efficacy of Risankizumab (BI 655066) in patients with plaques psoriasis who have completed the phase 2 trial 1311.2. Moreover, this trial was meant to offer patients continuous treatment with Risankizumab until the marketing approval and availability of Risankizumab in the respective participating countries.

In the course of the acquisition of Risankizumab by Abbvie and the transition of responsibilities from BI to Abbvie it is planned to transfer the patients who are treated in 1311.13 into M15-997 which is sponsored and conducted by Abbvie. M15-997 is an open label extension trial in which patients who have completed one of the Risankizumab pivotal trials in the indication of plaques psoriasis receive 150 mg Risankizumab every 12 weeks.

For patients who discontinue study medication before Extended end of treatment (for any reason), or before approval of this amendment and start to rollover patients to the M15-997 from 01-May-2018 an early Extended EOT visit should be scheduled. If the decision to discontinue study participation is taken at a regular study visit, the visit should be turned into an Extended EOT visit. If the decision to discontinue study participation is taken in between study visits, an Extended EOT visit is to be scheduled at the earliest convenience and by the latest at the next upcoming visit according to the Flow Chart. This early Extended EOT visit will include the same procedures as the normal EOT, and the patient will subsequently enter a follow up period of 12 weeks, until a final Extended EOS visit is performed. If the decision to discontinue is taken in the Extended follow up period, the Extended EOS visit is to be scheduled at the earliest convenience. The procedures described at Extended EOS will be performed and the information will be recorded in the CRFs.

The end of study procedures are listed in Flow Chart.

6.2.3.1 Vital status

In case of early discontinuation, information should be collected to differentiate between patients lost to follow-up (investigator not able to contact the patient despite multiple attempts) versus patients the investigator was able to contact who elected to discontinue study participation for any reason. Patients will be asked to give consent to be contacted (or for their primary care physician to be contacted) by the study team to obtain vital status information preferably at the time of study entry. This consent must be documented in the patient notes. Patient's vital status, including cause of death, will be collected every 12 months from Extended EOS until the last patient completes the regular scheduled Extended EOS. Vital status data will be collected in the eCRFs.

All clinically significant abnormal values (including laboratory parameters) will be followed up using the appropriate tests until a return to a medically acceptable level is achieved. AEs persisting after trial completion must be followed up, until they have normalised or been sufficiently characterised.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a double arm extension trial of patients treated with BI 655066 after participation in a clinical trial of BI 655066. Descriptive statistical models include a responder analysis (e.g., achieving $PASI_{90}$, sPGA of clear or almost clear, etc.), time to loss of response (e.g., achieving $PASI_{90}$, sPGA of clear or almost clear, etc.), time to AESI, and time to antibody development formation. No statistical testing will be done.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The primary hypothesis is that BI 655066 will sustain effectiveness without emergent safety issues during the extended visit period. This will be characterized descriptively. There is no formal statistical hypothesis testing in this study.

7.3 PLANNED ANALYSES

The descriptive analyses will be based on proportions of patients achieving a response (e.g., achieving $PASI_{90}$, sPGA of clear or almost clear, etc.), Kaplan Meier empirical survival curves to describe patterns of event incidence, and cumulative event rates at critical time-point.

The study is designed to gain as much exposure as possible with adequate documentation of safety, efficacy, and antibody emergence.

For all analyses, baseline refers to the baseline value in the 1311.2 study.

7.3.1 Primary analyses

The achievement of PASI90 at week 48 in the Extended dosing period is the primary efficacy endpoint, which is a binary variable.

For primary safety, the overall incidence rates of AEs, drug related AEs, and SAEs will be calculated.

7.3.2 Secondary analyses

The same methods as discussed for the primary analyses will be used to analyse all binary secondary and other endpoints, which include achievement of PASI50 / PASI75 / PASI90 / PASI100 at all Extended dosing period visits where PASI is collected and achievement of sPGA of clear or almost clear at all Extended dosing period visits where sPGA is collected.

Time to loss of $PASI_{50}$ / $PASI_{75}$ / $PASI_{90}$ / $PASI_{100}$, and time to loss of sPGA of clear or almost clear will be analysed using a Kaplan-Meier estimate.

Percent change from baseline in Pain-VAS for patients with non-zero baseline will be summarized descriptively at time points collected.

DLQI will be summarized descriptively at time points collected.

Additional information on these analyses will be provided in the trial statistical analysis plan.

7.3.3 Safety analyses

All subjects who received one dose of study drug will be included in the safety evaluation.

Safety analyses will focus on adverse events related to early discontinuation, immune suppression and injection site effects. AEs will be coded using the Medical Dictionary for Drug Regulatory Affairs (MedDRA). All AEs occurring up to 12 weeks after the last trial medication administration will be assigned to the treatment period for evaluation. The evaluation of adverse events will comprise various frequency tabulations. The additional analyses of pre-defined AESI will consider the frequency, intensity, time to first onset of the AE, duration of the AE and clinical consequences (e.g. study discontinuation).

Analysis of laboratory measures will similarly focus on hematologic measures of immune suppression. Descriptive statistics of laboratory values over time and for the difference from baseline will be provided. Frequency tables of changes with respect to the reference range between baseline and last/worst value on treatment and patients with possible clinically significant abnormalities will also be presented.

Immunogenicity will be evaluated in terms of time to antibody emergence starting from the time of first exposure to BI 655066 in either 1311.2 or 1311.13. This will be analysed using a Kaplan-Meier estimate.

Safety will also be assessed by evaluation of vital signs (BP, PR, RR, oral or tympanic body temperature) and local tolerability.

7.3.4 Interim analyses

Results will be analysed periodically by the sponsor and DMC in order to review the accumulating safety data of BI 655066 in psoriasis.

7.3.5 Pharmacokinetic analyses

Individual concentration-time data with descriptive statistics for trough concentrations will be presented in the clinical trial report.

Population pharmacokinetic/pharmacodynamic analysis, if performed, will be reported separately.

7.3.6 Pharmacodynamic analyses

Serum/plasma biomarkers will be summarized over time and correlated with clinical endpoints (i.e. PASI, PGA).

7.3.7 Pharmacogenomic analyses

Not applicable.

7.4 HANDLING OF MISSING DATA

Use of inappropriate concomitant medication to treat psoriasis will be considered as failure when deriving response variables, e.g. $PASI_{90}$.

Further details on the handling of missing data will be provided in the Trial Statistical Analysis Plan.

7.5 RANDOMISATION

There is no randomisation for this study. All patients will be assigned to the same regimen and dose of BI 655066, regardless of the treatment and dose received in the 1311.2 study.

7.6 DETERMINATION OF SAMPLE SIZE

The sample size is determined by the completion of previous trial and the consenting for the extension.

8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS

The trial will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, in accordance with the International conference on harmonisation (ICH) Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI Standard Operating Procedures (SOPs). Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The investigator should inform the sponsor immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the protocol/ICH GCP.

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

Insurance Cover: The terms and conditions of the insurance cover are made available to the investigator and the patients via documentation in the ISF (Investigator Site File).

8.1 STUDY 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.

The patient must be informed that his/her personal trial-related data will be used by Boehringer Ingelheim in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by Boehringer Ingelheim, by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

8.2 DATA QUALITY ASSURANCE

A quality assurance audit/inspection of this trial may be conducted by the sponsor or sponsor's designees or by IRBs/IECs or by regulatory authorities. The quality assurance

auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the sponsor, either on paper or via remote data capture. 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 entered in the eCRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; also current medical records must 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. CRFs/eCRFs 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. Food and Drug Administration (FDA)). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs/eCRFs, and written informed consents. The accuracy of the data will be verified by reviewing the documents described in Section 8.3.1.

8.4 LISTEDNESS AND EXPEDITED REPORTING OF ADVERSE EVENTS

8.4.1 Listedness

To fulfil the regulatory requirements for expedited safety reporting, the sponsor evaluates whether a particular adverse event is "listed", i.e. is a known side effect of the drug or not. Therefore a unique reference document for the evaluation of listedness needs to be provided. For the BI 655066 this is the current version of the Investigator's Brochure (U12-3042). The current version of this reference document is to be provided in the ISF. No AEs are classified as listed for matching placebo, study design, or invasive procedures.

8.4.2 Expedited reporting to health authorities and IECs/IRBs

Expedited reporting of serious adverse events, e.g. suspected unexpected serious adverse reactions (SUSARs) to health authorities and IECs/IRBs, will be done according to local regulatory requirements. Further details regarding this reporting procedure are provided in the Investigator Site File.

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 i.e. the CA.

8.6 COMPLETION OF TRIAL

The EC/competent authority in each participating EU member state needs to be notified about the end of the trial (last patient out, unless specified differently in Section 6.2.3 of the CTP) or early termination of the trial.

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Submitted for publication

10. APPENDICES

10.1 PASI SCORE DEFINITION AND INSTRUCTIONS

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

The PASI score is calculated according to the following formula:

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

10.2 STATIC PHYSICIAN'S GLOBAL ASSESSMENT (SPGA) OF THE NPF PSORIASIS SCORE (NPFPS)

The NPF Psoriasis Score (NPFPS) was devised by the National Psoriasis Foundation Medical

Advisory Board to address deficiencies inherit in the PASI, and to provide a dynamic, reproducible, and easy 5-component method to measure clinically significant improvement in trials of new or existing psoriatic therapies (R03-1207, R03-1208). The static Physician Global Assessment (sPGA) is one of five components of the NPFPS, and may be used independently (R03-1207, R03-1208).

The primary sPGA variable to be analysed will be the proportion of patients that are "clear or almost clear". This has been shown to correlate well with PASI75 or higher score.

For patients to be considered “clear,” the average of the 3 components must be zero (with standard rounding rules, i.e., 0.333 rounds to 0) and the score for thickness must equal zero.

For patients to be considered “almost clear,” the average of the 3 components must be 1 (with standard rounding rules, i.e., 1.333 rounds to 1) and each of the individual components must be less than 3 (in other words, each of the 3 components must be equal 0, 1, or 2).

Additionally, patients with an average of the 2 components equal to zero but with a thickness score of 1 will be considered as “almost clear.”

Static Physician Global Assessment (averaged over all lesions)

0	clear	= cleared, except for residual discoloration
1	almost clear	= majority of lesions have individual scores for thickness (a), erythema (b) and scaling (c) that averages 1.
2	mild	= majority of lesions have individual scores for thickness (a), erythema (b) and scaling (c) that averages 2.
3	moderate	= majority of lesions have individual scores for thickness (a), erythema (b) and scaling (c) that averages 3.
4	marked	= majority of lesions have individual scores for thickness (a), erythema (b) and scaling (c) that averages 4.
5	severe	= majority of lesions have individual scores for thickness (a), erythema (b) and scaling (c) that averages 5.

(a) Thickness (averaged over all lesions)

0 = no evidence of plaque elevation
1 = minimal plaque elevation, ≈ 0.25 mm
2 = mild plaque elevation, ≈ 0.5 mm

3 = moderate plaque elevation, ≈ 0.75 mm
4 = marked plaque elevation, ≈ 1 mm
5 = severe plaque elevation, ≈1.25 mm or more

Thickness in the sPGA may be graded with the aid of a reference card, which has embossed elevations ranging from 0 to 1.25 mm that increase linearly at 0.25 mm increments corresponding to varying levels of thickness (0-5) for each target lesion. The dermatologist should select 3 or more representative lesions (e.g., lesions not on the face, scalp, intertriginous areas or only on elbows or knees) at the time of the visit and measure their thickness. These can be averaged to derive the thickness score. The investigator should assess the average degree of thickness and then select the number that most represents this. For any assessments that fall half way between any two numbers on the scale, the investigator will be told to always round up to the higher number. This would result in then the following implied range: 0 = 0 to <0.125 mm, 1 = ≥0.125 to <0.375 mm, 2 = ≥0.375 to <0.625mm, 3 = ≥0.625 to <0.875mm, 4 = ≥0.875 to <1.25mm and 5 = ≥1.25mm.

(b) Erythema (averaged over all lesions)

0 = no evidence of erythema, hypo- or hyper-pigmentation may be present
1 = faint erythema
2 = light red coloration
3 = moderate red coloration
4 = bright red coloration
5 = dusky to deep red coloration

(c) Scaling (averaged over all lesions)

0 = no evidence of scaling
1 = minimal; occasional fine scaling over less than 5% of the lesion
2 = mild; fine scaling predominates
3 = moderate; coarse scaling predominates
4 = marked; thick, non-tenacious scaling predominates
5 = severe; very thick tenacious scaling predominates

10.3 PAIN VISUAL ANALOG SCALE (VAS)

If a patient has psoriatic arthritis, the patient will assess their psoriatic arthritis at each protocol defined time point. A global estimate of pain caused by joint disease will be estimated by the patient's response to the question: "The very left end of the scale is equivalent to "no pain" at all whereas the right end of the scale is equivalent to "worst possible pain". How much pain have you had because of your illness in the past week?" Response is captured using a VAS (range 0 to 100, where 100 is highest severity) and results will be summarized.

10.4 DERMATOLOGY LIFE QUALITY INDEX

DLQI is a subject-administered,10-question, validated, quality of life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment. 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 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.

10.5 PSORIATIC ARTHRITIS SCREENING AND EVALUATION TOOL

If a patient has psoriatic arthritis or if psoriatic arthritis is suspected at the roll-over visit , the psoriatic arthritis screening and evaluation (PASE) questionnaire should be performed. It will then be measured once per year until study end. The PASE questionnaire is a self-administered tool that can be used to screen for psoriatic arthritis among patients with psoriasis. PASE can distinguish between symptoms of psoriatic arthritis and osteoarthritis (R13-3802).

Psoriatic Arthritis Screening and Evaluation (PASE) Questionnaire

Please circle or mark ONLY ONE of the five choices on the following 15 questions. The answers to these questions will help us better understand your symptoms. This should take about 5 to 6 minutes to complete. Thank you for your time.

Symptoms subscale	**Strongly disagree**	**Disagree**	**Neutral**	**Agree**	**Strongly agree**
1. I feel tired for the most of the day	1	2	3	4	5
2. My joints hurt	1	2	3	4	5
3. My back hurts	1	2	3	4	5
4. My joints become swollen	1	2	3	4	5
5. My joints feel “hot”	1	2	3	4	5
6. Occasionally, an entire finger or toe becomes swollen, making it look like a “sausage”	1	2	3	4	5
7. I have noticed that the pain in my joints moves from one joint to another, e.g. my wrist will hurt for a few days then my knee will hurt and so on	1	2	3	4	5
Symptom Score (Max 35)	Add scores for questions 1-7 and write next to A				A.
Function subscale	**Strongly disagree**	**Disagree**	**Neutral**	**Agree**	**Strongly agree**
8. I feel that my joint problems have affected my ability to work	1	2	3	4	5
9. My joint problems have affected my ability to care for myself, e.g. getting dressed or brushing my teeth	1	2	3	4	5
10. I have had trouble wearing rings on my fingers or my watch	1	2	3	4	5
11. I have had trouble getting into or out of a car	1	2	3	4	5
12. I am unable to be as active as I used to be	1	2	3	4	5
13. I feel stiff for more than two hours after waking up in the morning	1	2	3	4	5
14. The morning is the worst time of the day for me	1	2	3	4	5
15. It takes me a few minutes to get moving to the best of my ability, any time of the day	1	2	3	4	5
Function Score (Max 40)	Add scores for questions 8-15 and write next to B				B.
Total PASE Score (Max 75)	Add scores in boxes A and B and write next to C				C.

10.6 CLINICAL EVALUATION OF LIVER INJURY

10.6.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.2.2.1 (Adverse Events of Special Interest), are to be further evaluated using the following procedures:

10.6.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours and provide additional blood sample to the central laboratory for automatic reflex testing of the below listed laboratory parameters. Only in case whereby the central laboratory is not immediately available (e.g. if the logistics are such that the patient´s repeat specimen would not reach the central laboratory in a reasonable timeframe), ALT, AST, and bilirubin (total and direct) will be evaluated by local laboratory and results are made available to the investigator and to BI as soon as possible. If in such a case ALT and/or AST >3 fold ULN combined with an elevation of total bilirubin >2 fold ULN are confirmed, results of the laboratory parameters described below must be made available to the investigator and to BI as soon as possible.

In addition,

- obtain a detailed history of current symptoms and concurrent diagnoses and medical history according to the “DILI checklist” provided in the ISF
- obtain history of concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets according to the “DILI checklist” provided in the ISF;
- obtain a history of exposure to environmental chemical agents (consider home and work place exposure) according to the “DILI checklist” provided in the ISF;

and report these via the CRF.

Clinical chemistry
alkaline phosphatase, albumin, PT or INR, CK, CK-MB, ceruloplasmin, α-1 antitrypsin, transferrin, amylase, lipase, fasting glucose, cholesterol, triglycerides

Serology
Hepatitis A (Anti-IgM, Anti-IgG), Hepatitis B (HbsAg, Anti-HBs, DNA), Hepatitis C (Anti-HCV, RNA if Anti-HCV positive), Hepatitis D (Anti-IgM, Anti-IgG), Hepatitis E (Anti-HEV, Anti-HEV IgM, RNA if Anti-HEV IgM positive), Anti-Smooth Muscle antibody (titer), Anti-nuclear antibody (titer), Anti-LKM (liver-kidney microsomes) antibody, Anti-mitochondrial antibody

Hormones, tumormarker
TSH

Haematology
Thrombocytes, eosinophils

- Provide abdominal ultrasound to rule out biliary tract, pancreatic or intrahepatic pathology, e.g. bile duct stones or neoplasm.

- Initiate close observation of subjects by repeat testing of ALT, AST, and total bilirubin (with fractionation by total and direct) at least weekly until the laboratory ALT and / or AST abnormalities stabilize or return to normal, then according to the protocol. Depending on further laboratory changes, additional parameters identified e.g. by reflex testing will be followed up based on medical judgement and Good Clinical Practices (GCP).

10.7 SEVERITY OF AE AS DESCRIBED IN THE RHEUMATOLOGY COMMON TOXICITY CRITERIA V. 2.0

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
	Asymptomatic, or transient Short duration (< 1 week) No change in life style No medication or over the counter medication (OTC)	Symptomatic Duration (1–2 weeks) Alter lifestyle occasionally Meds relieve. (may be prescription), Study drug continued	Prolonged symptoms, reversible, major functional impairment Prescription meds/partial relief May be hospitalized < 24h Temporary study drug discontinuation, or/and dose reduced	At risk of death Substantial disability, especially if permanent. Multiple meds Hospitalization > 24h Study drug discontinued
A. ALLERGIC/IMMUNOLOGIC				
A1. Allergic reaction/hyper-sensitivity (including drug fever)	Transient rash; drug fever < 38°C: transient asymptomatic bronchospasm	Generalised urticaria responsive to meds; or drug fever > 38° C, or reversible bronchospasm	Symptomatic bronchospasm, requiring meds; symptomatic urticaria persisting with meds, allergy related oedema/angioedema	Anaphylaxis, laryngeal/ pharyngeal oedema, requiring resuscitation

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
A. ALLERGIC/IMMUNOLOGIC				
A2. Autoimmune reaction	Serologic or other evidence of autoimmune reaction, but patient asymptomatic: all organ function normal and no treatment is required (e.g. vitiligo)	Evidence of autoimmune reaction involving a non-essential organ or functions, requiring treatment other than immunosuppressive drugs (e.g. hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or toxicity requiring short term immunosuppressive treatment (e.g. transient colitis or anaemia)	Causes major organ dysfunction, or progressive, not reversible, or requires long term administration of high dose immunosuppressive therapy
A3. Rhinitis (includes sneezing, nasal stuffiness, post-nasal discharge)	Transient, non-prescription meds relieve	Prescription med. required, slow	Corticosteroids or other prescription med. with persistent disabling symptoms such as impaired exercise tolerance	NA

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
ALLERGIC/IMMUNOLOGIC				
A4. Serum sickness	Transient, non-prescription meds relieve	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Prolonged; symptoms only partially relieved by meds; parenteral corticosteroids required	Major organ dysfunction, requires long-term high-dose immunosuppressive therapy
A5. Vasculitis	Localised, not requiring treatment; or rapid response to meds; cutaneous	Symptomatic, slow response to meds (e.g. oral corticosteroids)	Generalised, parenteral corticosteroids required or/and short duration hospitalisation	Prolonged, hospitalisation, ischemic changes, amputation
B. CARDIAC				
B1. Arrhythmia	Transient, asymptomatic	Transient, but symptomatic or recurrent, responds to meds	Recurrent/persistent; maintenance prescription	Unstable, hospitalisation required; parenteral meds

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
B. CARDIAC				
B2. Cardiac function decreased	Asymptomatic decline in resting ejection fraction by > 10%, but < 20% of baseline value	Asymptomatic decline of resting ejection fraction ≥ 20% of baseline value	Congestive heart failure (CHF) responsive to treatment	Severe or refractory CHF
B3. Edema	Asymptomatic (e.g. 1+ feet/calves), self-limited, no therapy required	Symptomatic (e.g. 2+ feet/calves), requires therapy	Symptoms limiting function (e.g. 3+ feet/calves, 2+ thighs), partial relief with treatment, prolonged	Anasarca; no response to treatment
B4. Hypertension (new onset or worsening)	Asymptomatic, transient increase by > 20 mm Hg (diastolic), or to > 150/100 if previously normal, no therapy required	Recurrent or persistent increase > 150/100 or by > 10 mmHg (diastolic), requiring and responding readily to treatment	Symptomatic increase > 150/100 > 20 mm Hg, persistent, requiring multi-agent therapy, difficult to control	Hypertensive crisis

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
B. CARDIAC				
B5. Hypotension (without underlying diagnosis)	Transient, intermittent, asymptomatic orthostatic decrease in blood pressure> 20 mm Hg	Symptomatic, without interference with function, recurrent or persistent > 20 mm Hg decrease, responds to treatment	Syncope or symptomatic, interferes with function, requiring therapy and sustained medical attention, dose adjustment or drug discontinuation	Shock
B6. Myocardial ischaemia	Transient chest pain/ECG changes; rapid relief with nitro	Recurring chest pain, transient ECG ST-T changes; treatment relieves	Angina with infarction, no or minimal functional compromise, reduce dose or discontinue study drug	Acute myocardial infarction, arrhythmia or/and CHF
B7. Pericarditis/pericardial effusion	Rub heard, asymptomatic	Detectable effusion by echocardiogram, symptomatic, NSAID required	Detectable on chest x-ray, dyspnea; or pericardiocentesis; requires corticosteroids	Pulsus alternates with low cardiac output; requires surgery
B8. Phlebitis/thrombosis/ embolism (excludes injection sites)	Asymptomatic, superficial, transient, local, or no treatment required	Symptomatic, recurrent, deep vein thrombosis, no anticoagulant therapy required	Deep vein thrombosis requiring anticoagulant therapy	Pulmonary embolism

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
C. GENERAL (constitutional)				
C1. Fatigue/malaise (asthenia)	Increase over baseline; most usual daily functions maintained, short term	Limits daily function intermittently over time	Interferes with basic ADL, persistent	Unable to care for self, bed or wheelchair bound > 50% of day debilitating, hospitalisation
C2. Fever (pyrexia) (note: fever due to drug allergy should be coded as allergy)	Transient, few symptoms 37.7–38.5°C	Symptomatic, recurrent, 38.6-39.9°C. Relieved by meds.	≥ 40°C; ≤ 24h, persistent symptoms; partial response to meds.	≥ 40°C, debilitating, > 24h, hospitalisation; no relief with meds
C3. Headache	Transient or intermittent, no meds or relieved with OTC	Persistent, recurring, non-narcotic analgesics relieve	Prolonged, with limited response to narcotic medicine	Intractable, debilitating, requires parenteral meds.

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
C. GENERAL				
C4. Insomnia	Difficulty sleeping, short term, not interfering with function	Difficulty sleeping, interfering with function, use of prescription med.	Prolonged symptoms, with limited response to narcotic meds.	Debilitating, hospitalisation; no relief with meds
C5. Rigors, chills	Asymptomatic, transient, no meds, or non-narcotic meds relieve	Symptomatic, narcotic meds relieve.	Prolonged symptoms, with limited response to narcotic meds.	Debilitating, hospitalisation; no relief with meds
C6. Sweating (diaphoresis)	Episodic, transient	Frequent, short term	Frequent, drenching, disabling	Dehydration, requiring IV fluids/hospitalization > 24hr
C7. Weight gain	5–9.9%	10–19.9%	20–30%	NA
C8. Weight loss	5–9.9%	10–19.9%	20–30%	NA

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
D. DERMATOLOGIC				
D1. Alopecia	Subjective, transient	Objective, fully reversible	Patchy, wig used, partly reversible	Complete or irreversible even if patchy
D2. Bullous eruption	Localised, asymptomatic	Localised, symptomatic, requiring treatment	Generalised, responsive to treatment; reversible	Prolonged, generalised, or requiring hospitalisation for treatment
D3. Dry skin	Asymptomatic, controlled with emollients	Symptoms eventually (1-2 wks) controlled with emollients	Generalised, interfering with ADL >2 wks, persistent pruritus, partially responsive to treatment	Disabling for extended period, unresponsive to ancillary therapy and requiring study drug discontinuation for relief
D4. Injection site reaction	Local erythema, pain pruritus, < few days	Erythema, pain, oedema, may include superficial phlebitis, 1-2 wks	Prolonged induration, superficial ulceration; includes thrombosis	Major ulceration necrosis requiring surgery
D5. Petechiae (without vasculitis)	Few, transient asymptomatic	Dependent areas, persistent up to 2 wks	Generalised, responsive to treatment; reversible	Prolonged, irreversible, disabling

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
D. DERMATOLOGIC				
D6. Photosensitivity	Transient erythema	Painful erythema and oedema requiring topical treatment	Blistering or desquamation, requires systemic corticosteroids	Generalised exfoliation or hospitalisation
D7. Pruritus	Localised, asymptomatic, transient, local treatment	Intense, or generalised, relieved by systematic medication	Intense or generalised; poorly controlled despite treatment	Disabling, irreversible
D8. Rash (not bullous)	Erythema, scattered macular/papular eruption; pruritus transient, OTC or no meds	Diffuse macular/papular eruption or erythema with pruritus; dry desquamation; treatment required	Generalised, moist desquamation, requires systemic corticosteroids; responsive to treatment; reversible	Exfoliative or ulcerating; or requires hospitalisation; or parenteral corticosteroids
D9. Induration/fibrosis/ Thickening (not sclerodermal)	Localized, high density on palpation, reversible, no effect on ADL and no disfiguring	Local areas < 50% body surface, not disfiguring, transient interference with ADL, reversible	Generalised, disfiguring, interferes with ADL, reversible	Disabling, irreversible, systemic symptoms

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
E. EAR/NOSE/THROAT				
E1. Hearing loss	Transient, intermittent, no interference with function	Symptomatic, treatment required, reversible	Interferes with function; incomplete response to treatment	Irreversible deafness
E2. Sense of smell	Slightly altered	Markedly altered	Complete loss, reversible	Complete loss, without recovery
E3. Stomatitis	Asymptomatic	Painful, multiple, can eat	Interferes with nutrition, slowly reversible	Requires enteral support, residual dysfunction
E4. Taste disturbance (dysgeusia)	Transiently altered; metallic	Persistently altered; limited effect on eating	Disabling, effect on nutrition	NA
E5. Tinnitus	Intermittent, transient, no interference with function	Requires treatment, reversible	Disabling, or associated with hearing loss	Irreversible deafness
E6. Voice changes (includes hoarseness, loss of voice, laryngitis)	Intermittent hoarseness, able to vocalise	Persistent hoarseness, able to vocalise	Whispered speech, slow return of ability to vocalise	Unable to vocalize for extended

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
E. EAR/NOSE/THROAT				
E7. Xerostomia (dry mouth)	Transient dryness	Relief with meds	Interferes with nutrition, slowly reversible	Extended duration interference with nutrition, requires parenteral nutrition
F. EYE/OPHTHALMOLOGIC				
F1. Cataract	Asymptomatic, no change in vision, non-progressive	Symptomatic, partial visual loss, progressive	Symptoms impairing function, vision loss requiring treatment, including surgery	NA
F2. Conjunctivitis	Asymptomatic, transient, rapid response to treatment	Symptomatic, responds to treatment, changes not interfering with function	Symptoms prolonged, partial response to treatment, interferes with function	NA
F3. Lacrimation increased (tearing, watery eyes)	Symptoms not requiring treatment, transient	Symptomatic, treatment required, reversible	Unresponsive to treatment with major effect on function	NA

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
F. EYE/OPHTALMOLOGIC				
F4. Retinopathy	Asymptomatic, non-progressive, no treatment	Reversible change in vision; readily responsive to treatment	Disabling change in vision ophthalmological findings reversible, sight improves over time	Loss of sight
F5. Vision changes (e.g. blurred, photophobia, night blindness, vitreous floaters)	Asymptomatic, transient, no treatment required	Symptomatic, vision changes not interfering with function, reversible	Symptomatic, vision changes interfering with function	Loss of sight
F6. Xerophthalmia (dry eyes)	Mild scratchiness	Symptomatic without interfering with function, requires artificial tears	Interferes with vision/function, corneal ulceration	Loss of sight
G. GASTROINTESTINAL				
G1. Anorexia	Adequate food intake, minimal weight loss	Symptoms requiring oral nutritional supplementation	Prolonged, requiring iv support	Requires hospitalization for nutritional support

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
G. GASTROINTESTINAL				
G2. Constipation	Asymptomatic, transient, responds to stool softener, OTC laxatives	Symptomatic, requiring prescription laxatives, reversible	Obstipation, requiring medical intervention	Bowel obstruction. Surgery required.
G3. Diarrhea	Transient, increase of 2–3 stools/day over pre-treatment (no blood or mucus), OTC agents relieve	Symptomatic, increase 4–6 stools/day, nocturnal stools, cramping, requires treatment with prescription meds.	Increase > 6 stools/day, associated with disabling symptoms, e.g. incontinence, severe cramping, partial response to treatment	Prolonged, dehydration, unresponsive to treatment, requires hospitalization.
G4. Dyspepsia (heartburn)	Transient, intermittent, responds to OTC antacids, H-2 blockers	Prolonged, recurrent, requires prescription meds, relieved by meds	Persistent despite treatment, interferes with function, associated with GI bleeding	NA

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
G. GASTROINTESTINAL				
G5. GI bleed (gastritis, gastric or duodenal ulcer diagnosed-define aetiology)	Asymptomatic, endoscopic finding, haemocult + stools, no transfusion, responds rapidly to treatment	Symptomatic, transfusion ≤2 units needed; responds to treatment	Haematemesis, transfusion 3–4 units, prolonged interference with function	Recurrent, transfusion > 4 units, perforation, requiring surgery, hospitalisation
G6. Haematochezia (rectal bleeding)	Haemorrhoidal, asymptomatic, no transfusion	Symptomatic, transfusion ≤2 units, reversible	Recurrent, transfusion > 3–4 units	> 4 units, hypotension, requiring hospitalization
G7. Hepatitis	Laboratory abnormalities, asymptomatic, reversible	Symptomatic laboratory abnormalities, not interfering with function, slowly reversible	Laboratory abnormalities persistent >2wks, symptoms interfere with function	Progressive, hepato-renal, anasarca, pre-coma or coma
G8. Nausea, or nausea/vomiting (use diagnostic term)	Transient, intermittent, minimal interference with intake, rapid response to meds.	Persistent, recurrent, requires prescription meds, intake maintained	Prolonged, interferes with daily function and nutritional intake, periodic iv fluids	Hypotensive, hospitalization, parenteral nutrition, unresponsive to out-patient management

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
G. GASTROINTESTINAL				
G9. Pancreatitis	Amylase elevation, intermittent nausea/vomiting, transient, responds rapidly to treatment	Amylase elevation with abdominal pain, nausea, occasional vomiting, responsive to treatment	Severe, persistent abdominal pain with pancreatic enzyme elevation, incomplete or slow response to treatment	Complicated by shock, haemorrhage (acute circulatory failure)
G10. Proctitis	Perianal pruritus, haemorrhoids (new onset), transient, or intermittent, relieved by OTC meds	Tenesmus or ulcerations, anal fissure, responsive to treatment, minimal interference with function	Unresponsive to treatment, marked interference with function	Mucosal necrosis with haemorrhage, infection, surgery required.
H. MUSCULOSKELETAL				
H1. Avascular necrosis	Asymptomatic Magnetic resonance imaging (MRI) changes, non-progressive	MRI changes and symptoms responsive to rest and analgesia	MRI changes, symptoms requiring surgical intervention	Wheelchair bound; surgical repair not possible

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
H. MUSCULOSKELETAL				
H2. Arthralgia	Intermittent transient symptoms, no meds or relieved by OTC meds	Persistent or recurrent symptoms, resolve with meds, little effect on function	Severe symptoms despite meds impairs function	Debilitating, hospitalisation required for treatment
H3. Leg cramps	Transient, intermittent, does not interfere with function	Recurrent symptoms, minimally interferes with function or sleep, respond to meds	Persistent, prolonged interference with function or sleep, partial or no response to meds	NA
H4. Myalgia	Occasional; does not interfere with function	Frequent, requires meds (non- narcotic); minor effect on function	Major change in function/lifestyle, narcotic pain meds	Debilitating, profound weakness, requires wheelchair, unresponsive to meds
I. NEUROPSYCHIATRIC				
I-1. Anxiety or Depression (mood alteration)	Symptomatic, does not interfere with function; no meds	Frequent symptoms, responds to meds; interferes with ADL at times	Persistent, prolonged symptoms; partial or no response to meds, limits daily function	Suicidal ideation or danger to self

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
I. NEUROPSYCHIATRIC				
I-2. Cerebrovascular ischaemia	NA	Single transient ischaemic event, responsive to treatment	Recurrent transient ischemic events	Cerebrovascular vascular accident with permanent disability
I-3. Cognitive disturbance	Subjective symptoms, transient, intermittent, not interfering with function	Objective symptoms, persisting, interferes with daily function occasionally	Persistent, or worsening objective symptoms; interferes with daily routine	Debilitating/disabling and permanent; toxic psychosis
I-4. Depressed consciousness (somnolence)	Observed, transient, intermittent, not interfering with function	Somnolence or sedation, interfering with function	Persistent, progressive, obtundation, stupor	Coma
I-5. Inability to concentrate	Subjective symptoms, does not interfere with function	Objective findings, interferes with function	Persistent, prolonged objective findings; or organic cause	NA

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
I. NEUROPSYCHIATRIC				
I-6. Insomnia (in absence of pain)	Occasional difficulty sleeping, transient intermittent, not interfering with function	Recurrent difficulty sleeping; requires meds for relief; occasional interference with function	Persistent or worsening difficulty sleeping; severely interferes with routine daily function	NA
I-7. Libido decreased	Decrease in interest	Loss of interest; influences relationship	Persistent, prolonged, interfering with relationship	NA
I-8. Peripheral motor neuropathy	Subjective or transient loss of deep tendon reflexes; function maintained	Objective weakness, persistent, no significant impairment of daily function	Objective weakness with substantial impairment of function	Paralysis
I-9. Peripheral sensory neuropathy (sensory disturbance)	Subjective symptoms without objective findings, transient, not interfering with function	Objective sensory loss, persistent, not interfering with function	Prolonged sensory loss or paraesthesias interfering with function	NA

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
I. NEUROPSYCHIATRIC				
I-10. Seizure	NA	Recurrence of old seizures, controlled with adjustment of medication	Recurrence/exacerbation with partial response to medication	Recurrence not controlled, requiring hospitalization; new seizures
I-11. Vertigo (dizziness)	Subjective symptoms, transient, intermittent, no treatment	Objective findings, recurrent, meds relieve, occasionally interfering with function	Persistent, prolonged, interfering with daily function; partial response to medication	Debilitating without response to medication, hospitalization
J. PULMONARY				
J1. Asthma	Occasional wheeze, no interference with activities	Wheezing, requires oral meds, occasional interference with function	Debilitating, requires nasal O_2	Requires ventilator assistance
J2. Cough	Transient, intermittent, occasional OTC meds relieve	Persistent, requires narcotic or other prescription meds for relief	Recurrent, persistent coughing spasms without consistent relief by meds, interferes with function	Interferes with oxygenation; debilitating

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
J. PULMONARY				
J3. Dyspnea	Subjective, transient, no interference with function	Symptomatic, intermittent or recurring, interferes with exertional activities	Symptomatic during daily routine activities, interferes with function, treatment with intermittent nasal O_2 relieves	Symptomatic at rest, debilitating, requires constant nasal O_2
J4. Pleuritic pain (pleurisy)	Transient, intermittent symptoms, no treatment or OTC meds relieve	Persistent symptoms, requires prescription meds for relief	Prolonged symptoms, interferes with function, requires frequent narcotic pain relief	Debilitating, requiring hospitalisation
J5. Pneumonitis (pulmonary infiltrates)	Asymptomatic radiographic changes, transient, no treatment required	Symptomatic, persistent, requiring corticosteroids	Symptomatic, requiring treatment including O_2	Debilitating, not reversible; or requiring assisted ventilation

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
J. PULMONARY				
J6. Pulmonary function decreased (Forced vital capacity (FVC) or carbon monoxide diffusion capacity— DLCO)	76–90% of pre-treatment value	51–75% of pre-treatment value	26–50% of pre-treatment value	≤25% of pre-treatment value
LABORATORY DATA				
K. HAEMATOLOGY				
K1. Hgb (g/dl) decrease from pre-treatment	1.0–1.4	1.5–2.0	2.1–2.9; or Hgb < 8.0, > 7.0	≥3.0; or Hgb < 7.0
K2. Leukopenia (total WBC) x 1000	3.0–3.9	2.0–2.9	1.0–1.9	< 1.0
K3. Neutropenia (x 1000)	1.5–1.9	1.0–1.4	0.5–0.9	< 0.5

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
LABORATORY DATA				
K. HAEMATOLOGY				
K4. Lymphopenia (x 1000)	1.5–1.9	1.0–1.4	0.5–0.9	< 0.5
K5. Platelets (x 1000)	75– Lower limit of normal (LLN)	50–74.9	20–49.9; platelet transfusion required	< 20; recurrent platelet transfusions
LABORATORY DATA				
L. CHEMISTRY				
L1. Hypercalcaemia (mg/dl)	1.1 x ULN–11.5	11.6–12.5	12.6–13.5; or symptoms present	> 13.5; or associated coma
L2. Hyperglycaemia (mg/dl) Fasting	140–160	161–250	251–500	>500, or associated with fasting ketoacidosis

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
LABORATORY DATA				
L. CHEMISTRY				
L3. Hyperkalaemia (mg/dl)	5.5–5.9	6.0–6.4	6.5–7.0 or any ECG change	> 7.0 or any arrhythmia
L5. Hypocalcaemia (mg/dl)	0.9 x LLN–7.8	7.7–7.0	6.9–6.5; or associated with symptoms	< 6.5, or occurrence of tetany
L6. Hypoglycemia (mg/dl)	55–64 (no symptoms)	40–54 (or symptoms present)	30–39 (symptoms impair function)	< 30, or coma
L7. Hyponatraemia (mg/dl)	NA	125–129	120–124	< 120
L8. Hypokalaemia (mg/dl)	NA	3.0–3.4	2.5–2.9	< 2.5
L9. CPK (also if polymyositis- disease)	1.2–1.9 x ULN	2.0–4.0 x ULN	> 4.0 x ULN with weakness but without life-threatening signs or symptoms	> 4.0 x ULN with signs or symptoms of rhabdomyolysis or life-threatening

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
LABORATORY DATA				
L. CHEMISTRY				
L10.Serum uric acid	1.2–1.6 x ULN	1.7–2.9 x ULN	3.0–5.0 x ULN or gout	NA
L11. Creatinine (mg/dl)	1.1–1.3 x ULN	1.3–1.8 x ULN	1.9–3.0 x ULN	> 3.0 x ULN
L12. SGOT (AST)	1.2–1.5 x ULN	1.6–3.0 x ULN	3.1–8.0 x ULN	> 8.0 x ULN
L13. SGPT (ALT)	1.2–1.5 x ULN	1.6–3.0 x ULN	3.0–8.0 x ULN	> 8.0 x ULN
L14. Alkaline phosphatase	1.1–2.0 x ULN	1.6–3.0 x ULN	3.0–5.0 x ULN	> 5.0 x ULN
L15. T. bilirubin	1.1–1.4 x ULN	1.5–1.9 x ULN	2.0–3.0 x ULN	> 3.0 x ULN
L16. LDH	1.3–2.4 x ULN	2.5–5.0 x ULN	5.1–10 x ULN	> 10 x ULN

	1 - Mild	2 - Moderate	3 - Severe	4 - Includes Life Threatening
LABORATORY DATA				
M. URINALYSIS				
M1. Haematuria	Micro only	Gross, no clots	Clots, transfusion < 2 units	Transfusions required
M2. Proteinuria (per 24 h)	300–500 mg (tr/1+)	501–1999 mg (2+)	2–5.0 mg (3+) nephrotic syndrome	> 5.0 g (4+) anasarca
M3. WBC in urine	NA	NA	Indicating acute interstitial nephritis	Associated with acuterenal failure
M4. Uric acid crystals	Present without symptoms	NA	With stones or symptoms of stones (e.g. renal colic)	Causing renal outflow obstruction and hospitalization

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

Number of global amendment		1
Date of CTP revision		26 September 2014
EudraCT number		2014-001687-36
BI Trial number		1311.13
BI Investigational Product(s)		BI 655066
Title of protocol		An open label extension trial assessing the safety and efficacy of BI 655066 administered subcutaneously in patients with moderate to severe chronic plaque psoriasis.
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		CLINICAL TRIAL PROTOCOL SYNOPSIS, Trial site(s)
Description of change		Change wording to ‘Multicenter, multi national’
Rationale for change		Number of sites and countries will change during the trial conduct.
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS, Objective(s)
Description of change		Change from ‘Long term’ to ‘Additional’ safety and efficacy data.
Rationale for change		Modification of Objective to correlate with FDA requirement of maximum duration of administration of BI655066 of one year.

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS, Duration of treatment
Description of change		Change from 'Approximately 4 years' to 'Maximum duration of administration to patient is one calendar year after receiving first dose of BI 655066'
Rationale for change		Modification to correlate with FDA requirement

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS, Criteria for efficacy
Description of change		Modification of endpoint due to reduction in study duration and maximum administration of study medication of one year.
Rationale for change		Modification to correlate with FDA requirement

Section to be changed		FLOW CHART 1
Description of change		Change of duration of treatment period and Follow up period, as well as correct footnotes and numbering. Additional text is added to footnote 1 to better explain roll-over from trial 1311.2, footnote 4 covering visits beyond visit 18 is deleted and wording for footnote 5 describing variable timing of EOT is modified to adapt the maximum duration of administration of one year. Corrective words have been added to footnote 9 and 12, Vital signs has been added to all scheduled visits, and footnote 19 has been added to better describe drug administration.
Rationale for change		These are administrative changes to correct duration of treatment period and follow up period, numbering of footnotes and to correct wordings in the footnotes to correlate with FDA requirement of maximum duration of administration of BI655066 of one year.

Section to be changed		2.1 RATIONALE FOR PERFORMING THE TRIAL
Description of change		Change of wording from 'Long term' to 'Additional' safety and efficacy data, and add wording for 48 week follow up.
Rationale for change		Modification due to reduction in study duration and maximum administration of study medication of one year.

Section to be changed		2.2 TRIAL OBJECTIVES
Description of change		Change of wording from 'Long term' to 'Additional' safety and efficacy data.
Rationale for change		Modification due to reduction in study duration to one year administration of study medication.

Section to be changed		2.3 BENEFIT – RISK ASSESSMENT
Description of change		Further description of signs of hypersensitive reactions is added.
Rationale for change		Include further, adequate details concerning the performance of monitoring after IMPs injections, for all treated patients.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Change of wording from 'Long term' to 'Additional' safety and efficacy data.
Rationale for change		Modification due to reduction in study duration to one year administration of study medication.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Description of how to proceed if a subject is eligible for 1311.13 and the protocol is not yet approved.
Rationale for change		To be able to re-evaluate subjects eligible for 1311.13 while protocol not yet approved. This situation is applicable for possible roll-overs from 1311.2 during the period the study initiation has been on hold. Procedures for re-evaluation is specified.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Figure 3.1:2 'Drug Administration in trial 1311.13' is added
Rationale for change		Table is added to explain drug administration at different visit throughout the trail.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Delete text describing adjustment of dosing to 180 mg and text describing possible reduction of dosing after study data from 1311.2 is revealed.
Rationale for change		Due to FDA regulation, maximum dosage is 90 mg per 12 week, 180 mg dose is no longer applicable in this trial.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		$PASI_{75}$ is added as standard clinical endpoint and to be assessed at each visit.
Rationale for change		The plaque psoriasis will be evaluated by PASI score at each visit. The standard clinical endpoints of $PASI_{50,}$ $PASI_{75}$ and $PASI_{90}$ will be assessed at each visit.

Section to be changed		FIG 3.1:2 Guideline for assessment dose adjustment
Description of change		Figure is deleted.
Rationale for change		Figure describes possible dose adjustment between 90 mg and 180 mg dose. Due to FDA regulation, maximum dosage is 90 mg per 12 week, 180 mg dose is no longer applicable in this trial.

Section to be changed		3.1.1 ADMINISTRATIVE STRUCTURE OF THE TRIAL
Description of change		Change of number of participating sites and countries.
Rationale for change		Number of participating sites and countries has been modified, to reflect the current status for this.

Section to be changed		3.2 DISCUSSION OF TRIAL DESIGN
Description of change		Delete text describing adjustment of dosing to 180 mg.
Rationale for change		Due to FDA regulation, maximum dosage is 90 mg per 12 week, 180 mg dose is no longer applicable in this trial.

Section to be changed		3.2 DISCUSSION OF TRIAL DESIGN
Description of change		Change of wording from ‘Long term’ to ‘Additional’ safety and efficacy data, and adding ‘following one year drug administration’.
Rationale for change		Modification due to reduction in study duration and administration of study medication.

Section to be changed		3.3.4.1 REMOVAL OF INDIVIDUAL PATIENTS
Description of change		Corrections to reflect new study duration of 48 week follow up instead of 15 days.
Rationale for change		Study duration changed to 48w follow up after one year maximum study drug administration.

Section to be changed		4.1.2 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS
Description of change		Delete text describing adjustment of dosing to 180 mg.
Rationale for change		Due to FDA regulation, maximum dosage is 90 mg per 12 week, 180 mg dose is no longer applicable in this trial.

Section to be changed		4.1.3 SELECTION OF DOSES IN THE TRIAL
Description of change		Delete text describing adjustment of dosing to 180 mg and possible adjustment of dosing once the 1311.2 study results are available.
Rationale for change		Due to FDA regulation, maximum dosage is 90 mg per 12 week, 180 mg dose is no longer applicable in this trial.dose applicable for this study.

Section to be changed		TABLE 4.1.4.1. Dose regimens
Description of change		Table is deleted.
Rationale for change		Table describes dose regimens for 90 mg and 180 mg dose. Dose of 90 mg is the only dose applicable for this study.

Section to be changed		4.1.4 DOSE ASSIGNMENT AND ADMINISTRATION OF DOSES
Description of change		Further description of signs of hypersensitive reactions is added.
Rationale for change		Include further, adequate details concerning the performance of monitoring after IMPs injections, for all treated patients. Requirement from French HA.

Section to be changed		5.1.1 ENDPOINTS OF EFFICACY
Description of change		Time of evaluation of primary and secondary endpoints has been changed from 12 week to 48 week.
Rationale for change		Change of timing of evaluation for endpoints necessary to reflect maximum study drug administration of one calendar year.

Section to be changed		TABLE 5.2.3:2 SAFETY LABORATORY TESTS
Description of change		Test for ESR (erythrocyte sedimentation rate after 1 hour) is deleted.
Rationale for change		ESR test is not to be performed, due to evaluations from 1311.2. The test had to be performed at local lab, and the interpretation of the test results is not validated to give reliable values.

Section to be changed		6.2.2 TREATMENT PERIOD(S)
Description of change		Description of how to proceed if a subject is eligible for 1311.13 and the amended protocol is not yet approved. Also added in section 3.1.
Rationale for change		To be able to re-evaluate subjects eligible for 1311.13 while protocol not yet approved. This situation is applicable for possible roll-overs from trial 1311.2 during the period the study 1311.13 has not yet been initiated due to review of protocol amendment. Procedures for re-evaluation are specified.

Section to be changed		6.2.2 TREATMENT PERIOD(S)
Description of change		Text describing adjustment of dosing to 180 mg is deleted.
Rationale for change		Dose of 90 mg is the only dose applicable for this study.

Section to be changed		6.2.3 END OF TRIAL AND FOLLOW_UP PERIOD
Description of change		Specification of end of trial is changed, adding description of 48 week follow up period.
Rationale for change		Specification of end of trial is changed due to reduction in study duration and administration of study medication of maximum one year.

Section to be changed		7.2 NULL AND ALTERNATIVE HYPETHESIS
Description of change		Change of wording regarding duration of study drug administration.
Rationale for change		Modification due to reduction in study duration and maximum administration of study medication of one year.

Section to be changed		7.3 PLANNED ANALYSIS
Description of change		Deleting text describing critical time-points beyond 1 year.
Rationale for change		Modification due to reduction in study duration and maximum administration of study medication of one year.

Section to be changed		7.3.1 PRIMARY ANALYSIS
Description of change		Modification of endpoint due to reduction in study duration and maximum administration of study medication of one year.
Rationale for change		Modification to correlate with FDA requirement

Number of global amendment		2
Date of CTP revision		15 October 2014
EudraCT number		2014-001687-36
BI Trial number		1311.13
BI Investigational Product(s)		BI 655066
Title of protocol		An open label extension trial assessing the safety and efficacy of BI 655066 administered subcutaneously in patients with moderate to severe chronic plaque psoriasis.
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		FLOW CHART 1
Description of change		Change of wording for day and week to relate to EOT instead of absolute numbers. Change of text in footnote 4 to better explain drug administrations. Addition of footnote 20 and 21 to better explain procedures for prematurely discontinuation and collection of vital signs and vital status follow up. Assessment for Tolerability (safety and efficacy) has been deleted, as this was primarily for evaluation of dose adjustments which are no longer applicable, so has local tolerability test for follow up period after FU2.
Rationale for change		These are administrative changes to clarify timing of visit, and study procedures for drug administrations, withdrawals and collection of vital signs and vital status follow up.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Study number 1311.13 added in text to clarify drug administration for patients that did not receive BI655066 in trial 1311.2
Rationale for change		Text added to clarify.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Figure 3.1:2 deleted and replaced by Flow Chart 2 to better explain drug administration
Rationale for change		Figure revised to clarify drug administration.

Section to be changed		3.3.4 REMOVAL OF PATIENTS
Description of change		Text added to clarify procedures for withdrawal in follow up period
Rationale for change		Text added to clarify.

Section to be changed		5.2.5 ASSESSMENT OF OTHER SAFETY PARAMETER
Description of change		Text explaining 'Tolerability (safety and efficacy)' has been deleted, as this was primarily for evaluation of dose adjustments which are no longer applicable.
Rationale for change		Assessment no longer applicable, as only one dose applicable in this trial.

Section to be changed		6.2.2.TREATMENT PERIOD
Description of change		'EOT' removed from text to avoid mix with EOS. Added text regarding study window removed, misleading.
Rationale for change		Text removed to clarify.

Section to be changed		6.2.2.TREATMENT PERIOD
Description of change		Text added to clarify drug administration for patients that did not receive BI655066 in trial 1311.2. Also ref to Flow Chart 2 added to clarify.
Rationale for change		Text and reference to Flow Chart 2 added to clarify.

Section to be changed		6.2.3 END OF TRIAL AND FOLLOW-UP PERIOD
Description of change		Text added to clarify procedures for withdrawal in follow up period
Rationale for change		Text added to clarify.

Section to be changed		6.2.3 END OF TRIAL AND FOLLOW-UP PERIOD
Description of change		Text added to describe collection of consent for

		vital status follow up.
Rationale for change		Text added to clarify.

Number of global amendment		3
Date of CTP revision		10 June 2015
EudraCT number		2014-001687-36
BI Trial number		1311.13
BI Investigational Product(s)		BI 655066
Title of protocol		An open label extension trial assessing the safety and efficacy of BI 655066 administered subcutaneously in patients with moderate to severe chronic plaque psoriasis.
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		CLINICAL TRIAL PROTOCOL SYNOPSIS, Objective(s)
Description of change		Change from ‘Additional’ to ‘Long term’ safety and efficacy data.
Rationale for change		Return to original CTP wording with approx 4 years duration of treatment. New toxicity data cancel FDA requirement of maximum duration of administration of BI655066 of one year.

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS, No. patients each treatment
Description of change		Text including possible increase to 180 mg dosing every 12 week is added.
Rationale for change		Possibility to increase to 180 mg dosing depending on efficacy at 12 week added. Patients

		should all reach >$PASI_{90}$.

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS, Test product (s)
Description of change		'180 mg dosing every 12 week' added
Rationale for change		Possible increase to 180 mg dosing depending on efficacy at 12 week.

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS, Duration of treatment
Description of change		Change from 'Maximum duration of one calendar year' to 'Approximately four years of administration'. '48 week follow up period' deleted.
Rationale for change		Return to original CTP wording with approx 4 years duration of treatment. New toxicity data cancel FDA requirement of maximum duration of administration of BI655066 of one year. Follow up period will now be REP i.e. 12 weeks.

Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS, Criteria for efficacy
Description of change		Added 'in the Extended dosing period'
Rationale for change		To clarify that point of achievement will be at 48 week in the extended dosing period only.

Section to be changed		FLOW CHART
Description of change		Previous Flow Chart 1 deleted and replaced by a new. Visit scheduling of previous Flow Chart 1 is now added as Figure 3.1.3. New Flow Chart is called 'Extended dosing period'. Change of wording for visit to relate to Extended period. Footnotes added or modified to explain new study procedures related to the extension of the trial and possible re-start of treatment.
Rationale for change		Flow Chart has been modified to reflect procedures and timing related to the extension of the trial and possible re-start of treatment for the patients with low response (<$PASI_{90}$) at week 12.

Section to be changed		FLOW CHART 2
Description of change		Flow Chart 2 is deleted. (Replaced by Fig 3.1.3)
Rationale for change		Flow Chart 2 is no longer applicable, due to no limitation of maximum one year dosing per

		patient. Headings kept as reference in Fig 3.1.3

Section to be changed		ABBREVIATIONS
Description of change		Abbreviations added for PASE, EV, OPU, ISF, Th and IgG.
Rationale for change		Missed or added since previous amendment.

Section to be changed		2.1 RATIONALE FOR PERFORMING THE TRIAL
Description of change		Change from 'one' to 'approximately four years' treatment, '48 weeks follow up' deleted.
Rationale for change		Return to original CTP wording with approx 4 years duration of treatment. New toxicity data cancel FDA requirement of maximum duration of administration of BI655066 of one year.

Section to be changed		2.2 TRIAL OBJECTIVES
Description of change		Change from 'one' to 'approximately four years' treatment, change from 'up to one year' and 'additional' to 'long term'.
Rationale for change		Return to original CTP wording with approx 4 years duration of treatment. New toxicity data cancel FDA requirement of maximum duration of administration of BI655066 of one year.

Section to be changed		2.3 BENEFIT – RISK ASSESSMENT
Description of change		'Visit 1' replaced by 'rollover visit' . 'Extended' added.
Rationale for change		TB testing only to be performed at the initial roll-over visit. Extended EOT replacing previous EOT.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Change from 'total of one' to 'approximately four years' treatment. Description of study end added.
Rationale for change		Return to original CTP wording with approx 4 years duration of treatment. The study is planned to continue until marketing approval of BI655066 in each country.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Procedure for roll-over to 'Extended visit 1' described in the text and Figure 3.2.3.added to refer to previous visit schedule.
Rationale for change		New visit schedule for 'Extended dosing period' is implemented, procedures for how to roll-over new and existing patients into this are added.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Figure 3.1.2.added
Rationale for change		Figure added to give guideline for assessment of dose adjustment.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Figure 3.1.3.added
Rationale for change		Headings from previous Flow Chart kept as reference to visit schedule naming.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		'$PASI_{100}$' and 'Extended' added.
Rationale for change		To be in accordance with section 5.1.1.1.2 and 7.3.2.

Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		Number of sites and countries corrected.
Rationale for change		Since last AM, number of participating sites and countries has been modified.

Section to be changed		3.2 DISUSION OF TRIAL DESIGN…
Description of change		'…option of moving to a higher dose (180 mg) if loss of clinically activity is noted' is added.
Rationale for change		Possible increase to 180 mg dosing depending on efficacy at 12 week. Patients should all reach >$PASI_{90}$.

Section to be changed		3.3 SELECTION OF TRIAL POPULATION
Description of change		'Visit 1' changed to 'roll-over visit' in inclusion and exclusion criteria. REP changed from 15 to 12 weeks.
Rationale for change		To adapt wording to new visit schedule naming and design. REP changed according to new IB ver 5 for BI 6550066.

Section to be changed		3.3.4 REMOVAL OF PATIENTS FROM THERAPY
Description of change		Sentence regarding FU visit is deleted. 'Extended' added to all visits mentioned in the text. Follow up period changed from 48 to 12 weeks. 'Visit 1' replaced by 'roll-over visit'.
Rationale for change		FU visits no longer in the revised Flow Chart. 'Extended' added to reflect visit schedule naming in new flow Chart.

Section to be changed		4.1 TREATMENT TO BE ADMINISTERED

Description of change		Text added to describe possible increase in dosing to 180 mg if lack of response. Text to explain selection of dose has been modified. Instruction for injection of 180 mg added.
Rationale for change		Possible increase to 180 mg dosing depending on efficacy at 12 week. Text to explain selection of dose has been modified to reflect new findings from the interim analysis of 1311.2.

Section to be changed		4.2.2 RESTRICTIONS
Description of change		'Extended' added and Visit 1' changed to 'roll-over visit' in Table 4.2.2.1
Rationale for change		'Extended' added to reflect visit schedule naming in new flow Chart.

Section to be changed		5.1 EFFICACY -PHARMACODYNAMICS
Description of change		'in Extended dosing period' added in text.
Rationale for change		Added to clarify that prim endpoint will be achieved at 48 w in Extended dosing period only.

Section to be changed		5.2.2. ASSESSMENT OF ADVERSE EVENTS
Description of change		Time window for EV1 changed to 6 weeks. REP changed from 15 to 12 weeks.
Rationale for change		Time window for entering EV1 from EOS of 1311.2 changed from 7 days to 6 weeks, to be able to include patients that had to wait for the approval of this amendment for their roll-over. REP changed to 12 weeks/ 84 days according to IB ver 6 for IB655066.

Section to be changed		5.2.3 ASSESSMENT OF SAFETY LABORATORY PARAMETERS
Description of change		'Visit 1' changed to 'roll-over visit' in table 5.2.3:2. 'Extended' added.
Rationale for change		Changed to clarify and reflect visit schedule naming in new flow Chart.

Section to be changed		5.2.4 ELECTROCARDIOGRAM
Description of change		Specification of visits were ECG will be obtained is deleted.
Rationale for change		ECG will be obtained every 24 weeks according to new Flow Chart.
Section to be changed		5.2.5 ASSESSMENT OF OTHER SAFETY PARAMETERS
Description of change		'Visit 1' changed to 'roll-over visit'
Rationale for change		Changed to clarify procedure according to new visit schedule.

Section to be changed		6.2.2 TREATMENT PERIOD
Description of change		Text modified and added to reflect procedures and assessments according to current Flow Chart.
Rationale for change		Flow Chart with footnotes covering Extended Dosing Period will replace former visit schedule and procedures.

Section to be changed		6.2.3. END OF TRIAL AND FOLLOW UP PERIOD
Description of change		Text modified and added to reflect procedures and assessments according to current Flow Chart. Text regarding collection of vital status changed to open for collection of consent also at EV1.
Rationale for change		Flow Chart with footnotes covering Extended Dosing Period will replace former visit schedule and procedures.

Section to be changed		7.1 STATISTICAL DESIGN
Description of change		Text ‘single’ arm replaced by ‘double’ arm.
Rationale for change		Double arm design due to introduction of possible 180 mg dose at EV2.

Section to be changed		7.2 NULL AND ALTERNATIVE HYPETHESIS
Description of change		‘one year’ replaced by ‘extended visit period’.
Rationale for change		Text changed to reflect current visit schedule.

Section to be changed		7.3 PLANNED ANALYSIS
Description of change		‘in Extended dosing period’ added. REP changed to 12 weeks from 15 weeks.
Rationale for change		Added to specify time of efficacy endpoint. REP changed according to current IB ver 6.

Section to be changed		10.5 PASE
Description of change		‘Visit 1’ replaced by ‘roll-over visit’ to reflect current flow chart and procedures
Rationale for change		To reflect current flow chart and procedures for EV1.

Number of global amendment		4
Date of CTP revision		12 October 2016
EudraCT number		2014-001687-36
BI Trial number		1311.13
BI Investigational Product(s)		BI 655066
Title of protocol		An open label extension trial assessing the safety and efficacy of BI 655066/ ABBV-066/ (risankizumab) administered subcutaneously in patients with moderate to severe chronic plaque psoriasis.
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, Synopsis
Description of change		Changed BI drug or BI investigational product or BI 655066 to refer to either names for this compound: BI 655066/ ABBV-066/risankizumab.
Rationale for change		In February 2016, AbbVie entered into a license agreement with BI related to risankizumab, and in October 2016, the US IND for risankizumab transitioned from BI to AbbVie. This protocol change reflects that AbbVie will now be the Sponsor of this study in the US, as well as the modifications to certain study conduct responsibilities as a result of that license agreement are listed as separate changes below.

Section to be changed		3.1.1 ADMINISTRATIVE STRUCTURE OF THE TRIAL

Description of change		1. Changed sponsor from Boehringer Ingelheim (BI) to AbbVie in the US and BI for all other participating countries. 2. Changed text to specify Statistical Evaluation will be done by AbbVie according to their SOPs.
Rationale for change		Refer to rational for first change listed
Section to be changed		3.3.4.2 DISCONTINUATION OF THE TRIAL BY THE SPONSOR
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

Number of global amendment		5
Date of CTP revision		30 January 2018
EudraCT number		2014-001687-36
BI Trial number		1311.13
BI Investigational Product(s)		BI 655066
Title of protocol		An open label extension trial assessing the safety and efficacy of BI 655066/ ABBV-066/ (risankizumab) administered subcutaneously in patients with moderate to severe chronic plaque psoriasis.
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		FLOW CHART-extended dosing period
Description of change		Added at the EOS visit: After the approval of this protocol amendment in each respective country patients who have completed the study without early treatment discontinuation will be offered to roll over to M15-997 open label extension (OLE) trial if they fulfil the in- and exclusion criteria for the M15-997 trial. Refer to section 6.2.3. Next visit and also the last visit after 1st May and approval of this amendment will be the extended EOS visit .Termination of trial medication page should be completed in the eCRF and treatment completed registered in IRT.
Rationale for change		Transition of patients from 1311.13 to M15-997 study

Section to be changed		FLOW CHART-extended dosing period
Description of change		Serum pregnancy testing and TB screening added to the EOS visit.
Rationale for change		Added to the EOS visit because this will be the last visit in the study instead for EOT visit for patients not prematurely discontinued.

Section to be changed		FLOW CHART-extended dosing period
Description of change		Consent for vital status follow up deleted from EOS visit.
Rationale for change		No longer applicable as the patients will be transferred to the M15-997 and this study will end.

Section to be changed		FLOW CHART-extended dosing period
Description of change		•Footnote 4: Variable depending on marketing approval of BI 655066 deleted •Footnote 5: If study is ongoing beyond Extended visit 18, forthcoming visits should be repeated in cycles as described in Extended visit 6 -18 until the patient withdraws, or the end of study is declared. Visits will be numbered consecutively (Extended visit 19, Extended visit 20, …) deleted
Rationale for change		No longer applicable as it is decided when the study will end.

Section to be changed		3.1OVERALL TRIAL DESIGN AND PLAN
Description of change		Text deleted: The study is planned to continue in each country in which it is conducted, until BI 655066 is approved and available on the market in that country. Text added: After 01-May-2018 and approval of this protocol amendment in each respective country, the next study visit will be the Extended EOS visit and therewith the last visit in this study. Patients who have completed the study without early treatment discontinuation will be offered to roll over to M15-997 open label extension (OLE) trial if they fulfil the in- and exclusion criteria for the M15-997 trial. Refer to section 6.2.3.
Rationale for change		Transition of patients from 1311.13 to M-15-997

Section to be changed		6.3 End of trial and Extended follow-up period
Description of change		Update why and how the 1311.13 study should end
Rationale for change		Study drug is not marketed yet and the patient

		will be offered to roll over to M15-997 open label extension study and have the opportunity to continue with Risankizumab (BI 655066).

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-06

Title: An open label extension trial assessing the safety and efficacy of BI 655066/ ABBV-066/risankizumab administered subcutaneously in patients with moderate to severe chronic plaque psoriasis.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Approval-[redacted]	[redacted]	30 Jan 2018 14:53 CET
Approval-[redacted]		30 Jan 2018 15:50 CET
Author-[redacted]		30 Jan 2018 17:39 CET
Approval-[redacted]		01 Feb 2018 14:51 CET
Verification-Paper Signature Completion		01 Feb 2018 15:05 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed