Clinical Trial Protocol

Document Number:		**c08917790-03**
EudraCT No.: **EU Trial No:**	2016-000613-79	
BI Trial No.:	1297.12	
BI Investigational Product(s):	BI 695501	
Title:	Efficacy, Safety, and Immunogenicity of BI 695501 versus Humira® in Patients with Moderate to Severe Chronic Plaque Psoriasis: A Randomized, Double-Blind, Parallel-Arm, Multiple-Dose, Active Comparator Trial	
Lay Title:	Efficacy, Safety, and Immunogenicity of BI 695501 versus Humira® in Patients with Moderate to Severe Chronic Plaque Psoriasis	
Clinical Phase:	Phase III	
Trial Clinical Monitor:	Tel.:	
Coordinating Investigator:	Tel.: Fax.:	
Status:	Final Protocol	
Version and Date:	**Version: 1.0**	**Date:26 Apr 2016**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Name of company:		**Boehringer Ingelheim**	
Name of finished product:		NA	
Name of active ingredient:		BI 695501	
Protocol date: 26 Apr 2016	**Trial number:** 1297.12		**Revision date:**

Title of trial:	Efficacy, Safety, and Immunogenicity of BI 695501 versus Humira® in Patients with Moderate to Severe Chronic Plaque Psoriasis: A Randomized, Double-Blind, Parallel-Arm, Multiple-Dose, Active Comparator Trial
Coordinating Investigator:	
Trial site(s):	Multi-national, multi-center trial in approximately 50 clinical sites across approximately 10 countries
Clinical phase:	Phase III
Objective(s):	The primary objective of this trial is to evaluate equivalence in efficacy between BI 695501 and US-licensed Humira® at Week 16 in patients with active moderate to severe chronic plaque psoriasis. The secondary objectives of this trial are to compare the safety and efficacy profiles of BI 695501 and US-licensed Humira.
Methodology:	This is a randomized, double-blind, parallel-arm, multiple-dose, active comparator trial of BI 695501 and US-licensed Humira with a screening period of up to 28 days, a 24-week treatment period and a 10-week safety follow-up period in patients with chronic plaque psoriasis and a primary endpoint assessment at Week 16. Patients will be randomized 1:1 to either BI 695501 or Humira. Each patient will receive 80 mg of BI 695501 or US-licensed Humira at Baseline (Randomization) (Day 1, Week 0), followed by 40 mg of BI 695501 or Humira 1 week later (Week 1), and then 40 mg of BI 695501 or Humira every other week. After Week 16, only patients who achieve a 50% reduction in Psoriasis Area and Severity Index (PASI 50) will continue the trial receiving their originally randomized treatment. Those patients not achieving at least PASI 50 will not be treated further with the study drugs but only followed up for safety.
No. of patients: **Total entered:**	Approximately 300 patients will be randomized.
Each treatment:	Patients will be allocated to treatment in a 1:1 ratio to receive BI 695501 or US-licensed Humira.
Diagnosis:	Moderate to severe chronic plaque psoriasis.
Main criteria for inclusion:	This study will include male or female participants at least 18 years of age who have a diagnosis of moderate to severe chronic plaque psoriasis of at least 6 months duration. The patient's chronic plaque psoriasis must have been stable for the last 2 months with no meaningful changes in morphology or significant flares. At inclusion, patients must have a PASI score ≥ 12, Static Physician's Global Assessment of psoriasis (sPGA) ≥ 3, and a body surface area (BSA) involvement ≥ 10% at Screening and at baseline. Patients must be suitable for systemic treatment.

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	Patients with prior exposure to more than 1 biologic (must not be adalimumab) will be excluded from this trial.
Test product(s):	BI 695501, solution for subcutaneous (s.c.) injection in single-use prefilled syringe (40 mg)
dose:	Starting 1 week after a first administration of 80 mg BI 695501 after randomization, patients will receive 40 mg every other week.
mode of administration:	Subcutaneous injection
Comparator products:	US-licensed Humira, solution for s.c. injection in single-use prefilled syringe (40 mg)
dose:	Starting 1 week after a first administration of 80 mg Humira after randomization, patients will receive 40 mg every other week via a single prefilled glass syringe.
mode of administration:	Subcutaneous injection
Duration of treatment:	Patients are planned to be treated with trial medication for 24 weeks. Seven days after a first 80 mg administration of either BI 695501 or US-licensed Humira, patients will receive 40 mg of either BI 695501 or US-licensed Humira every other week up to efficacy assessment at Week 16. Only patients achieving at least a PASI 50 response will continue the treatment after 16 weeks, ending at Week 24.
Endpoints	**Efficacy endpoints will be measured at Week 16 (equivalence assessment) and Week 24.** Primary efficacy endpoint: • Proportion of patients with a 75% reduction in Psoriasis Area and Severity Index (PASI 75) response at Week 16 Secondary endpoints: <u>Efficacy</u> • Proportion of patients with a PASI 75 response at Week 24 • Mean percentage improvement in PASI at Week 16 • Proportion of patients with a sPGA ≤ 1 (clear or almost clear) at Week 16 • Proportion of patients achieving a Dermatology Life Quality Index (DLQI) of 0 or 1 at Week 16 <u>Safety</u> • Proportion of patients with drug-related adverse events (AEs)
Safety criteria:	Physical examination, vital signs (blood pressure, pulse rate, body temperature), 12-lead electrocardiogram (ECG), laboratory tests, continuous AE monitoring, and local tolerability.
Statistical methods:	**Primary analysis** To conclude equivalence, the 95% confidence interval (CI) of the difference in PASI 75 response rate at Week 16 between BI 695501 and Humira must be fully

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	within the equivalence limits of ± 18%. **Secondary analysis** For the secondary efficacy endpoints, point estimates (risk difference for binary endpoints) and CIs will be calculated, but will be interpreted in a descriptive manner. Safety endpoints and AESIs will be presented descriptively. Risk ratio together with 95% CI will be presented for the secondary safety endpoint.		

FLOW CHART

Visit[1]	**1**	**2**	**3**		**4**			**5**			**6**			**7**			**8**			**9**	**10**
Week	**Screen -4 to -1**	**Base line 0**	**1**	**3**	**4**	**5**	**7**	**8**	**9**	**11**	**12**	**13**	**15**	**16**	**17**	**19**	**20**	**21**	**23**	**24 EoT**	**33 SFU**[2]
Days	**-28 to -1**[11]	**1**	**8**	**22**	**29**	**36**	**50**	**57**	**64**	**78**	**85**	**92**	**106**	**113**	**120**	**134**	**141**	**148**	**162**	**169**	**232**
Permitted visit window (days)	-	-1/ +2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	+ 3
Informed consent	X																				
Assessment of eligibility	X	X																			
Demographics	X																				
Medical history	X																				
LAB/SAFETY ASSESSMENTS[3]																					
Infection screen: TB, hepatitis B (HBsAg, anti-HBc), hepatitis C (anti-HCV), HIV	X																				
Chest X-ray	X[4]																				
TB testing (IGRA or PPD testing)[5]	X																				X
Pregnancy test	X	X						X						X						X	X
Physical examination	X	X						X						X						X	X
Vital signs[6]	X	X						X						X						X	X
Safety Laboratory tests	X	X						X						X						X	X
12-lead ECG	X							X						X						X	X

Visit[1]	**1**	**2**	**3**		**4**			**5**			**6**			**7**			**8**			**9**	**10**
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Permitted visit window (days)	-	-1/ +2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 2	± 3	± 3	± 3	± 3	± 3	± 3	± 3	+ 3
Previous and concomitant therapy	◄———											X									———►
Adverse events[7]	◄———											X									———►
EFFICACY ASSESSMENTS[3]																					
PASI	X	X			X			X			X			X			X			X	
sPGA	X	X			X			X			X			X			X			X	
DLQI	X	X			X			X			X			X			X			X	
TRIAL MEDICATION																					
Contact IRT[11]	X	X	X 12		X 12			X 12			X 12			X 12			X 12				
Trial medication[9]		X	X	X		X	X		X	X		X	X		X	X		X	X		
Review patient diary[13]					X[13]			X[13]			X[13]			X[13]			X[13]			X[13]	X[13]
Randomization[10]		X																			

Abbreviations: ; AE=adverse event; anti-HBc=anti-hepatitis B core antibodies; anti-HCV=anti-hepatitis C antibodies; DLQI=Dermatology Life Quality Index; EoT=End of Treatment; IRT=Interactive Response Technology; HBsAg=hepatitis B surface antigen; HIV=human immunodeficiency virus; IGRA=interferon gamma-releasing assay; ; PASI=Psoriasis Area and Severity Index; PPD=purified protein derivative; SFU=Safety Follow-up; sPGA=Static Physician's Global Assessment of psoriasis; TB=tuberculosis.

1. Patients will have to visit the site for efficacy assessments and to provide samples for / safety. For other visits (Weeks 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23), patients are be allowed to self-administer the drug at home (after training).
2. Patients who discontinue the trial early (also those not achieved PACI 50 at week 16) will, at discontinuation, have an End of Treatment (EoT) Visit equivalent to the Week 24 assessments (except trial medication administration). Every effort should be made for all patients to return for a Safety Follow-up (SFU) Visit 10 weeks after last drug administration.
3. All efficacy (e.g., PASI, and sPGA) and safety assessments will be performed by blinded personnel.
4. A chest X-ray is to be taken at Screening. Alternatively, results from a chest X-ray taken within 12 weeks of Screening can be used.
5. Patients must have a negative tuberculosis (TB) screening assessment, including a purified protein derivative (PPD) skin test or interferon gamma-releasing assay (IGRA) (e.g., QuantiFERON® TB Gold or T-SPOT®.TB). In addition, a TB test can be performed at any time during the trial if the investigator considers it clinically necessary.
6. Vital signs include measurement of body temperature, blood pressure, and pulse rate (all in the sitting position after a 5-minute rest).
7. Adverse events (AEs) will be collected from the time of informed consent. Adverse events continuing at the SFU Visit must be followed to resolution or followed up as agreed by the investigator and medical monitor. For patients who complete the trial or who discontinue the trial early, new AEs will be captured for up to 10 weeks after last drug administration (SFU Visit).
8.
9. Trial medication should be administered at Day 1, with the second injection 7 days later and subsequent injections every 2 weeks thereafter (± 2 days up to Week 14 and ± 3 days from Week 16 onward).
10. Randomization can occur through a randomization call or on Day 1 (-1 / +2) through a standard randomization visit call. The Day 1 randomization or call will depend on the trial site procedure. Patients will be randomized to each treatment in a 1:1 ratio (BI 695501:US-licensed Humira®). For some sites, the registration call might be made approximatelly10 days prior to the planned first administration of trial medication. Patients will be tentatively assigned to each treatment at random in a 1:1 ratio (BI 695501:US-licensed Humira®) and a position on the randomization scheme will be reserved. On Day 1 (or when the drug is at site), a randomization number will be assigned and patients will then be confirmed on the randomization scheme and will receive their first administration of trial medication according to their randomization.
11. Interactive Response Technology (IRT) will be contacted on indicated Visits.
12. One or two syringes might be dispensed to the patient for the self-administration at home.
13. The patient will complete a diary, documenting the date and time of trial medication self-administration and any AEs experienced between study visits.

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ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
anti-HBc	anti-hepatitis B core antibodies
AST	aspartate aminotransferase
β-hCG	beta-human Chorionic Gonadotropin
BI	Boehringer Ingelheim
BSA	body surface area
CA	Competent Authority
CI	confidence interval
CK-MB	Creatine Kinase-MB
CRA	Clinical Research Associate
CRO	Contract Research Organization
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	drug-induced liver injury
DLQI	Dermatology Life Quality Index
ECG	electrocardiogram
eCRF	Electronic Case Report Form
ELISA	enzyme-linked immunosorbent assay
EoT	End of Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOXP3	forkhead box P3
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
GMP	Good Manufacturing Practice
GOT	Glutamic-Oxaloacetic Transaminase
GPT	Glutamic-Pyruvic Transaminase
Hb	hemoglobin
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus
Hct	Hematocrit
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IgG1	immunoglobulin G1

IGRA	interferon gamma-release assay
IL	interleukin
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	intrauterine device
i.v.	intravenous
k	kappa
K_2EDTA	dipotassium ethylenediaminetetraacetic acid
LOCF	last observation carried forward
LPDD	Last Patient Drug Discontinuation
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	multiple imputation
MTX	methotrexate
nAb	neutralizing antibody
NRI	non-responder imputation
NSAID	non-steroidal anti-inflammatory drug
PASI	Psoriasis Area and Severity Index
PASI50	50% reduction in Psoriasis Area and Severity Index
PASI75	75% reduction in Psoriasis Area and Severity Index
PPD	purified protein derivative
PPS	per-protocol set
PUVA	psoralen with ultraviolet A light
RA	rheumatoid arthritis
RBC	red blood cell
REP	residual effect period, after the last dose of medication with measureable drug levels or pharmacodynamic effects still likely to be present
SAE	serious adverse event
SAF	safety analysis set
s.c.	subcutaneous
SFU	Safety Follow-up
SOP	standard operating procedure (s)
SPC	summary of product characteristics
sPGA	static Physician's Global Assessment
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
Th17	T helper 17 cells
TNF	tumor necrosis factor
TSAP	Trial Statistical Analysis Plan
ULN	upper limit of normal
US-PI	United States Package Insert
UVA	Ultraviolet A light

UVB	Ultraviolet B light
WHO	World Health Organization

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Psoriasis is the most prevalent immune-mediated skin disease that affects 1% to 3% of the population worldwide, with an equal sex distribution. The most common form of the disease, termed “plaque psoriasis”, is observed in more than 80% of psoriasis patients and is characterized by erythematous scaly plaques, typically on elbows, knees, scalp, and buttocks. Twenty-five percent of patients have moderate to severe disease, with considerable negative impact on their psychosocial and economic status (R11-1259). Psoriasis causes a high degree of morbidity and decreased quality of life, largely due to flares and disfiguring lesions in visible areas of the skin, systemic manifestations, and drug-related side effects.

Histological examination of psoriatic plaques reveals keratinocyte hyperproliferation, with parakeratosis and elongation of rete ridges, increased angiogenesis and dermal infiltration by inflammatory cells, including T-cells, neutrophils, macrophages and dendritic cells. Psoriasis is probably a complex multifactorial disease in which various environmental triggers (e.g., trauma, stress, infections and drugs) promote, in genetically predisposed individuals, an exaggerated and poorly controlled immuno-inflammatory response in the skin which leads to excessive keratinocyte proliferation.

It is increasingly recognized that psoriasis is more than a skin disease, with up to 30% of patients having joint involvement and a high correlation between psoriasis and obesity, diabetes, depression, metabolic syndrome, and cardiovascular risk (R15-1393).

Current Treatment Options
Psoriasis treatment varies with the extent and severity of the disease. Current treatment options include topical treatments (topical corticosteroids, vitamin D analogues, anthralin, topical retinoids, calcineurin inhibitors, salicylic acid, coal tar, and moisturizers), phototherapy, and systemic treatments. Topical treatments are generally used for more localized and mild forms of psoriasis. Exposure of skin to artificial ultraviolet A or B light, either alone or in combination with medications such as psoralen, has also been shown to be quite effective for mild to moderate psoriasis. For more resistant or moderate to severe psoriasis, systemic oral or parenteral medications are used for better efficacy. Systemic oral medications such as methotrexate (MTX), cyclosporine and retinoids have traditionally been the most commonly prescribed drugs for moderate to severe psoriasis. Over the last few years, the introduction of biologic immunosuppressive drugs, such as anti-tumor necrosis factor agents (TNFs), anti-interleukin (IL)12/23 and anti-IL17, has significantly changed the treatment paradigm for moderate to severe psoriasis. These molecules have a much higher efficacy and better safety profile due to their specific targeting of immunopathologic pathways involved in psoriasis. Owing to the higher costs of biologic therapies, they are generally reserved for patients who have been unable to tolerate or are resistant to other systemic psoriasis therapies.

1.2 DRUG PROFILE

The mechanisms of action of anti-TNF agents in psoriasis, including Humira, are not fully understood and may vary in different disease settings.

TNF-α antagonists enhance T helper 17 cells (Th17) function, but suppress forkhead box P3 (FoxP3) + Tregs (regulatory T cells) in the skin in the murine psoriasis-like model (R16-0235).
Humira (adalimumab) has received regulatory approval for psoriasis in the US, the EU, and many other countries (R15-5978 and R16-0358). BI 695501 is being developed as a proposed biosimilar to US-licensed Humira and EU-approved Humira.

Adalimumab (Humira) has a generally favorable clinical safety profile, and is not associated with AEs that would suggest a high risk to subjects participating in this trial. In patients treated with Humira, most common adverse reactions (incidence >10%) include infections (e.g., upper respiratory, sinusitis), injection site reactions, headache, rash, abdominal pain, musculoskeletal pain, nausea, and vomiting. Allergic reactions (e.g., allergic rash, anaphylactoid reaction, fixed drug reaction, non-specified drug reaction, urticaria) have been observed in approximately 1% of patients.

Cases of hepatitis B virus (HBV) reactivation have been reported in patients receiving anti-TNF therapy. Some cases have been fatal, the majority of which were in patients concomitantly receiving other immunosuppressive medications.

Tuberculosis (TB) reactivation or new TB infections have been observed in patients receiving Humira and other TNF-inhibitors, including patients who had previously received treatment for latent or active TB.
BI 695501 is a monoclonal antibody being developed as a proposed biosimilar to the TNF-alpha blocker US-licensed and EU-approved Humira® (adalimumab). Adalimumab is a recombinant humanized monoclonal immunoglobulin (Ig) G1 antibody specific to human TNF-alpha. Humira binds specifically to TNF-alpha (not to TNF-beta) and blocks its interaction with the p55 and p75 cell surface TNF receptors. It has human-derived heavy and light chain variable regions and human immunoglobulin (Ig) G1:k (kappa) constant regions and is produced in a mammalian cell expression system (R15-5978 and R16-0358).

The preclinical studies that support the clinical program include:

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To date, a total of 175 male healthy subjects were treated with 40 mg s.c. of BI 695501 administered via prefilled glass syringe in 2 trials with healthy subjects 1297.1 and 1297.8 (U13-1096-01 and c03070713). The PK similarity of BI 695501 to US-licensed Humira and EU-approved Humira was demonstrated in a healthy volunteers study using the final commercial formulation (c03070713). Single s.c. doses of 40 mg BI 695501, US-licensed Humira and EU-approved Humira were generally well tolerated by healthy male subjects. There were no notable differences between the 3 treatment arms with respect to safety, tolerability, and immunogenicity.

Overall, the adverse events (AEs) seen in 2 healthy subject trials for BI 695501 and both EU-approved Humira and US-licensed Humira were in line with the known safety profile presented in the US prescribing information for Humira (R15-5978) and in the summary of product characteristics (SPC) for EU-approved Humira (R16-0358).

A phase III trial (1297.2) in patients with moderate to severe rheumatoid arthritis (RA) is ongoing. A total of 645 patients with moderate to severe RA were included in the study and are being treated with either BI 695501 or US-licensed Humira. The observed blinded AE profile revealed no unexpected safety findings and showed no clinically relevant safety concerns.

For further detailed description of the BI 695501 profile please refer to the current 'Investigator's Brochure' (IB) (c01843589) and for the US-licensed Humira to the United States Package Insert (US-PI) (R15-5978).

2. RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1 RATIONALE FOR PERFORMING THE TRIAL

The current trial is being performed to establish an equivalence of efficacy between BI 695501 and US-licensed Humira in patients with active moderate to severe chronic plaque psoriasis. It is expected that, based on the data from pivotal study in RA, BI 695501 will be granted extrapolation to all other indications of Humira. However, this additional study to generate comparative efficacy and safety data in psoriasis will be important to show scientific evidence for biosimilar BI 695501.

2.2 TRIAL OBJECTIVES

The primary objective of this trial is to establish equivalence in efficacy between BI 695501 and US-licensed Humira at Week 16 in patients with active moderate to severe chronic plaque psoriasis.

The secondary objectives of this trial are to compare the safety and efficacy profiles of BI 695501 and US-licensed Humira.

A description of the selected endpoints and the observations along with specific information on how to collect the data is provided in Section 5.

2.3 BENEFIT-RISK ASSESSMENT

Participation in this study may help to generate future benefit for larger groups of patients with psoriasis.

Patient risk will be minimized in this trial by implementing conservative eligibility criteria. Adverse events, body temperature, vital signs, electrocardiograms (ECGs) and safety laboratories as well as immunogenicity will be monitored at different time points during the trial and during the long term safety follow-up period up to 10 weeks after the last administration of trial medication.
Although rare, a potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory alterations in selected liver laboratory parameters to ensure patients' safety, see also Section 5.3.6.1.

All safety aspects will be regularly monitored by both the Sponsor and a Contract Research Organization (CRO) during the Medical Quality Review Meetings.

To avoid a risk of reactivating TB and other infections, TB tests (interferon-gamma release assay [IGRA] or purified protein derivative [PPD] skin test), Hepatitis B surface antigen (HBsAg; qualitative), Hepatitis B antibody (anti-HBc; qualitative), Hepatitis C antibodies (Anti-HCV; qualitative), human immunodeficiency virus (HIV)-1 and HIV-2 antibody (at the discretion of the investigator where clinically indicated) will be performed to exclude subjects who test positive. Risk to subjects will also be minimized in this trial by implementing conservative eligibility criteria.

In the controlled portions of clinical trials of some TNF-inhibitors, including Humira, more cases of malignancies have been observed among TNF-inhibitor-treated adult patients compared to control-treated adult patients. Therefore, a possibly increased risk for the development of malignancies cannot be excluded.
TNF-antagonists including Humira have been associated, in rare instances, with new onset or exacerbation of clinical symptoms and / or radiographic evidence of central nervous system demyelinating disease, including multiple sclerosis and optic neuritis, and peripheral demyelinating disease including Guillain-Barre syndrome. Prescribers should exercise caution in considering the use of Humira in patients with pre-existing or recent-onset central or peripheral nervous system demyelinating disorders.
To minimize the risks, patients with a significant disease other than psoriasis will be excluded from the trial participation.

The PK similarity of BI 695501 to US-licensed and EU-approved Humira was established in the phase I trial 1297.8 (c03070713). Additionally, there were no notable differences with respect to safety, tolerability, and immunogenicity between BI 695501 to US-licensed and EU-approved Humira in this phase I trial, and the dose of 40 mg BI 695501 was safe and well tolerated in male healthy volunteers. The observed blinded AE profile in the phase III trial 1297.2 (c02158186) revealed no unexpected safety findings and showed no clinically relevant safety concerns. The review of safety data in 1297.2 trial by the Independent Data Monitoring Committee (IDMC) to date has not suggested any clinically relevant differences in safety profile between Humira and BI 695501.

There were no clinically relevant findings with respect to clinical laboratory evaluation, vital signs, ECGs, or injection site reactions. Based on extensive preclinical, analytical, functional, and toxicological testing carried out prior to initiation of this trial, and the Phase I data described above, BI 695501, as a proposed biosimilar to Humira, is expected to show a similar efficacy, safety, immunogenicity and PK profile in patients with psoriasis.
Patients not achieving at least PASI 50 (patients showing lack of efficacy), will not continue receiving their treatment up to Week 24 with the study drug, but only followed up for safety. These patients will receive an alternative treatment as deemed appropriate by the investigator.

The benefit-risk profile for the patients participating in this trial remains favorable and similar to the originator product.

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This is a multinational, randomized, double-blind, parallel-arm, multiple-dose, active comparator trial of BI 695501 and US-licensed Humira.

In total, approximately 300 patients with moderate to severe chronic plaque psoriasis are planned to be randomized in this trial.

Patients are included in the study once they have signed the informed consent. Patients suitable after screening will be eligible to participate in the 24-week treatment period and will be randomized at a ratio of 1:1 in a blinded fashion to 1 of 2 treatment arms (BI 695501 or US-licensed Humira) shown in Figure 3.1: 1.

After Week 16, only patients who achieve at least a 50% reduction in Psoriasis Area and Severity Index (PASI 50) response will continue the trial receiving their randomized treatment up to Week 24. Those patients not achieving at least PASI 50 (or who discontinue the trial early), will not be treated with the study drugs, but only followed up for safety. Patients will undergo visits and trial procedures as shown in the Flow Chart.

All patients who receive at least 1 injection of BI 695501 will have a Safety Follow-up visit 10 weeks after the last dose of trial medication.

Every effort should be made for all patients who complete the 24-week treatment period or who discontinue the trial early (and do not withdraw their consent), to return for a safety follow-up visit 10 weeks after the last administration of trial medication.

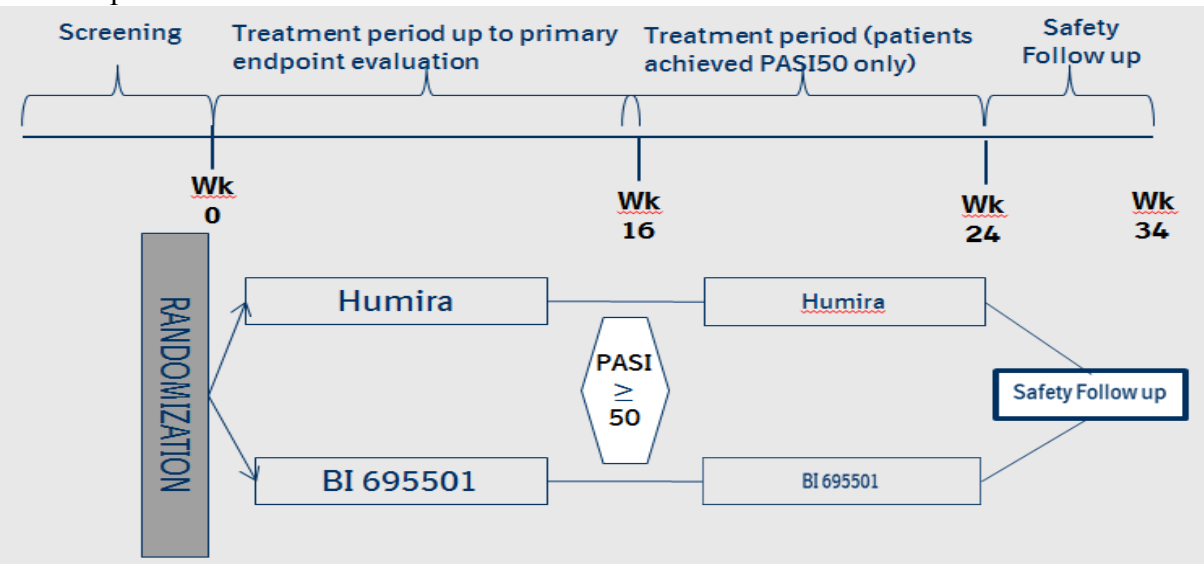


Figure 3.1: 1 Trial design

3.1.1 Administrative structure of the trial

The trial is sponsored by Boehringer Ingelheim International (BI).

CRO will perform Project Management, Clinical Field Monitoring, Medical Monitoring, Data Management, and Statistical Evaluation according to CRO Standard Operating Procedures (SOPs). A list of responsible persons and relevant local information can be found in the Investigator Site File (ISF).

A Coordinating Investigator will be responsible to coordinate Investigators at different centers participating in this multicenter trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in the electronic trial master file.

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

- manage the trial in accordance with applicable regulations and applicable Boehringer Ingelheim and CRO SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate oversight of vendors.

A list of responsible persons and relevant local information can be found in the ISF.

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

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP

The current trial is being performed to establish an equivalence of efficacy between BI 695501 and US-licensed Humira in patients with active moderate to severe chronic plaque psoriasis.

This is a randomized, double-blind, parallel arm, multiple dose, active comparator trial of BI 695501 and US-licensed Humira with a planned 24-week treatment period followed by a 10-week safety follow up, in patients with active moderate to severe chronic plaque psoriasis.

The treatment groups will be blinded throughout the whole trial, to minimize any bias that could be introduced by knowledge of the treatment by either the investigator or the patient.

3.3 SELECTION OF TRIAL POPULATION

A total of approximately 300 patients is planned to be randomized in the current trial.

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

3.3.1 Main diagnosis for trial entry

Patients must have moderate to severe chronic plaque psoriasis, stable for the last 2 months with no meaningful changes in morphology or significant flares, defined as ≥ 10% body surface area (BSA) involvement, Psoriasis Area and Severity Index (PASI) score ≥ 12 and static Physician's Global Assessment (sPGA) score ≥ 3.

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

3.3.2 Inclusion criteria

1. Males and females aged ≥ 18 to < 80 years who have a diagnosis of moderate to severe chronic plaque psoriasis (with or without psoriatic arthritis) for at least 6 months before the first administration of study drug (a self-reported diagnosis confirmed by the investigator is acceptable), and which has been stable for the last 2 months with no changes in morphology or significant flares at both Screening and Baseline (Randomization):
    a. involved BSA ≥ 10% and
    b. PASI score ≥ 12 and
    c. sPGA score of ≥ 3.

2. Participants of reproductive potential （childbearing potential[1]) must be willing and able to use highly effective methods of birth control per International Council for Harmonization (ICH) M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly during the trial and for 6 months following completion or discontinuation from the trial medication. A list of contraception methods meeting these criteria is provided in the Section 4.2.2.2 and patient information.
3. Signed and dated written informed consent in accordance with Good Clinical Practice (GCP) and local legislation prior to admission to the trial.
4. Patients who are candidates for systemic therapy.

[1] Women of childbearing potential are defined as:
- having experienced menarche and
- not postmenopausal (12 months with no menses without an alternative medical cause) and
- not permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

3.3.3 Exclusion criteria

1. Active ongoing inflammatory diseases other than psoriasis that might confound trial evaluations according to investigator's judgment.
2. Previous treatment with more than 1 biological agent, or adalimumab or adalimumab biosimilar. No prior biologic exposure within last 6 months of screening will be permitted
3. Patients with a significant disease other than psoriasis and/or a significant uncontrolled disease (such as, but not limited to, nervous system, renal, hepatic, endocrine, hematological, autoimmune or gastrointestinal disorders). A significant disease is defined as a disease which, in the opinion of the investigator, may (i) put the patient at risk because of participation in the trial, or (ii) influence the results of the trial, or (iii) cause concern regarding the patient's ability to participate in the trial.
4. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned within 6 months after screening, e.g., total hip replacement.
5. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.
6. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
7. Currently enrolled in another investigational device or drug study, or less than 30 days since ending another investigational device or drug study(s), or receiving other investigational treatment(s).
8. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes the patient an unreliable study subject or unlikely to complete the trial.
9. Women who are pregnant, nursing, or who plan to become pregnant during the course of this study or within the period at least 6 months following completion or discontinuation from the trial.
10. Forms of psoriasis (e.g., pustular, erythrodermic and guttate) other than chronic plaque psoriasis. Drug-induced psoriasis (i.e., new onset or current exacerbation from e.g., beta-blockers or lithium).
11. Primary or secondary immunodeficiency (history of, or currently active), including known history of HIV infection or a positive HIV test at screening (per the investigator discretion and where mandated by local authorities).
12. Known chronic or relevant acute tuberculosis,; IGRA TB test or PPD skin test will be performed according to the labelling for Humira. If the result is positive, patients may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active tuberculosis. If latent tuberculosis is confirmed, then treatment must have been initiated before randomization and continued according to local country guidelines[2].

[2] For Germany: patients with positive IGRA TB test or PPD skin test will be excluded from the study participation.

13. Known clinically significant coronary artery disease, significant cardiac arrhythmias, moderate to severe congestive heart failure (New York Heart Association Classes III or IV) or interstitial lung disease observed on chest X-ray.
14. History of a severe allergic reaction, anaphylactic reaction, or hypersensitivity to a previously used biological drug or its excipients.
15. Positive serology for hepatitis B virus (HBV) or hepatitis C virus (HCV).
16. Receipt of a live/attenuated vaccine within 12 weeks prior to the Screening Visit; patients who are expecting to receive any live/attenuated virus or bacterial vaccinations during the trial or up to 3 months after the last dose of trial drug.
17. Any treatment (including biologic therapies) that, in the opinion of the investigator, may place the patient at unacceptable risk during the trial.
18. Known active infection of any kind (excluding fungal infections of nail beds), any major episode of infection requiring hospitalization or treatment with intravenous (i.v.) anti-infectives within 4 weeks of the Screening Visit or completion of oral anti-infectives within 2 weeks of the Screening Visit.
19. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 times upper limit of normal (ULN) at Screening.
20. Hemoglobin < 8.0 g/dL at Screening.
21. Platelets < 100,000/µL at Screening.
22. Leukocyte count < 4000/µL at Screening.
23. Creatinine clearance < 60 mL/min/1.73 m^2 at Screening.
24. Patients with a history of any clinically significant adverse reaction to murine or chimeric proteins, or natural rubber and latex, including serious allergic reactions.

3.3.4 Removal of patients from therapy or assessments

3.3.4.1 Removal of individual patients

All patients have the right to withdraw from the study at any time without the need to justify their decision. The investigator has the right to remove patients from the study for non-compliance or other reasons.

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

- The patient decides to discontinue participation in the trial by withdrawal of consent. In this case, no more investigations will be performed.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- Lack of efficacy defined as PASI 50 not reached at Week 16.
- Development of a toxicity or adverse event which warrants BI 695501/Humira discontinuation including but not limited to serious adverse events (SAEs) or suspected unexpected serious adverse reactions (SUSARs).
- The patient has an AE that is categorized as a serious infection. A serious infection is defined as an infection requiring i.v. antibiotics or meeting the regulatory definition of a

SAE (including, but not limited to, systemic fungal infections, HIV, HBV, HCV, TB, infected joint prosthesis).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).
- If the trial treatment is not in the patient's best interest at the investigator's discretion. (e.g. severe worsening of psoriasis). The patient will be discontinued from the trial to receive treatment as deemed appropriate by the investigator.
- The patient has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.

If a patient permanently discontinues trial medication for any reason (including lack of efficacy), every effort should be made to have the patient return for a safety follow-up visit 10 weeks after the last dose of trial medication.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart (Safety Follow-up [SFU] visit) and Section 6.2.3.

For all patients the reason for withdrawal (e.g., AEs) must be recorded in the electronic Case Report Form (eCRF). These data will be included in the trial database and reported.

3.3.4.2 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for reasons including but not restricted to:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the Clinical Trial Protocol (CTP), or the contract impairing the appropriate conduct of the trial.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

The trial medication will be provided by BI.

4.1.1 Identity of the Investigational Medicinal Products

BI 695501 and US-licensed Humira will be used in this study. Details of the trial medication are provided in Tables 4.1.1: 1, and 4.1.1: 2.

Table 4.1.1: 1 Test product

Substance:	BI 695501
Pharmaceutical formulation:	Solution for injection in prefilled syringe
Source:	BI Pharma GmbH & Co. KG, Germany
Unit strength:	40 mg / 0.8 mL
Posology	80 mg (loading dose) on Day 1 / Week 0, 40 mg every other week from Week 2 to Week 23
Route of administration:	Subcutaneous injection

Table 4.1.1: 2 Reference product

Substance:	US-licensed Humira (adalimumab)
Pharmaceutical formulation:	Solution for injection in prefilled syringe
Source:	AbbVie Inc.
Unit strength:	40 mg / 0.8 mL or 40 mg / 0.4 mL
Posology	80 mg (loading dose) on Day 1 / Week 0, 40 mg every other week from Week 1 to Week 23
Route of administration:	Subcutaneous injection

BI 695501 prefilled syringe will be provided as sterile, preservative-free, non-pyrogenic, single-use prefilled glass syringes containing 40 mg of BI 695501 per 0.8 mL. One syringe will be used per injection except for Week 0/Day 1, at which 2 syringes (80 mg) will be used. The needle cap of the syringe contains dry, natural rubber.

US-licensed Humira will be provided in sterile, preservative-free, non-pyrogenic, single-use, prefilled glass syringes containing 40 mg of adalimumab per 0.8 mL or 0.4 mL of solution. One syringe will be used per injection except for Week 0 / Day 1, at which 2 syringes (80 mg) will be used.
Any unused product or waste material will be disposed of in accordance with local requirements.

4.1.2 Selection of doses in the trial

In the US and EU, adalimumab (Humira) has received health authority approval for the treatment of RA, Crohn's disease, plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis and Hidradenitis suppurativa. The doses of BI 695501 and Humira selected for this trial are identical due to the similarity of both compounds (an initial dose of 80 mg s.c. injection followed 1 week later and subsequently every other week by 40 mg) and are the doses that were used to assess the efficacy of the originator compound and are as per Humira label.

4.1.3 Method of assigning patients to treatment groups

Once patients have completed screening, have met all the inclusion criteria and none of the exclusion criteria, a pre-treatment call will be made using the IRT system. Screen failure patients may be rescreened once based on investigator judgment and prior permission from medical monitor of the study.

The registration call will depend on the trial site procedure. The process for treatment assignment might be different depending on the country and respective trial medication shipping timelines. In countries where trial medication needs to be sent to sites in advance due to long shipping timelines (e.g., cross border shipments), trial medication will be provided to the sites in advance and patients will be assigned treatment on Day 1. For countries where trial medication can be provided on short notice (short shipping times) a registration call will be made as described below and trial medication will be shipped. The registration call might be made within 10 days prior to the planned first administration of trial medication. Eligible patients will then be confirmed to the randomization scheme on Day 1 (or when the drug is at site), according to their randomization.

Patients will be randomized to each treatment in a 1:1 ratio (BI 695501 or US-sourced Humira) at Visit 2.
Initial randomization will be stratified according to prior exposure to a biologic agent (yes / no).
Randomization will be performed in a blinded fashion via IRT. Patients will be randomized sequentially (the lowest sequentially available randomization number).

Each syringe of trial medication will be labeled with the trial code and a unique medication identification number. The IRT system will be used for the randomization, allocation, and supply of trial medication throughout the study. The IRT will assign each patient a unique medication number for each drug administration. Details of the IRT system will be provided in the ISF.

Access to the randomization code will be controlled and documented. All persons directly involved in the conduct and analysis of the trial will have no access to the treatment allocation prior to final database lock.

4.1.4 Drug assignment and administration of doses for each patient

Each patient will receive 80 mg of BI 695501 or US-licensed Humira at the Baseline Visit (Day 1, Week 0) followed by 40 mg of BI 695501 or US-licensed Humira 1 week later, and then 40 mg of BI 695501 or US-licensed Humira every other week until Week 16 (primary endpoint).
After Week 16 (Day 112), patients achieving at least a PASI 50 response will continue receiving their randomized treatment (40 mg BI 695501 or Humira every other week) until Week 24 in a blinded fashion.

Patients not achieving at least PASI 50 at Week 16 will not be further treated with the study drugs, but only followed up for safety.

The prefilled syringe must be removed from refrigeration 30 minutes before administration to permit the medication to warm. Injecting cold medication can cause discomfort. Once taken out of the refrigerator, the trial medication should be administered within 1 hour. A syringe must not be used if it is frozen or if it has been left in direct sunlight.

The patient will administer the injection in an area of the skin where post-administration assessments of any reaction would not be compromised by the presence of impairment to skin integrity. The location for the trial medication injection will be the lower abdomen (excluding a 2-inch [5-cm] area around the navel) and upper thigh. A different injection site should be selected for each injection (at least 1 inch [2.5 cm] away from the previous site).

For the duration of the trial, trial medication will be administered either at the trial site by dedicated trial personnel, or at home by the patients themselves. At all designated site visits (Weeks 0 and 1), the patient must administer BI 695501 while at the trial site. Between designated site visits (Weeks 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 23), the patient may choose to come to the site to self-inject the trial medication with the support of suitably qualified, designated trial site personnel or the patient may self-inject the trial medication at home. Patients will be instructed to accurately record the dates and times of dosing, problems encountered with dosing, the occurrence of any AEs, the use of concomitant therapies, and the prefilled syringe storage conditions on the provided diary cards between the trial site visits.
For self-administration, handling and administration of trial medication will be described in detail in the handling instructions. Cool bags and handling instructions will be provided to the patient (refer to the ISF).

In case of implementation of the third-party blinded procedure, for the duration of the trial, BI 695501 / US-sourced Humira will be administered by a dedicated trial personnel (designated unblinded person will administer the drug to patients but will not be involved in any assessment of safety or efficacy), either at the site or at the patient's home. These trial personnel will be allowed to perform drug administrations and home visits only after suitable training has been received and they are considered to be qualified to perform the subcutaneous injections and the home visits.

After the first injection (Visit 2), the patient will remain at the clinical site for at least 1 hour for observation of any AEs.

Dose modification is not permitted during this trial. If a patient misses a dose of trial medication then the dose should be administered as soon as possible.

The 2-week regimen for trial medication administration should resume from the time the last dose is administered. The last injection is planned to occur at Week 23 for all eligible patients. The treatment period will not be extended past this time point.

In the event of an anaphylactic or other serious hypersensitivity reaction, the administration of trial medication will be discontinued immediately, the patient will be discontinued from the trial and appropriate therapy will be initiated.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

This is a double-blind trial, therefore patients, Investigators and everyone involved in trial conduct (except the trial personnel administering the trial medication–third-party blinding) in this double-blind trial will remain blinded with regard to the randomized treatment assignments until after the final database lock.

The randomization code will be kept secret by Clinical Trial Support up to database lock. Bioanalytics will not disclose the randomization code or the results of their measurements until the trial is officially unblinded.

It is planned to conduct the study using 0.8 mL BI 695501 or a pre-filled Humira syringe as the reference product thoughout.
However, if 0.8 mL Humira is not available, the study conduct may have to be continued using the 0.4 mL pre-filled Humira syringe as the reference product. Taking into account that 0.8 mL BI 695501 and 0.4 mL Humira might differ in their presentations, the blinding of treatments will be maintained by using a third-party blinding, where the study drug will be administered to the patients by persons who are independent of the other clinical trial procedures and not involved in other aspects of the study (see Appendix 10.3 for details on third party blinding procedure).
The secondary packaging (boxes containing syringes) will be identical for both BI 695501 and Humira, allowing the blinding of the site pharmacy.

4.1.5.2 Unblinding and breaking the code

Emergency unblinding will be available to the Investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the Investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. If unblinding is required in the interest of the safety of a patient, and time allows, the investigator will discuss the matter with the Medical Advisor before unblinding

whenever possible. If the code is broken for a patient (via the IRT) the sponsor must be informed immediately. The reason for unblinding must be documented in the source documents and appropriate eCRF page along with the date and the initials of the person who broke the code.

Due to the requirements to report SUSARs, it may be necessary for a representative from the BI Pharmacovigilance group to access the randomization code for individual patients during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives and not be shared further.

4.1.6 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

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

4.1.7 Storage conditions

All trial medications must be kept in a secure place under appropriate storage conditions and handled according to GMP and GCP. The trial medication must be stored in a refrigerator at a controlled temperature (2°C to 8°C [36°F to 46°F]) and must not be frozen. A temperature log will be kept at the trial site and will be completed (with a minimum and maximum reading) on each business day. Syringes will be kept in their outer carton in order to protect from light. Detailed storage conditions will be described on the trial medication labels.

Patients self-injecting at home will be instructed on the correct storage of the trial medication at home and will be required to document storage conditions in the patient diary.

If the storage conditions are found to be outside the specified range, the local clinical monitor (as provided in the list of contacts) must be contacted immediately.

4.1.8 Drug accountability

The designated person at each site will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the trial protocol by the Institutional Review Board (IRB) / Independent Ethics Committee (IEC),
- Availability of a signed and dated clinical trial contract between the sponsor and the Principal Investigator,
- Approval/notification of the regulatory authority, e.g., competent authority (CA),
- Availability of the curriculum vitae of the Principal Investigator,
- Availability of a signed and dated CTP,

- Availability of the proof of a medical license for the Principal Investigator,
- Availability of Form 1572

The designated person must maintain records of the product's delivery to the trial site, the inventory at the site, the administration to each patient, and disposal of unused products. Unused trial medication will be destroyed in accordance with local requirements and the records will be maintained.

These records will include dates, quantities, batch / serial numbers, expiry ('use by') dates, and the unique code numbers assigned to the investigational product and trial patients. The designated person will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of disposal of unused products, the designated unblinded person must verify that all unused or partially used drug supplies have been returned by the clinical trial patient and that no remaining supplies are in the Investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no specific rescue drugs foreseen for the treatment of AEs. There are no special emergency procedures to be followed.

In case of AEs in need of treatment, the investigator can authorize an appropriate therapy. In those cases, subjects will be treated as necessary and, if required, kept under supervision at the trial site or transferred to a hospital until all medical evaluation results have returned to an acceptable level.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study or must refer them for appropriate ongoing care according to local guidelines and daily practice, respectively.

4.2.2 Restrictions

Restrictions on prior and concomitant medications during the course of the trial are described in Table 4.2.2: 1.

Patients must be instructed not to take any new medications or to change the dose regimen of any existing medication (including over-the-counter products, herbal medications, and complementary therapies) without first consulting the investigator. All changes must be noted in the concomitant medication section of the eCRF.

Other medication that is considered necessary for the patient's safety (e.g., as a result of an AE) may be given at the investigator's discretion. Investigators are encouraged to adhere to the restrictions listed in Table 4.2.2: 1.

Any concomitant medications will be recorded in the appropriate sections of the eCRF.

Table 4.2.2: 1 Prior and concomitant treatments

Treatment	**Restriction**
Biologic agents (e.g., TNF antagonists, anti-IL12/23 and anti-IL17)	Prior treatment with more than 1 biologic agent is not permitted Prior treatment with adalimumab or adalimumab biosimilar is not permitted. No prior biologic exposure within last 6 months of screening will be permitted.
Cyclophosphamide	Cyclophosphamide will not be permitted within 6 months prior to Day 1 and for the duration of the study.
Topical steroids	Topical steroid treatment applied on psoriatic lesions/scalp/nails will not be permitted within 2 weeks prior to Day 1 and for the duration of the study. Topical corticosteroid under occlusion in any location will not be permitted within 2 weeks prior to Day 1 and for the duration of the study. Topical corticosteroids of low potency (WHO group VI/VII) are permitted during the study except within 24 hours before study visits.
Other topical treatments	Other topical treatment applied on psoriatic lesions/scalp/nails that is likely to impact signs and symptoms of psoriasis (e.g., vitamin D analogues, pimecrolimus, retinoids, salicyl vaseline, salicylic acid, lactic acid, tacrolimus, tar, urea, hydroxy or fruit acids will not be permitted within 2 weeks of Day 1 and for the duration of the study. However, use of emollients (moisturizing treatments) will be permitted during the study duration except within the 24-hour period immediately prior to each clinic visit.
UVB, UVA or PUVA treatment (photo [chemo] therapy)	Treatment with UVB or UVA (without psoralen) will not be permitted within 2 weeks prior to Day 1 and for the duration of the trial. PUVA treatment will not be permitted within 4 weeks prior to randomization.
Traditional synthetic agents	Systemic treatment with traditional synthetic agents (e.g., methotrexate, sulphasalazine, azathioprine, retinoids, fumarates) will not be permitted within 4 weeks prior to Day 1 and for the duration of the study.
Nutraceutical treatments	Nutraceuticals intended for the treatment of psoriasis will not be permitted within 4 weeks prior to Day 1 and for the duration of this study.
Other systemic or locally acting medications	Treatment with any other systemic or locally acting medications which might counter or influence the objective of the study (e.g., nonsteroidal anti-inflammatory drug [NSAID], antihistamine) is only permitted for occasional (single dose) use; medications known to potentially provoke or aggravate psoriasis (e.g., lithium, beta-blockers or antimalarial drugs), will only be permitted if the doses of such agents are stable within 4 weeks prior to Day 1 and are planned to remain so for the duration of this study.
Live/attenuated vaccine	Not permitted within 12 weeks prior to the Screening Visit, for the duration of the trial and up to 3 months after the last dose of trial drug.
Any drug/therapy that has not received regulatory approval for any indication	Not permitted within 12 weeks or a minimum of five half-lives, whichever is longer, prior to Day 1.
IV Gamma Globulin	Not permitted within 6 months of the Screening Visit.
Intravenous, intramuscular, intra-articular or parenteral corticosteroids	Not permitted within 6 weeks prior to Day 1 and throughout the trial.
Oral corticosteroids	Not permitted within 4 weeks prior to Day 1 and throughout the trial.
Prosorba® Column	Not permitted within 6 months of the Screening Visit.

Leflunomide	Not permitted within at least 8 weeks prior to Day 1 and throughout the trial.

Abbreviations: IL=interleukin; NSAID=nonsteroidal anti-inflammatory drug; TNF=tumor necrosis factor; UVA=ultraviolet A light; UVB=ultraviolet B light.

4.2.2.1 Restrictions on diet and life style

Moisturizers/emollients containing retinoids and the use of tanning beds are not allowed during the study.
Male subjects with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the trial and for 6 months after the last dose of trial drug.

4.2.2.2 Restrictions regarding women of childbearing potential

A serum beta-human Chorionic Gonadotropin (β-hCG) test will be performed at Screening in women of childbearing potential. A local urine pregnancy test will be then performed as indicated in the Flow Chart. Any woman with a confirmed positive pregnancy test during screening is not eligible for the trial. A positive urine pregnancy test during the treatment periods of the study requires immediate interruption of study treatment until serum β-hCG is performed and found to be negative. If the serum β-hCG test is positive, the patient must be discontinued from the trial.
Female patients of childbearing potential must use the contraception methods described in Section 3.3.2 and the patient information. Acceptable methods of birth control include, for example, birth control pills, intrauterine devices (IUDs), surgical sterilization, vasectomized partner and double barrier method (for example male condom in combination with female diaphragm/cervical cap plus spermicidal foam/gel/film/cream/suppository).

*Women of childbearing potential are defined as:

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

4.2.2.3 Restrictions regarding male participants of reproductive potential

Male participants with female partner(s) of child-bearing potential must agree to use a medically acceptable method of contraception during the trial and for 6 months after the last dose of trial drug. Males should use a condom. Female partners must additionally use 1 of the following methods if they are not pregnant: hormonal contraception, intrauterine device (IUD), diaphragm, or cervical cap. If their partner is pregnant, males must agree to use a condom and no additional method of contraception is required for the pregnant partner. Male subjects must also agree to not donate sperm during the trial and for a period of 6 months after the last dose of trial drug

4.3 TREATMENT COMPLIANCE

Compliance on study visit days (Weeks 0 and 1) will be assured by the observation of trial medication administration by dedicated trial personnel considered qualified to perform or observe the subcutaneous injections.
Between designated site visits (Weeks 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23), the patient may self-inject the trial medication at home. Patients will be instructed to notify the site if they miss a dose or receive a partial dose so the Investigator can determine any necessary follow-up. For all trial medication injections, patients will be asked to complete a patient diary documenting the date and time of the injections and problems encountered with dosing (missed or incomplete injections should be recorded as well).
All used and unused syringes must be returned to the site at each visit.

Patients showing poor compliance as assessed by missing their allocated days for trial medication administration must be counseled on the importance of good compliance to the trial dosing regimen.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial by the investigator after consultation with the sponsor or sponsor's representative, and the eCRF will be completed accordingly.

5. VARIABLES AND THEIR ASSESSMENT

Please refer to the Flow Chart for the Schedule of Assessments for the trial.

The trial endpoints are listed in Section 5.1 below. Efficacy assessments are described in more detail in Section 5.2, safety assessments in Section 5.3, and PK sample collection in Section 5.4.

5.1 TRIAL ENDPOINTS

5.1.1 Primary Endpoint

The primary endpoint is:

- Proportion of patients with a 75% reduction in Psoriasis Area and Severity Index (PASI 75) response at Week 16

5.1.2 Secondary Endpoints

Secondary endpoints are:

Efficacy

- Proportion of patients with a PASI 75 response at Week 24
- Mean percentage improvement in PASI at Week 16
- Proportion of patients with a sPGA ≤ 1 (clear or almost clear) at Week 16
- Proportion of patients achieving a Dermatology Life Quality Index (DLQI) of 0 or 1 at Week 16

Safety

- Proportion of patients with drug-related AEs

Safety

- Proportion of patients with AEs, SAEs and AEs of Special Interest (AESIs) (e.g., serious infections and hypersensitivity reactions);

5.2 ASSESSMENT OF EFFICACY

The following assessments will be made at the time points indicated in the Flow Chart for the purpose of calculating the PASI, sPGA, and DLQI scores.

5.2.1 PASI

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

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

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

To calculate the PASI, the 4 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.(Figure 10.2: 2)

The **signs of severity, erythema (E), induration (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 = severe erythema, and 4 = very severe 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
(Appendix 10.2, Figure 10.2: 4)

5.2.2 Static Physician's Global Assessment

The sPGA is a 5-point score ranging from 0 to 4, based on the physician's assessment of the average thickness, erythema, and scaling of all psoriatic lesions. The assessment is considered "static", which refers to the subject's disease state at the time of the assessments, without comparison to any of the subject's previous disease states (dynamic), whether at Baseline or at a previous visit (Appendix 10.2, Figure 10.2: 1).
A lower score indicates less body coverage, with 0 being clear and 1 being almost clear.

Erythema	(0)	Normal (Post-inflammatory hyperpigmentation may be present
	(1)	Pink coloration of lesions
	(2)	Light red coloration of lesions
	(3)	Dull to bright red coloration of lesions
	(4)	Bright to deep red coloration of lesions
Induration	(0)	None
	(1)	Just detectable
	(2)	Mild thickening
	(3)	Clearly distinguishable to moderate thickening
	(4)	Severe thickening with hard edges
Scaling	(0)	No scaling
	(1)	Minimal focal scaling
	(2)	Predominately fine scaling
	(3)	Moderate scaling
	(4)	Severe /coarse scaling covering almost all or all lesions

Scoring:

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

5.2.3 Dermatology Life Quality Index

The DLQI is a subject-administered, ten-question, quality of life questionnaire that covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships and treatment (R05-2548). The DLQI has a one-week recall period. Item scores range from 0 (not relevant) and 1 (not at all) to 3 (very much). Question 7 is a "yes"/ "no" question where "yes" is scored as 3.

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

The DLQI will be analyzed under 6 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 1 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 (Figure 10.2: 3).

5.3 ASSESSMENT OF SAFETY

At the Screening Visit, the medical examination will include documentation of subject information, informed consent, demographics including height and body weight, smoking and alcohol history, relevant medical history and concomitant therapy, review of inclusion and exclusion criteria, review of vital signs (blood pressure, pulse rate, temperature), 12-lead ECG, laboratory tests (including virus screening, IGRA/PPD test [where applicable], pregnancy test for females), and a physical examination.
On all other visits, it will include review of vital signs, 12-lead ECG, laboratory tests (including IGRA at SFU), pregnancy test for females and a physical examination.
Adverse events and concomitant therapies will be assessed throughout the trial.
Whenever possible, the same person should perform the physical examination throughout the trial (i.e., for all patients at each trial site).

5.3.1 Physical examination

A physical examination will be performed at the visits indicated in the Flow Chart.

The physical examination will include assessment of general appearance, skin, head, neck, throat, lymph nodes, cardiovascular and neurological systems, thyroid gland, musculoskeletal system/limbs, respiratory tract and abdomen.

linically relevant abnormal findings will be reported as Baseline conditions or AEs.

5.3.2 Vital Signs

Vital signs will be assessed at the visits indicated in the Flow Chart.

Blood pressure and pulse rate measurements should be taken following at least 5 minutes rest while the patient is in a sitting position. The patient's body temperature will also be recorded. The method of measuring body temperature (oral/aural) should be consistent at a specific trial site.

The investigator must assess all vital signs findings and if the investigator finds any clinically relevant abnormalities, these must be reported as AEs / SAEs as appropriate.

5.3.3 Safety laboratory parameters

The laboratory tests listed in Table 5.3.3: 1 will be analyzed by a central laboratory. The central laboratory provider will also provide the materials for blood sampling. Instructions for the labeling, storage, and shipment of the samples as well as details of all blood variable units and reference ranges can be found in the Laboratory Manual.

Pregnancy testing will be performed by a central laboratory using serum at Screening and local laboratory using urine at all applicable visits thereafter.

For time points of laboratory sampling, see the Flow Chart.

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

The investigator must assess all laboratory results, evaluate any change in laboratory values, and review all clinical laboratory tests for potential clinical significance at all time points throughout the trial. The investigator should endeavor to provide a reason for all out-of-range results deemed not clinically significant. If the investigator determines a laboratory abnormality to be clinically significant, it will be considered an AE / SAE (see Section 5.3.6.1); however, if the laboratory value abnormality is consistent with a current diagnosis, it will be documented accordingly.

Table 5.3.3: 1 Laboratory tests

Category	Test name
Haematology	Hct Hb RBC count / erythrocytes White blood cells / leukocytes Platelet count / thrombocytes
Diff. Automatic	Neutrophils (relative count) Lymphocytes (relative count)
Diff. Manual (if Diff Automatic is abnormal)	Neutrophils, bands (stabs) Neutrophils, polymorphonuclear Lymphocytes
Enzymes	AST (GOT) ALT (GPT) Creatine Kinase CK-MB, **only if CK is elevated** Gamma-Glutamyl Transferase (GGT)
Electrolytes	Calcium Sodium Potassium Chloride
Substrates	Glucose Creatinine Bilirubin total Bilirubin direct **(if total is elevated)** Bilirubin indirect **(if total is elevated)** Total protein Albumin Cholesterol, total
Urine Pregnancy test (only for female patients of childbearing potential) at randomization and continued as indicated in the Flow Chart (including EoT and End of Observational Period Visit)	Human Chorionic Gonadotropin in the urine
Serum Pregnancy test (only for female patients of childbearing potential) at screening and if urine pregnancy test is positive)	Human Serum Chorionic Gonadotropin
Urinalysis (dipstick)	Urine Protein Urine Glucose Urine RBC / erythrocytes
Screening for infections (only at screening)	HBsAg (qualitative) Hepatitis C antibodies (qualitative) HIV-1, and HIV-2 antibody (qualitative, where mandated by local authorities at the discretion of the investigator where clinically indicated)
Screening for infections (only at screening and EoT Visit)	TB test (IGRA: QuantiFERON® Gold assay/T-SPOT®.TB) (PPD skin test at the discretion of the investigator where clinically indicated)[1]

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; CK-MB=Creatine Kinase-MB; EoT=End of Treatment; Gamma- GGT=Glutamyl Transferase; GOT=Glutamic-Oxaloacetic Transaminase; GPT=Glutamic-Pyruvic Transaminase; Hb=hemoglobin; Hct=hematocrit; HIV=human immunodeficiency virus; IGRA=interferon gamma-release assay; PPD=purified protein derivative; TB=tuberculosis.

[1] There is the trial site option to perform a PPD skin test, although this will not be provided or performed at Central Lab.

5.3.4 Electrocardiogram

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

ECGs will be recorded after the patients have rested for at least 5 minutes in a supine position and will always precede blood sampling.

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

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

The original ECG traces and variables must be stored in the patients' medical record as source data. A physician familiar with interpretation of ECG will evaluate the ECG from a clinical perspective and the result (whether the ECG result is normal, abnormal not clinically relevant or abnormal clinically relevant) will be recorded in the appropriate section of the eCRF.

5.3.5 Other safety parameters

5.3.5.1 Local tolerability

The assessment of injection site reactions will be done by the blinded investigator/designee according to "swelling", "hardening", "heat", "redness", "pain", "itching", "bruising", or "other symptoms". If any injection site reactions are observed, these findings should also be reported on the AE eCRF page.

5.3.6 Assessment of adverse events

5.3.6.1 Definitions of AEs

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

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

Adverse reaction
An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from

occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse, and medication errors.

Serious adverse event

An SAE is defined as any AE which:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.
- requires inpatient hospitalization or
- prolongation of existing hospitalization,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect,
  or
- is deemed serious for any other reason if it is an important medical event when based on medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

AEs considered "Always Serious"

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

In accordance with the European Medicines Agency initiative on Important Medical Events, BI has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE cited above.

A copy of the latest list of "Always Serious AEs" can be found in the ISF and eCRF. These events should always be reported as SAEs as described above.

Adverse events of special interest

The term AESI relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g., the potential for AEs based on knowledge from other compounds in the same class.

AESI need to be reported to the sponsor's/sponsor designee Pharmacovigilance Department within the same timeframe that applies to SAE, please see above.

The following are considered as AESIs:

1. Hepatic injury

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

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

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

2. Anaphylactic reactions

3. Serious infection (defined as infections requiring IV antibiotics or meeting the regulatory definition of a SAE)

4. Hypersensitivity reactions

Intensity of AEs

The intensity of the AE should be judged based on the following:

Mild:	Awareness of sign(s) or symptom(s) that is/are easily tolerated
Moderate:	Sufficient discomfort to cause interference with usual activity
Severe:	Incapacitating or causing inability to work or to perform usual activities

Causal relationship of AEs

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

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

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g., pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g., Stevens-Johnson syndrome).
- An indication of dose-response (i.e., greater effect size if the dose is increased, smaller effect size if dose is diminished).

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

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

5.3.6.2 Adverse event collection and reporting

AE Collection

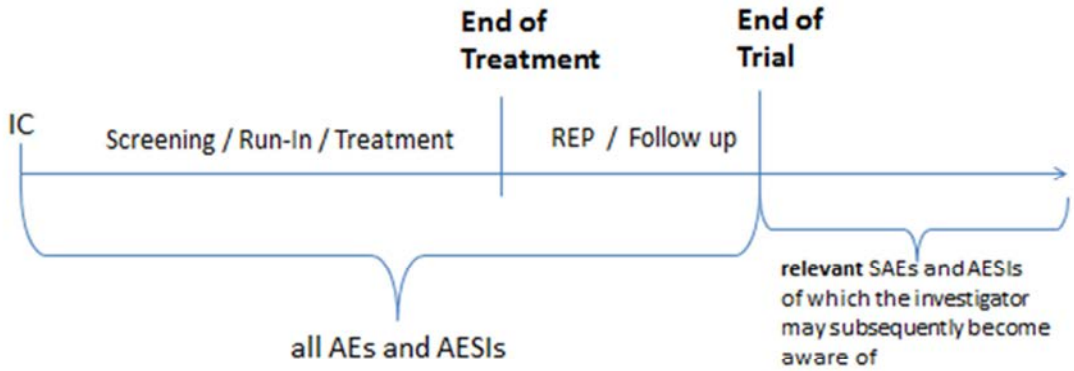
The Investigator shall maintain and keep detailed records of all AEs in their patient files. The following must be collected and documented on the appropriate eCRF(s) by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP, 10 weeks after the last study drug administration), until individual patient's end of trial:
    - all AEs (serious and non-serious) and all AESIs.

  However, if an individual patient discontinues trial medication prematurely but stays in the trial (i.e., if further visits including telephone visits or vital status assessments

are planned) from then on and until the individual patient's end of the trial the Investigator must report related SAEs and related AESIs.

- After the individual patient's end of trial:
    - the Investigator does not need to actively monitor the patient for AEs but should only report relevant SAEs and relevant AESIs of which the Investigator may become aware of.



The residual effect period (REP) is defined as 10 weeks after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment. Events which occurred after the REP will be considered as post treatment events.

AE reporting to sponsor and timelines
The Investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's / sponsor's designee unique entry point (contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the Investigator could inform the sponsor / sponsor designee upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form.

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

Information required
For each AE, the Investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form. The Investigator should determine the causal relationship to the trial medication and any possible interactions between the investigational drugs.

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

- Worsening of the underlying disease that cannot be explained with the natural fluctuation of disease severity or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the Investigator.
- If such abnormalities already pre-exist prior to trial inclusion they will be considered as Baseline conditions.

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

Pregnancy
In rare cases pregnancy may occur in a clinical trial. Once a patient has been enrolled into this clinical trial and has taken trial medication, the Investigator must report immediately (within 24 hours) a potential drug exposure during pregnancy to the sponsor's / sponsor designee unique entry point (contact details will be provided in the ISF). The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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

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

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

5.7 APPROPRIATENESS OF MEASUREMENTS

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

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

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

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

A schedule of assessments is provided in the Flow Chart.

Each visit date (with its window) is to be counted from Day 1 (randomization). If any visit has to be rescheduled, the 2-week regimen for trial medication administration should resume from the time the last dose was administered. Additional visits for the purpose of re-testing of laboratory parameters or AE monitoring may be included as deemed necessary by the investigator.

- A visit window of -1 / + 2 days is permitted for Visit 2 (Day 1)
- A visit window of ± 2 days is permitted from Visit 3 up to Visit 7
- A visit window of ± 3 days is permitted for Visit 8 to Visit 10

All assessments should be performed prior to administration trial medication, unless otherwise specified. Laboratory samples must be drawn prior to trial medication injection.

The questionnaire will be completed at the site by the patient (DLQI) before any investigations or discussions about their disease with the clinic staff and may only be recorded by a trial nurse/investigator on behalf of the patient if the patient has difficulty writing during the visit or is unable to read. This must be documented clearly in the patient notes.

Also the scales are to be completed by study site personnel (PASI sPGA,

All questionnaires and scales are detailed in Appendix 10.

The total estimated volume of blood that will be drawn from each patient during the course of the trial is shown in Table 6.1: 1.

Table 6.1: 1 Estimated blood sample volumes per patient

Parameter	Sample volume (mL)	Number of samples	Total volume (mL)
Laboratory tests (including serum chemistry, serum pregnancy test)	3	6	18
Hematology	3	6	18
Infection screen	4	1	4
TB test	3	2	6
Approximate total			82

Abbreviations: ADA=anti-drug antibodies; nAb=neutralizing ADA; TB=tuberculosis.
Additional samples may be required if medically indicated, e.g., at unscheduled visits to follow safety findings.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

6.2.1 Screening and run-in period(s)

Screening Period
Once the patient has provided informed consent (before any trial-specific procedures or assessments are performed), meets the inclusion criteria and does not meet the exclusion criteria (see Section 3.3), the following will be performed/collected:

- Demographic information (including gender, date of birth, ethnicity, and race), and medical and surgical history (including psoriasis history and history of opportunistic infection)
- Infection screen (TB, HBsAg, anti-hepatitis B core antibodies [anti-HBc], anti-HCV, and HIV test, per the investigator's discretion)
- Chest X-ray, unless taken within the previous 12 weeks
- TB test
- Serum pregnancy test for women of child-bearing potential
- Physical examination, including height (cm) and weight (kg)
- Vital signs (blood pressure, pulse rate, and body temperature)
- Laboratory testing (serum chemistry, hematology, and urinalysis)
- 12-lead ECG
- Previous and concomitant therapy
- Assessment of AEs
- Efficacy assessments: PASI, sPGA, DLQI,

Once patients have completed screening, have met all the inclusion criteria and none of the exclusion criteria, randomization can occur through a registration call through a standard randomization visit call, using the IRT system. The Day 1 randomization or registration call will depend on the trial site procedure. Patients will be randomized to each treatment in a 1:1 ratio (BI 695501: US-licensed Humira) according to the stratification factors. The registrationcall can be made within 10 days prior to the planned first administration of trial medication. Eligible patients will then be confirmed to the randomization scheme on Day 1 (or when the drug is at site), according to their randomization. Eligible patients will be randomized in blocks to double-blind treatment at Day 1 according to the randomization. Patients will be randomly assigned in a blinded fashion to BI 695501 or US-licensed Humira.

6.2.2 Treatment period

Baseline, Visit 2 (Day 1)

For the duration of the trial, BI 695501 / US-licensed Humira will be administered by a suitably qualified, designated trial personnel, either at the site or at the patient's home.

Eligible patients will be randomized and will receive their first administration of trial medication on Day 1.

The following will also be performed/collected:

- Urine pregnancy test for women of child-bearing potential
- Physical examination (see Section 5.3.1)
- Vital signs
- Laboratory testing (serum chemistry, hematology and urinalysis)
- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs (see Section 5.3.6)
- Previous and concomitant therapy
- Efficacy assessments: PASI, sPGA, DLQI, (see Section 5.2)
-

- Contact IRT
- The first injection of trial medication

Visit 3

The following will be performed/collected:
- Assessment of AEs and concomitant therapy
- Contact IRT, training and administer trial medication

Visits 4 to 9

On study days with self-administration of BI 695501 or Humira, patients must complete a patient diary. This occurs on Weeks 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23. Trial site personnel will instruct the patient on how to complete the patient diary. The purpose of the diary is to record events occurring between site visits. Patients will be instructed to accurately record the dates and times of trial medication dosing; problems encountered with dosing; the occurrence of any AEs; the use of concomitant therapies; and the prefilled syringe storage conditions on the provided diary cards between the site visits. The patient will be instructed to contact the site if they are experiencing any AEs between designated site visits.

The following will be performed/collected:

- Urine pregnancy test for women of child-bearing potential (Visits 5, 7, 9)

- Physical examination (Visits 5, 7, 9)
- Vital signs (blood pressure, pulse rate, and body temperature; see Section 5.3.2) (Visits 5, 7, 9)
- Laboratory testing (serum chemistry, hematology and urinalysis; see Section 5.3.3) (Visits 5, 7, 9)
- 12-lead ECG (Visits 5, 7, 9) (
- Assessment of AEs and concomitant therapy
- Review of the patient diary card entries
- Efficacy assessments: PASI, sPGA, DLQI; (see Section 5.2)
-

- Contact IRT and administer trial medication (see Section 4.1.4)

The patient will return all used and unused trial medication at each visit after Week 4 and will bring his / her patient diary for review. Prefilled syringes will be collected by the trial site personnel and destroyed in accordance with local requirements, as instructed in the ISF.

6.2.3 Follow-up Period and Trial Completion

Patients who discontinue the trial prematurely at any time after Day 1 including patients with discontinued treatment at week 16 due to lack of efficacy (but do not withdraw their consent) will, at discontinuation, have an End of Treatment (EoT) Visit equivalent to the Week 24 assessments (except trial medication administration). Patients who discontinue the trial will also be required to have all of the evaluations planned for Visit 10 (Week 34) 10 weeks after their last administered dose of trial medication. These patients should be registered as prematurely discontinued in IRT.

The following will be performed/collected:

- Urine pregnancy test for women of child-bearing potential
- Physical examination, including weight (kg) (see Section 5.3.1)
- Vital signs
- Laboratory testing (serum chemistry, hematology, and urinalysis)
- Previous and concomitant therapy (see Section 4.2)
- Assessment of AEs and concomitant therapy
- Review patient diary
- TB test

<u>Unscheduled visit assessments</u>

Patients may attend the trial site for unscheduled visits at any time for additional safety monitoring at the discretion of the investigator.

All abnormal values that are judged clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. Adverse

events persisting after trial completion must be monitored until they have normalized or have been sufficiently characterized.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This is a randomized, double-blind, parallel-arm, multiple-dose, active comparator, multi-center, multi-national trial.

The primary objective of this trial is to establish equivalence between BI 695501 and US-licensed Humira in terms of efficacy at Week 16 in patients with active moderate to severe chronic plaque psoriasis.

Equivalence in efficacy between BI 695501 and US-sourced Humira will be based on a comparison of:

- Proportion of patients with a PASI 75 response at Week 16 with a margin of ± 18%.

Based upon these design considerations, the trial will be analyzed using logistic regression, which will include term for baseline PASI as covariate. Details of the models are presented below.

7.2 NULL AND ALTERNATIVE HYPOTHESES

The test for equivalence will be performed with respect to BI 695501 versus US-sourced Humira.

The hypotheses for the equivalence test can be written as follows:

H_0: Difference in PASI 75 response rates at Week 16 (BI 695501 versus US-sourced Humira) is less than -18% or more than 18%

H_1: Difference in PASI 75 response rates at Week 16 (BI 695501 versus US-sourced Humira) is within [-18%, 18%]

To conclude equivalence, the two-sided 95% CI of the difference in PASI 75 response rate (BI 695501 – Humira) has to be fully within the equivalence limits of ± 18%.

7.3 PLANNED ANALYSES

The primary analysis set will be the Full Analysis Set (FAS) according to the intention to treat principle. For all efficacy analyses, the FAS consists of all randomized patients who received at least 1 dose of trial medication, and have all efficacy measures relevant for the PASI75, measured at baseline and at least once post-baseline.

A Per-Protocol Set (PPS) of patients who have followed the CTP in all essential criteria will be created for sensitivity analyses. Patients included in the FAS who have important protocol

violations relevant for efficacy will be excluded from the PPS. A protocol violation will be considered important if it can be expected to have a distorting influence on the assessment of the primary endpoint. Such important protocol violations will be defined further in the TSAP and include:

- Incorrect trial medication taken
- Severe violation of treatment compliance
- Severe violation of inclusion/exclusion criteria

All patients treated with at least 1 dose of trial medication will be included in the safety evaluation (Safety Analysis Set [SAF]).

Further details on the definition of the different analysis sets will be provided in the Trial Statistical Analysis Plan (TSAP).

7.3.1 Primary endpoint analyses

The primary analyses will be performed on the FAS. Patients will be assigned to the treatment they were randomized to.

The primary analysis of the observed difference in PASI 75 response rates at Week 16 will be based on logistic regression with subsequent transformation of the estimated parameters to the difference in proportions. Multiple imputation (MI) method will be used to deal with missing data (see Section 7.5).

The estimates from the logistic regression are on the logit scale, and the difference in proportions will be calculated as the difference between the predicted probabilities in the treatment groups on the original scale, with the variance calculated using the cumulative distribution function method of Reeve (Statistical Methods in Medical Research, forthcoming 2016); details will be provided in the TSAP.

The statistical model can be described as follows:

(M1) Logit(response to treatment at Week 16) = treatment + Baseline PASI + random error

This model includes fixed, categorical effects of:

- Treatment (BI 695501 versus US-sourced Humira)

and continuous effect of:

- Baseline PASI

The random error is assumed to be binomially distributed.

As sensitivity analysis the primary endpoint will also be analyzed on the PPS with non-responder imputation (NRI) using M1 as for the primary analysis.

7.3.2 Secondary endpoint analyses

7.3.2.1 Secondary efficacy endpoints

Secondary efficacy endpoints:

- Proportion of patients with a PASI 75 response at Week 24
- Mean percentage improvement in PASI at Week 16
- Proportion of patients with sPGA ≤ 1 at Weeks 16
- Proportion of patients achieving a DLQI of 0 or 1 at Week 16

All secondary analyses will be based on FAS with NRI.

For the proportions, the risk difference will be computed and presented together with its 95% CI.

For the percentage improvement from baseline in PASI, analysis of covariance (ANCOVA) will be used, comparing the mean percentage improvement from Baseline of PASI between BI 695501 versus US-licensed Humira at Week 16. The estimate of the difference will be computed with its 95% CI.

ANCOVA will be performed based on the following model:

(M2) PASI percentage improvement from baseline at Week 16 = treatment + Baseline PASI + random error

The covariates will be handled in a similar way to those described in model M1.

7.3.2.2 Secondary Safety Endpoints

The secondary endpoint is:
- Proportion of patients with drug-related AEs.

7.3.4 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). The analysis of AEs will be based on the concept of treatment-emergent AEs. That means that all AEs with an onset between start of treatment and end of the REP, a period of 10 weeks after the last dose of trial medication, will be assigned to the treatment

period for evaluation. AEs that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Other AEs will be assigned to the appropriate trial phases, i.e., screening or post-treatment.

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

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events. To this end, all adverse events occurring between start of treatment and end of the residual effect period will be considered 'treatment-emergent'. The residual effect period is defined as 10 weeks after last dose of trial medication. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

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

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

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

Safety analyses will be descriptive in nature. No formal inferential analyses are planned for safety comparison. The analyses will be on the SAF. Frequency of adverse events will be tabulated overall and by system organ class and preferred term after coding according to the current version of MedDRA. In addition, risk ratio together with 95% CIs will be presented for the overall proportion.

7.4 INTERIM ANALYSES

For this trial a "Fast track" analysis is planned for analyses of the primary efficacy endpoint. After all primary efficacy endpoint data are available and cleaned (i.e. approximately 16 weeks after the last patient has been randomized) a snapshot of the database will be taken. This snapshot will be used for performing the Fast track analysis.
Only cumulated results will be presented, i.e. patient level data will be excluded. Details regarding statistical analysis will be outlined in the TSAP.
Only a selected team, not involved into the trial activities, will have access to the unblinded snapshot data and need to sign a confidentiality agreement. To ensure that the data integrity of the continuing trial will not be violated, a charter will be prepared beforehand, outlining the procedures to be followed. This document will describe the measures to be implemented by the Sponsor to protect the integrity of the trial until the final database. Team members involved in the conduct of the trial as well as the site personnel and patients will remain blinded until the final database lock.

7.4.1 Final analysis

A final analysis (including all endpoints) will be performed when all trial data are available, i.e., approx. 34 weeks after the last patient has been randomized. In this analysis, all analyses performed for the fast track analysis will be repeated with the (partially) updated data, in particular with respect to safety collected at Week 34 and efficacy endpoints collected at Week 34. The results of the final analysis will be summarized in a CTR.

7.5 HANDLING OF MISSING DATA

7.5.1 Efficacy endpoints

For the primary endpoint, missing PASI 75 data will be imputed using MI as the imputation method. However, all patients who discontinue treatment, are lost-to-follow-up, or have any major protocol deviation related to any therapy that may significantly impact efficacy assessment (Table 4.2.2.1: 1) prior to the primary endpoint assessment will be considered as a non-responder. This is referred to as 'NRI'.

For other endpoints, rules for handling of missing data will be specified in the TSAP, if necessary.

7.5.2 Safety and other endpoints

In case of missing AE relationship status, the AE will be considered as related. For other safety endpoints, rules for handling of missing data will be specified in the TSAP, if necessary.

7.6 RANDOMIZATION

Patients who meet all the inclusion criteria and none of the exclusion criteria will be randomized 1:1 to either BI 695501 or Humira over the 24-week treatment period after the screening period. Randomization will be stratified according to prior exposure to a biologic agent (yes / no). Patients will be randomized sequentially (the lowest sequentially available randomization number)

Randomization can occur through a registrationcall or on Day 1 (-1 / +2) through a standard randomization visit call. The Day 1 randomization call will depend on the trial site procedure. Patients will be randomized to each treatment in a 1:1 ratio (BI 695501: US-sourced Humira) using an IRT system. The registration call might be made 10 days prior to the planned first administration of trial medication. Eligible patients will then be confirmed on to the randomization scheme on Day 1 (or when the drug is at site) and will receive their first administration of trial medication, according to their randomization.

Randomization will be performed in a blinded fashion by IRT. Boehringer Ingelheim Pharma GmbH & Co. KG, Clinical Trial Supply Unit or a third party appointed by the sponsor will provide the randomization list using a validated randomization number generating system. Access to the randomization code will be controlled and documented. All persons directly involved in the conduct of the trial have no access to the treatment allocation prior to final database lock. The block sizes of the randomization will be documented in the CTR.

7.7 DETERMINATION OF SAMPLE SIZE

To perform the equivalence test BI 695501 versus US-licensed Humira with ≥ 85% power, approximately 300 patients are needed for this comparison (FAS).

For the calculation of the sample size a meta-analysis on Week 16 data of the REVEAL and CHAMPION trials (R14-4849, R14-4898) was performed. This meta-analysis revealed a risk difference of 64.2% and a 95% CI (60.4% to 67.9%). Table 7.7: 1 shows the information used in the meta-analysis.

The classical 95-50-95 approach would give a non-conservative acceptance margin of 30.2% for the risk difference preserving 50% of the Humira effect.

Calculation of a conservative equivalence margin
Preserve 70% of the lower confidence limit (lcl) 60.4% (obtained from the meta-analysis) of the historical effect over placebo. Equivalence margin = (1 – preserved proportion)*lcl, (1-0.7)*60.4% = 18%.

Table 7.7: 1 CHAMPION and REVEAL results

Humira versus Placebo	Treatment			Placebo		
	Events	Total	%	Events	Total	%
CHAMPION	86	108	79.6%	10	53	18.9%
REVEAL	578	814	71%	26	398	7%

The weighted mean response rate is assumed to be the true response rate of 72%.
This sample size is based on an assumed treatment difference in proportions of patients with PASI 75 at Week 16 of 0%, a standard proportion of 72% and an equivalence margin of 18%. At a power of 85% the sample size would be 288.

Table 7.7: 2 presents the sample size at different margins and different power.

Table 7.7: 2 Sample size according to different scenarios

Assumed true response rate (RR)	**Margin**	**Confidence level (two-sided)**	**Power**	**Sample Size[#] Equivalence**
72%	15%	95%	75%	340
72%	15%	95%	80%	366
72%	15%	95%	85%	414
72%	15%	95%	90%	572
72%	18%	95%	75%	234
72%	18%	95%	80%	256
72%	**18%**	**95%**	**85%**	**288**
72%	18%	95%	90%	330
72%	20%	95%	75%	188
72%	20%	95%	80%	200
72%	20%	95%	85%	228
72%	20%	95%	90%	262

[#] Allocation ratio 1:1

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for GCP, relevant BI SOPs, the EU regulation 536/2014) and other relevant regulations.

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

The Investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP*.

The BI transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the Investigator and of the sponsor with regard to publication of the results of this trial are described in the Investigator contract.

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

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective IRB / IEC and 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 Investigator must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible. The patient must be given sufficient time to consider participation in the trial. The Investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The Investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

Electronic Case Report Forms for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
Data reported on the eCRF must be consistent with the source data, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the trial; current medical records must also be available.

For the eCRF, all data must be derived from source documents:

In accordance with regulatory requirements the Investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail).

Data reported on the eCRF must be consistent with the source data or the discrepancies must be explained.

Before providing any copy of patients' source documents to the sponsor, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted to ensure patient confidentiality.

If the patient is not compliant with the protocol, any corrective action, e.g., re-training must be documented in the patient file.

8.3.2 Direct access to source data and documents

An adaptive approach to clinical trial monitoring will be utilised. The sponsor will perform a risk assessment of the trial to determine the extent and nature of monitoring required in order to ensure the reliability and robustness of the results. Regular review of risk reports will provide sponsor oversight during trial conduct and direct monitoring activities to the areas of greatest risk which have the most potential impact to subject safety and data quality.
The Investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results. The Clinical Research Associate (CRA) and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and ICH GCP.

8.3.3 Storage period of records

Trial site(s):
The trial site(s) must retain the source and essential documents (including ISF) according to the national or local requirements (whatever is longer) valid at the time of the end of the trial.

Sponsor:
The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the World Health Organization (WHO) GCP handbook.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of GCP as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95).
- The BI-internal facilities storing and analyzing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by BI are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrollment of the first patient in the whole trial.

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Out").

The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual Investigators will be notified of SUSARs occurring with the trial medication until 10 weeks after LPDD at their site.

Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / CA in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within 1 year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

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10. APPENDICES

10.1 CLINICAL EVALUATION OF LIVER INJURY

10.1.1 Introduction

Alterations of liver laboratory parameters, as described in Section 5.3.6 (Protocol-specified AESIs), are to be further evaluated using the following procedures.

10.1.2 Procedures

Repeat the following laboratory tests: ALT, AST, and bilirubin (total and direct) - within 48 to 72 hours. If it is confirmed that ALT and/or AST values ≥ 3 times ULN occur in conjunction with an elevation of total bilirubin of ≥ 2 times ULN, the laboratory parameters listed below (clinical chemistry, serology, hormones, haematology) must be determined and 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, coeruloplasmin, α-1 antitrypsin, transferin, 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, tumor marker
TSH

Hematology
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 (total and direct) at least weekly until the laboratory ALT and/or AST abnormalities stabilize or return to normal, then monitor further as specified in the CTP. Depending on further laboratory changes, additional parameters identified, e.g., by reflex testing will be followed up based on medical judgement and GCP.

10.2 EFFICACY ASSESSMENTS

Score	Short description	Detailed description
0	**clear**	No signs of psoriasis Post-inflammatory hyperpigmentation may be present
1	**almost clear**	Normal to pink coloration No thickening No to minimal focal scaling
2	**mild**	Pink to light red coloration Just detectable to mild thickening Predominantly fine scaling
3	**moderate**	Dull to bright red coloration Clearly distinguishable to moderate thickening Moderate scaling
4	**severe**	Bright to deep dark red coloration Severe thickening with hard edges Severe coarse scaling covering almost all or all lesions

Figure 10.2: 1 sPGA Rating Scale for Overall Psoriatic Disease

Body Segment	% of Total BSA	Anterior Sites Affected (% of Total BSA)		Posterior Sites Affected (% of Total BSA)	Row percentage total (%)
Head	10%		+		
Trunk	30%		+		
Upper Limbs	20%		+		
Lower Limbs	40%		+		
Total	100%				

Figure 10.2: 2 Body Surface Area Involved in Psoriasis

DERMATOLOGY LIFE QUALITY INDEX

DLQI

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

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

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

Please check you have answered EVERY question. Thank you.

Figure 10.2: 3 Dermatology Life Quality Index

		Head	Upper extremities	Trunk	Lower extremities
1	Redness†				
2	Thickness†				
3	Scale†				
4	Sum of rows 1, 2, and 3				
5	Area score‡				
6	Score of row 4×row 5×the area multiplier	row 4×row 5×0.1	row 4×row 5×0.2	row 4×row 5×0.3	row 4×row 5×0.4
7	**Sum row 6 for each column for PASI score**				
**Steps in generating PASI score*					
(*a*) Divide body into four areas: head, arms, trunk to groin, and legs to top of buttocks.					
(*b*) Generate an average score for the erythema, thickness, and scale for each of the 4 areas (0=clear; 1–4=increasing severity)†.					
(*c*) Sum scores of erythema, thickness, and scale for each area.					
(*d*) Generate a percentage for skin covered with psoriasis for each area and convert that to a 0–6 scale (0=0%; 1=<10%; 2=10–<30%; 3=30–<50%; 4=50–<70%; 5=70–<90%; 6=90–100%).					
(*e*) Multiply score of item (*c*) above times item (*d*) above for each area and multiply that by 0.1, 0.2, 0.3, and 0.4 for head, arms, trunk, and legs, respectively.					
(*f*) Add these scores to get the PASI score.					
†Erythema, induration and scale are measured on a 0–4 scale (none, slight, mild, moderate, severe)					
‡*Area scoring criteria* (score: % involvement)					
0: 0 (clear)					
1: <10%					
2: 10–<30%					
3: 30–<50%					
4: 50–<70%					
5: 70–<90%					
6: 90–<100%					

Figure 10.2: 4 PASI

10.3 MEDICATION BLINDING PROCEDURE FOR THIRD PARTY BLINDING

This is a double-blind trial, therefore patients, investigators, and trial personnel (except the trial personnel administering the trial medication at site) will remain blinded with regard to the randomized treatment assignments until after database lock.

To prevent unblinding, a designated, person will receive the trial medication at site. In addition, a qualified unblinded designee will administer the trial medication, maintain records of the product's delivery to the trial site, the inventory at the site, as well as will be responsible for preparation of unused trial medication for return to the sponsor or destruction in a blinded fashion and in accordance with local requirements.

Records of the product's delivery to the trial site will include dates, quantities, batch/serial numbers, expiry ('use by') dates and the unique code numbers assigned to the investigational products and trial patients. The designated unblinded person will maintain records that document doses administration to patients and reconcile all investigational product received at site. These records should be kept separate from the patients file and not be accessible for the blinded personal. At the time of return to the sponsor or local destruction, the designated unblinded person must verify that no supplies remained at the trial site.

The unblinded trial personnel administering the trial medication will not be involved in any other trial assessments or procedures.

A description of the trial medication is provided in Table 4.1.1:1.

Patient blinding procedure

Trial medication will be administered by unblinded trial personnel and no self-administration will be allowed. To ensure patient's blinding during the administration process, the following procedures are to be applied:

- Syringes unpacked and prepared for injection are to be covered by a surgical drape at the time of patient preparation for dosing. The same procedure is to be applied to used syringes after injection.
- During the dose administration, patients are to be separated from the unblinded designee who will administer the trial medication, by surgical drape, screen or pillow.
- If a patient's dosing is required in a supine position, the screen or curtain (the way it is used during surgery) or towel are to be put at chest level.

Site staff blinding procedure

Responsibilities for blinded and unblinded study site staff are defined below. At each site, a form with the name(s) of the staff members, blinded and unblinded, with their respective responsibilities will be filled in.

(NOTE: all personnel noted below will have signed the Site Personnel Signature Log, clearly outlining each individual's responsibility).

In case of non-availability of blinded or unblinded study staff, the Clinical Research Organization and sponsor should be informed immediately.

Blinded Personnel	**Main Responsibilities**
Principal Investigator: **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Monitors patient status • Responsible for the delegation of tasks to appropriate staff and to ensure correctness of all assessments • Provides direct patient care • Works and communicates with blinded CRA • Ensures adequate unblinded pharmacy staff and medication administrator and facilities • Contacts IXRS® to enter screen failures, screened patients, randomizations and obtain subsequent medication assignments
Independent Joint Assessor: **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Joint assessment
Blinded Sub-Investigator or Study Coordinator/Study Nurse: **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Contacts IXRS to enter screen failures, screened patients, randomizations and obtain subsequent medication assignments • Monitors patient status • Provides direct patient care if applicable • Works and communicates with blinded monitor
Blinded CRA: **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS** **CANNOT ADMINISTER THE MEDICATION**	• Remains blinded to the medication assignment during the whole trial • Acts as the primary point of contact for the blinded site team • Provides ongoing site support in all areas of trial conduct, except accountability and reconciliation of trial medication • Conducts blinded site monitoring visits and performs source document verification

Unblinded Personnel	**Main Responsibilities**
Unblinded Pharmacist/Back-up Unblinded Pharmacist: **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS**	• Receives trial medication; unpacks, inventories and stores trial medication in a secure, limited access refrigerator • Reviews ELPRO Libero temperature monitoring device for shipment temperature excursions • Acknowledges trial medication receipt in IXRS • Registers the trial medication in IXRS • Completes the Master Drug Accountability Log and Subject Drug Dispensing Log • Monitors temperature using min/max. thermometer and completes refrigerator temperature storage log • Reports temperature excursions to unblinded monitor • Receives the kit numbers for injection from IXRS confirmation • Dispenses trial medication to the unblinded medication administrator • Trains back-up pharmacist(s), if applicable • Implements blinding plan • Monitors and maintains drug inventory at site • Reports all protocol deviations regarding dosing errors to the unblinded CRA • Ensures all accountability logs are kept separate from the medication blinded staff • Works and communicates with unblinded monitor • Retains used kits for reconciliation by unblinded monitor prior to destruction. Destroys used medication per SOPs.
Set Unblinded Trial Medication Administrator: (Sub-Investigator or study nurse) Back-up Unblinded Trial Medication Administrator: **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS**	• Cooperates with the unblinded pharmacist • Performs the trial medication administration and ensures patient is blinded during IP administration • Works and communicates with unblinded CRA
Unblinded CRA: **CANNOT MAKE SAFETY OR EFFICACY EVALUATIONS** **CANNOT ADMINISTER THE MEDICATION**	• Acts as the primary point of contact for the unblinded site team • Provides ongoing site support in the management of trial medication • Conducts unblinded site monitoring visits and monitors accountability of trial medication

CRA = clinical research associate

Training

All professional personnel taking part in the clinical trial are trained and aware of the need to respect study blinding principles as foreseen by the protocol. Blinded and unblinded study

site staff as well as blinded and unblinded CRAs will be trained on study blinding procedures before the start of any study activities at site. Unblinded study site staff is restricted to persons handling trial medications including the injection of study drug. Training in study blinding procedures for blinded and unblinded study CRAs will be provided during a CRA Meeting. Training in study blinding procedures for blinded and unblinded site staff will be provided at the Investigators' Meeting; during workshop sessions, separately designed for blinded and unblinded study personnel in which CRAs will participate, as well. Part of both workshops will review the Medication Blinding Procedures, with blinding procedures described. For the rest of site staff, who did not participate in an Investigators' Meeting, applicable training in study blinding procedures will be provided by a blinded CRA during the Site Initiation Visit, based on information in Study Protocol, Medication Blinding Procedures and Pharmacy Manual. Such training is a part of study specific agenda for Site Initiation Visit, as well as slide presentation prepared for the visit. All training will be documented.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

"This is the original protocol."

Number of global amendment		
Date of CTP revision		
EudraCT number		
BI Trial number		
BI Investigational Product(s)		
Title of protocol		
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		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c08917790 **Technical Version Number:3.0**

Document Name: clinical-trial-protocol

Title: Efficacy, Safety, and Immunogenicity of BI 695501 versus Humira in Patients with Moderate to Severe Chronic Plaque Psoriasis: A Randomized, Double-Blind, Parallel-Arm, Multiple-Dose, Active Comparator Trial

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Monitor		26 Apr 2016 13:33 CEST
Author-Clinical Program		26 Apr 2016 13:39 CEST
Approval-Therapeutic Area		26 Apr 2016 14:18 CEST
Author-Clinical Pharmacokineticist		27 Apr 2016 14:54 CEST
Author-Trial Statistician		28 Apr 2016 07:47 CEST
Verification-Paper Signature Completion		02 May 2016 11:08 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed